FEDERAL, PROVINCIAL, TERRITORIAL (F/P/T)
COMMITTEE ON HEALTH AND THE ENVIRONMENT (CHE)
BRIEFING NOTE
November 2017

AGENDA ITEM: Water

PRESENTED BY: FPT Committee on Drinking Water (CDW)

OBJECTIVE: Approval of guideline technical document on PFOA in drinking water

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DIRECTION/DECISION REQUESTED:

CHE approve the final guideline technical document on PFOA in drinking water.

BACKGROUND:

- The work on the guideline technical document on PFOA was initiated in 2013 by the FPT CDW Technical Secretariat.
- CDW thoroughly assessed the document and gave its approval for public consultation during the November 2015 meeting.
- The proposed guideline technical document for PFOA underwent a national consultation process ending in September 2016.
- All comments from the public consultation and all comments from provinces and territories have been considered, and the document has been finalized.
- The final guideline technical document for PFOA has been reviewed by CDW. Provincial and territorial concerns have been discussed and resolved. CDW members provided their approval by email following the May 2017 meeting.
- Please contact your CDW representative for details concerning the review and approval process (please refer to the latest CDW membership list).

ISSUE(S) FOR DISCUSSION:

- nil

RECOMMENDATION:

- CHE approve the guideline technical document for PFOA in drinking water.

ATTACHMENTS

- Guideline Technical Document: Part I. Overview and Application

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for perfluorooctanoic acid (PFOA) in drinking water is 0.0002 mg/L (0.2 µg/L), based on exposure solely to PFOA.

As the toxicological effects of PFOA and perfluorooctanoyl sulfonate (PFOS) are considered to be additive, the sum of the ratios of the detected concentrations to the corresponding MACs for PFOS and PFOA should not exceed 1.

2.0 Executive summary

PFOA is a man-made compound that does not occur naturally in the environment. It is used in the manufacture of stain/water-resistant coatings for various consumer products and in specialized chemical applications, such as fire-fighting foams, hydraulic fluids, and carpet spot removers. Environmental concentrations, and therefore potential exposure levels, may be higher in areas near facilities using high amounts of PFOA and near locations with extinguished fires if PFOA-containing fire-fighting foams were used.

This guideline technical document reviews and assesses all identified health risks associated with PFOA in drinking water. It incorporates available studies and approaches and takes into consideration the availability of appropriate treatment technology. Based on this review, the drinking water guideline for PFOA is a maximum acceptable concentration (MAC) of 0.0002 mg/L (0.2 µg/L), based on the general population.

2.1 Health effects

PFOA and its salts have been classified as possibly carcinogenic to humans (Group 2B) by the International Agency for Research on Cancer (IARC), based on limited epidemiological evidence demonstrating associations between PFOA and testicular and renal cancers, and on limited evidence in experimental animals. Non-cancer effects occurring at the lowest level of exposure to PFOA in animals include liver effects, reproductive and developmental effects and changes in serum lipid levels.

Both cancer and non-cancer endpoints were considered in the derivation of the MAC for PFOA in drinking water. The non-cancer approach, based on liver effects in rats, was used to calculate a MAC that is protective of human health from both cancer and non-cancer effects. Because PFOA remains in the human body longer than it does in rats, an approach that accounts for this difference was used in the derivation of the MAC for PFOA in drinking water.

2.2 Exposure

Canadians can be exposed to PFOA in food, consumer products, dust, and drinking water. Exposure is mainly from food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Although PFOA is not regularly monitored at water treatment plants in Canada, the analysis has been performed for a few locations. When detected in drinking water, it is usually found at levels below 0.003 µg/L.

2.3 Analysis and treatment

To date, the United States Environmental Protection Agency has not approved any methods for the analysis of PFOA in drinking water. There are some methods that can be used to measure PFOA in drinking water at levels well below the MAC.

The selection and effectiveness of a treatment strategy for PFOA removal is driven by several factors, including source water chemistry, concentration of PFOA and/or other perfluoroalkyl substances and pre-existing treatment processes. Conventional treatment is not effective for PFOA removal. Other treatment methods are promising, although full-scale studies are limited. Activated carbon adsorption can achieve treated water concentrations of PFOA below the MAC. However, proper operation of the system is essential to ensure that the performance of granular activated carbon (GAC) is not affected by the presence of natural organic matter in the source water. Membrane filtration techniques (reverse osmosis and nanofiltration) and anion exchange may also be effective. Although there are no residential treatment devices certified to remove PFOA, it is expected that the same treatment technologies would also be effective at the residential scale.

2.4 Additivity

The health effects of PFOA and PFOS are similar and well documented. Recent scientific evidence shows that PFOS and PFOA affect the same organ in similar ways. Thus, when PFOS and PFOA are found together in drinking water, the best approach to protect human health is to consider both chemicals together when comparing to the guideline values. This is done by adding the ratio of the observed concentration for PFOA to its MAC with the ratio of the observed concentration for PFOS to its MAC; if the result is below or equal to one, then the water is considered safe for drinking. Science currently does not justify the use of this approach for other PFAS.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

PFOA and perfluorooctane sulfonate (PFOS) are typically found in groundwaters and surface waters impacted by aqueous film-forming foam (AFFF) (i.e., fire-fighting foams). They may also be found in groundwaters and surface waters contaminated by: discharges from industrial facilities; effluents from wastewater treatment plants treating domestic or industrial waste; storm water runoff; or applications of biosolids from a municipal wastewater treatment plant to agricultural land. Like other groundwater contaminants, PFOA can reach drinking water wells through migration of a contaminated groundwater plume. It can also reach surface waters from air emissions of industrial facilities. Particle-bound volatile perfluoroalkyl substances (PFAS) including PFOA may be carried from disposal sites by the wind and deposited on land or surface water, thus explaining their presence in remote locations and in waters not impacted by a point source. PFOA migrates very slowly through the soil to groundwater.

PFOA salts are used as a processing aid in the production of fluoropolymers which are used in joining and sealing materials, which may contain trace amount of PFOA. Some of these materials may be used in distribution systems. The use of distribution system components that are certified to NSF/ANSI 61 would minimize the leaching of PFOA into drinking water.

Given the potential health effects from PFOS and PFOA, and the limited information on the risks and uncertainties of other PFAS, in the case of spill situations, a more thorough evaluation may be required to determine what substances are present. If other PFAS are found, jurisdictions have the option of contacting Health Canada for more information related to their possible health risks.

For drinking water supplies that occasionally experience short-term exceedances above the MAC, it is suggested that a plan be developed and implemented to address these situations. For more significant long-term exceedances that cannot be addressed through treatment, it is suggested that alternative sources of drinking water be considered.

3.1 Monitoring

It is important to note that the analysis for PFOA is highly specialized and should be conducted by a laboratory that is accredited or that has a stringent quality assurance/quality control (QA/QC) program in place to ensure data quality.

3.1.1 Source charcterization

Utilities should characterize their source water to assess PFOA and PFOS concentrations, particularly if source waters are impacted by firefighting training areas, military bases, airports, manufacturing sites and/or waste disposal sites. Once contamination is detected, the source should be sampled semi-annually to confirm that the sum of the ratios of the observed concentration to the MAC for PFOA and PFOS does not exceed 1. If treatment is required, the source should be sampled in conjuction with compliance monitoring. Utilities that have baseline data showing the absence of PFOA and PFOS may conduct less frequent monitoring.

If the main source of contamination is suspected to be from the use of AFFF, utilities may want to consider monitoring for other PFAS, including shorter chain compounds such as perfluorobutanoic acid and perfluorobutane sulfonate. These other PFAS are likely to co-occur at AFFF-impacted sites and are typically more mobile. As such, they can serve as an early warning sign of PFOA and PFOS contamination of a groundwater source.

3.1.2 Operational monitoring

Treatment systems should be specifically designed, operated and maintained for removal of PFOA and PFOS. The operational monitoring frequency will depend on the treatment technology the utility employs. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance. Utilities that use a GAC system for PFOA and PFOS removal may require quarterly monitoring of the treated water in order to assess the performance of the GAC system and to determine the timing of the regeneration or replacement. Utilities should also be aware that ozone or advanced oxidation processes may oxidize polyfluorinated pecursors present in the source water, which could result in an increased concentration of PFOA in the finished water.

3.1.3 Compliance monitoring

When treatment is in place for PFOA and PFOS removal, semi-annual monitoring of the treated water is recommended. Samples should be collected after treatment, but prior to distribution, typically at the entry point to the distribution system. Paired samples of source and treated water should be taken to confirm the efficacy of the treatment. The sum of the ratios of the measured concentration to the MAC for PFOA and PFOS should not exceed 1.

COMITÉ FÉDÉRAL-PROVINCIAL-TERRITORIAL (FPT)
SUR LA SANTÉ ET L'ENVIRONNEMENT (CSE)
NOTE D'INFORMATION
Novembre 2017

POINT À L'ORDRE DU JOUR : Eau

PRÉSENTÉ PAR : Comité FPT sur l'eau potable (CEP)

OBJECTIF : Approbation du document technique de la recommandation concernant l'APFO dans l'eau potable

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ORIENTATION/DÉCISION REQUISE
Que le CSE approuve la version finale du document technique de la recommandation concernant le PFOA dans l'eau potable.

CONTEXTE:

- Le travail sur le document technique de la recommandation sur l'APFO dans l'eau potable a été initié en 2013 par le secrétariat technique du CEP.
- Le document a été examiné en détails par le CEP, qui a donné son approbation durant la réunion de novembre 2015 pour que le document fasse l'objet d'une consultation publique.
- L'ébauche du document technique de la recommandation sur l'APFO a suivi un processus de consultation publique national se terminant en septembre 2016.
- Les commentaires de la consultation publique et des provinces et territoires ont été considérés, et le document a été finalisé.
- La version finale du document technique sur l'APFO a été examinée par le CEP. Les préoccupations des provinces et territoires ont été discutées et résolues. Les membres du CEP ont approuvé ce document par courriel après la réunion de mai 2017.
- Veuillez communiquer avec votre représentant du CEP pour obtenir des détails concernant le processus de révision et d'approbation (SVP, vous référer la liste des membres la plus récente).

SUJET(S) À DISCUTER :
- Sans objet

RECOMMANDATION
- Approbation, par le CSE, du document technique de la recommandation concernant l'APFO dans l'eau potable.

PIÈCES JOINTES
- Document technique : Partie I. Vue d'ensemble et application.

Partie I : Vue d'ensemble et application

1.0 Recommandation

La concentration maximale acceptable (CMA) pour l'acide perfluorooctanoïque (APFO) dans l'eau potable est de 0,0002 mg/L (0,2 µg/L), en fonction de l'exposition à l'APFO seulement.

Comme on considère que les effets toxicologiques de l'APFO et du sulfonate de perfluorooctane (SPFO) sont additifs, la somme des rapports des concentrations décelées aux CMA correspondantes ne devrait pas être au dessus de 1.

2.0 Sommaire

L'APFO est un composé artificiel qui ne se trouve pas naturellement dans l'environnement. Il est utilisé dans la fabrication de revêtements résistant à l'eau contenus dans divers produits grand public de même que dans certaines applications chimiques spécialisées telles que les mousses extinctrices, les fluides hydrauliques et les détachants de moquettes. Les concentrations dans l'environnement et, par conséquent, les niveaux d'exposition potentiels pourraient être plus élevés dans les régions proches des installations utilisant de grandes quantités d'APFO et à proximité des lieux où des incendies ont été éteints, si des mousses extinctrices à base d'APFO ont été utilisées.

Ce document technique passe en revue et évalue tous les risques connus pour la santé qui sont associés à la présence d'APFO dans l'eau potable. Il tient compte des études et approches disponibles, ainsi que des limites des méthodes d'analyse et des techniques de traitement. D'après cet examen, la recommandation pour l'APFO dans l'eau potable est une concentration maximale acceptable de 0,0002 mg/L (0,2 µg/L) pour la population générale.

2.1 Effets sur la santé

Le Centre international de recherche sur le cancer (CIRC) a classé l'APFO et ses sels parmi les substances de groupe 2B, c'est-à-dire susceptibles d'être cancérogènes pour l'être humain, d'après des preuves épidémiologiques limitées établissant des liens entre l'APFO et les cancers du testicule et du rein, et compte tenu de preuves limitées chez les animaux de laboratoire. Les effets non cancérogènes se produisant aux plus faibles niveaux d'exposition à l'APFO chez les animaux englobent des effets sur le foie, la reproduction et le développement, et des modifications touchant le niveau de lipides sériques.

Les effets cancérogènes et non cancérogènes ont tous deux été pris en considération dans l'établissement de la CMA pour l'APFO dans l'eau potable. L'approche basée sur les effets non cancer, fondée sur la base des effets sur le foie chez le rat, a servi à calculer une CMA qui protège la santé humaine à la fois des effets cancérogènes et non cancérogènes. Puisque l'APFO reste plus longtemps dans le corps humain que dans le rat, l'approche utilisée pour dériver la CMA pour l'APFO dans l'eau potable tient compte de cette différence.

2.2 Exposition

Les Canadiens peuvent être exposés à l'APFO dans les aliments, les produits de consommation, la poussière et l'eau potable. L'exposition est principalement liée aux aliments et aux produits de consommation, mais la proportion provenant de l'eau potable peut être plus élevée pour les individus résidant dans des régions où l'eau potable est contaminée. Bien que la

présence d'APFO ne soit pas régulièrement surveillée dans les usines de traitement de l'eau potable au Canada, une analyse a été effectuée à quelques endroits. Lorsque l'APFO est détecté dans l'eau potable, son niveau est généralement en dessous de 0,003 µg/L.

2.3 Analyse et traitement

À ce jour, l'U.S. Environmental Protection Agency n'a approuvé aucune méthode pour l'analyse de l'APFO dans l'eau potable. Il existe certaines méthodes permettant de mesurer les niveaux d'APFO présents dans l'eau potable à des niveaux bien inférieurs à la CMA.

Le choix et l'efficacité d'une stratégie pour l'enlèvement de l'APFO sont déterminés par plusieurs facteurs, tels que la composition chimique de l'eau brute, la concentration d'APFO et/ou d'autres substances perfluoroalkylées ainsi que les procédés de traitement déjà en place. Le traitement conventionnel n'est pas efficace pour enlever l'APFO. D'autres méthodes de traitement se montrent prometteuses, mais les études à pleine échelle sont limitées. La méthode d'adsorption sur du charbon actif peut permettre d'obtenir des concentrations d'APFO inférieures à la CMA. Cependant, l'opération appropriée du système est essentielle pour faire en sorte que le rendement du charbon actif en grains (CAG) ne soit pas entravé par la présence de matière organique naturelle dans l'eau brute. Les techniques de filtration sur membrane (osmose inverse et nanofiltration) et d'échange d'anions pourraient aussi s'avérer efficaces. Bien qu'il n'existe aucun dispositif de traitement à résidentiel certifié pour éliminer l'APFO, les mêmes techniques de traitement devraient être efficaces à l'échelle résidentielle.

2.4 Additivité

Les effets sur la santé de l'APFO et du SPFO sont similaires et bien documentés. Les preuves scientifiques récentes montrent que l'APFO et le SPFO agissent de façon similaire sur le même organe. Par conséquent, lorsque ces deux substances sont détectées ensemble dans l'eau potable, la meilleure façon de protéger la santé humaine est de les considérer en même temps pour faire une comparaison avec les recommandations. Pour ce faire, il faut additionner le rapport de la valeur observée pour l'APFO sur sa recommandation avec le rapport de la valeur observée pour le SPFO sur sa recommandation; si le résultat de cette addition est de un ou moins, l'eau est considérée propre à la consommation. La science actuelle ne permet pas de justifier l'utilisation de cette approche avec d'autres SPFA.

3.0 Application de la recommandation

Remarque : Des conseils spécifiques concernant l'application des recommandations pour l'eau potable devraient être obtenus auprès de l'autorité appropriée en matière d'eau potable dans le secteur de compétence concerné.

L'APFO et le sulfonate de perfluorooctane (SPFO) sont typiquement retrouvés dans les eaux souterraines et de surface affectées par des mousses à formation de pellicule aqueuse (mousse AFFF, utilisée pour l'extinction de feux). Ils peuvent aussi être retrouvés dans les eaux souterraines et de surface contaminées par des rejets provenant d'installations industrielles, des rejets issus d'usines de traitement des eaux usées domestiques ou industrielles, des eaux pluviales d'orage, ou de l'application de biosolides provenant d'usines municipales de traitement des eaux usées à des terres agricoles.. Tout comme d'autres contaminants d'eau souterraine, l'APFO peut atteindre les puits d'eau potable par la migration d'un panache d'eau souterraine contaminée. Il peut aussi atteindre l'eau de surface par les émissions dans l'atmosphère

provenant d'installations industrielles. Il est possible que des substances perfluoroalkyliques (SPFA) volatiles liées à des particules soient emportées par le vent à partir de sites d'élimination et qu'elles se déposent ensuite sur le sol ou l'eau de surface, ce qui explique la présence de substances chimiques anthropiques dans des lieux éloignés et dans des eaux non touchées par une source ponctuelle. L'APFO traverse le sol très lentement avant d'atteindre l'eau souterraine.

Des sels d'APFO sont utilisés comme adjuvants dans la production de fluoropolymères, lesquels sont utilisés dans des produits d'assemblage et de scellage qui peuvent donc contenir des traces d'AFPO. Certains de ces produits pourraient être utilisés dans les réseaux de distribution. L'utilisation de composantes de réseau de distribution qui sont certifiées conformes à la norme NSF/ANSI 61 réduirait le relargage d'APFO dans l'eau potable.

Compte tenu des effets possibles de l'APFO et du SPFO sur la santé, et de l'information limitée concernant les risques et les incertitudes liés aux autres SPFA, une évaluation en profondeur pourrait s'avérer nécessaire en cas de déversement. Si d'autres SPFA sont décelées, les secteurs de compétence peuvent choisir de communiquer avec Santé Canada pour obtenir plus d'information sur les risques possibles à la santé posés par ces substances.

Dans le cas d'approvisionnements en eau potable où on enregistre des dépassements transitoires de la CMA, on conseille d'élaborer et de mettre en œuvre un plan pour remédier à ces situations. Dans le cas de dépassements prolongés qui ne peuvent être résolus par le biais de traitements, on devrait envisager d'utiliser une autre source d'eau potable.

3.1 Surveillance

Il est important de noter que l'analyse de l'APFO est extrêmement spécialisée et devrait être faite par un laboratoire qui est accrédité ou qui a en place un processus rigoureux d'assurance et de contrôle de la qualité (AQ/CQ) pour donner des résultats justes.

3.1.1 Caractérisation de la source

Les services publics devraient caractériser leur source d'eau pour évaluer les concentrations d'APFO et de SPFO, particulièrement si les eaux de la source sont affectées par des endroits où aurait lieu de la formation pour la lutte contre l'incendie, des bases militaires, des aéroports, des manufactures ou des sites d'enfouissement. Si une contamination est décelée, des échantillons devraient être prélevés sur une base semestrielle afin de confirmer que la somme des rapports des concentrations décelées d'APFO et de SPFO aux CMA correspondantes ne dépasse pas 1. Si un traitement est requis, il faudrait prélever des échantillons d'eau de la source en même temps que les échantillons de conformité. Les services publics qui ont des données historiques démontrant l'absence d'APFO et de SPFO pourraient diminuer la fréquence d'échantillonnage.

Si l'on soupçonne que la contamination provient d'une mousse AFFF, le service public pourrait envisager de surveiller la présence d'autres SPFA, y compris les composés à chaîne plus courte tels que l'acide perfluorobutanoïque et le perfluorobutanesulfonate. Il est probable que ces autres SPFA soient aussi présents sur des sites affectés par des mousses AFFF et sont généralement plus mobiles. Par conséquent, ils peuvent servir de signe avant-coureur d'une contamination de la source d'eau souterraine par l'APFO et le SPFO.

3.1.2 Surveillance opérationnelle

Les systèmes de traitement devraient être conçus, exploités et entretenus spécifiquement pour l'enlèvement de l'APFO et du SPFO. La fréquence de surveillance opérationnelle dépendra

de la technique de traitement utilisée par le service public. La présence de matière organique naturelle (MON) dans la source d'eau pourrait dégrader le rendement du CAG. Les services publics qui utilisent un système au CAG pour l'enlèvement de l'APFO et du SPFO devront peut-être effectuer une surveillance trimestrielle de l'eau traitée afin de vérifier le rendement du système au CAG et d'identifier le meilleur moment pour sa régénération ou son remplacement. Les services publics devraient aussi savoir que l'utilisation d'ozone ou de processus d'oxydation avancé pourrait oxyder les précurseurs polyfluorés présents dans la source d'eau, ce qui entrainerait une augmentation de la concentration d'APFO dans l'eau traitée.

3.1.3 Surveillance de conformité

Lorsqu'un traitement est utilisé pour l'enlèvement de l'APFO et du SPFO, une surveillance semestrielle de l'eau traitée est recommandée. Les échantillons devraient être prélevés après le traitement mais avant la distribution, typiquement au point d'entrée du réseau de distribution. Il faudrait prélever des échantillons d'eau de la source et d'eau traitée en même temps afin de confirmer l'efficacité du traitement. La somme des rapports des concentrations décelées d'APFO et de SPFO aux CMA correspondantes ne devrait pas être au dessus de 1.

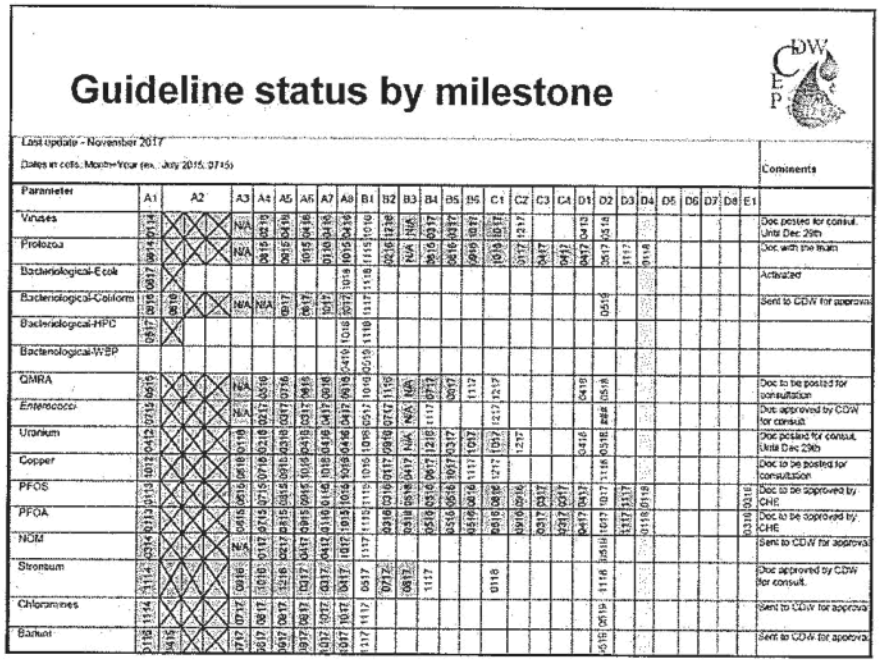
Item 2-C
CDW Status

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Guideline status by milestone



Last update - November 2017

Dates in cells: Month=Year (ex.: July 2015, 0715)

Parameter	A1	A2			A3	A4	A5	A6	A7	A8	B1	B2	B3	B4	B5	B6	C1	C2	C3	C4	D1	D2	D3	D4	D5	D6	D7	D8	E1	Comments
Viruses	0114	X	X	X	N/A	0216	0416	0416	0416	0416	1016	1216	N/A	0317	0317	1017	1017	1217			0413	0518								Doc posted for consul. Until Dec 29th
Protozoa	0914	X	X	X	N/A	0815	0915	1015	0116	1015	1115	0216	N/A	0816	0816	0916	1016	0117	0417	0417	0417	0517	1117	0118						Doc with the team
Bacteriological-Ecoli	0817	X								1018	1118																			Activated
Bacteriological-Coliform	0816	0816	X	X	N/A	N/A	0917	0817	1017	1017	1117											0519								Sent to CDW for approva
Bacteriological-HPC	0817	X								1018	1118																			
Bacteriological-WEP										0419	0519																			
QMRA	0616	X	X	X	N/A	0516	0716	0616	0616	0616	1016	1116	N/A	0717	0617	1117	1217				0418	0518								Doc to be posted for consultation
Enterococci	0715	X	X	X	N/A	0217	0317	0317	0417	0417	0517	0717	N/A	1117			1217					###								Doc approved by CDW for consult.
Uranium	0412	X	X	X	0118	0216	0316	0416	0416	0416	1016	0916	N/A	1216	0317	1017	1017	1217			0418	0518								Doc posted for consul. Until Dec 29th
Copper	1012	X	X	X	0616	0716	0916	1016	1016	1016	1016	0117	0417	0517	1017	1117	1217					1118								Doc to be posted for consultation
PFOS	0113	X	X	X	0616	0715	0815	0915	0116	1016	1115	0316	0516	0516	0516	0616	0616	0916	0317	0317	0417	1017	1117	0118					0316	Doc to be approved by CHE
PFOA	0113	X	X	X	0616	0715	0815	0915	0116	1015	1115	0316	0516	0516	0516	0516	0616	0916	0317	0317	0417	1017	1117	0118					0316	Doc to be approved by CHE
NOM	0314	X	X	X	N/A	0117	0217	0417	0412	1017	1117											0518								Sent to CDW for approva
Strontium	1114	X	X	X	0916	1016	1216	0317	0317	0417	0517	0717	0817	1117			0118					1118								Doc approved by CDW for consult.
Chloramines	1114	X	X	X	0717	0817	0817	0817	1017	1017	1117											0519								Sent to CDW for approva
Barium	0116	0416	X	X	0717	0817	0817	0817	1017	1017	1117											0519								Sent to CDW for approva

Guideline status by milestone (cont'd)

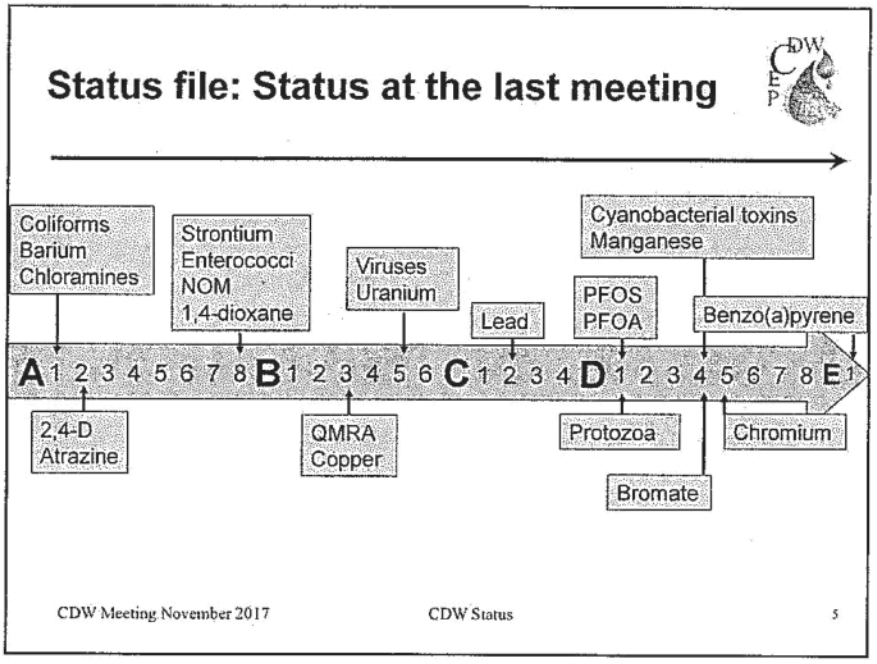
Last update - October 30th 2017

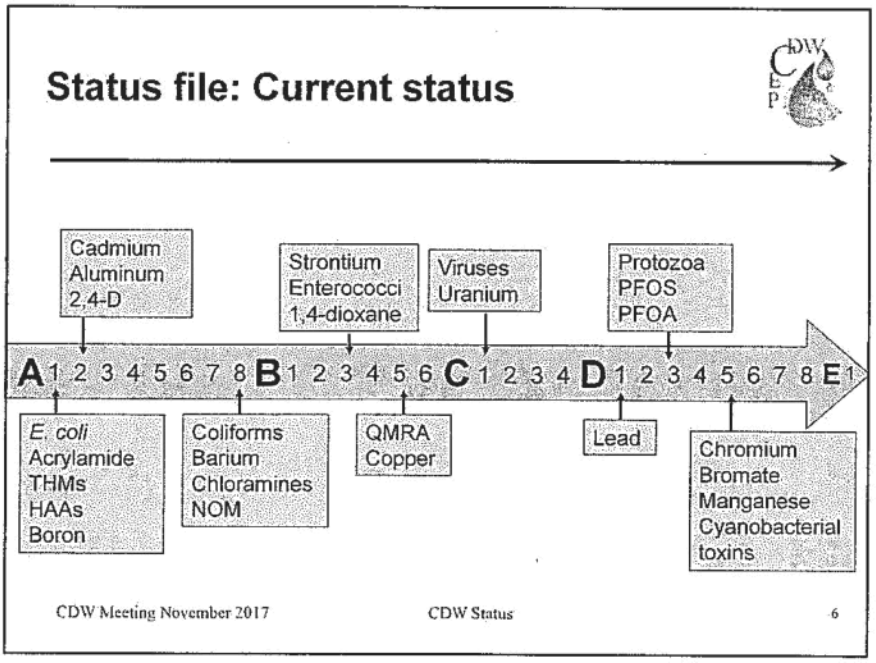
Dates in cells, Month-Year (ex.: July 2015: 0715)

Parameter	A1	A2	A3	A4	A5	A6	A7	A8	B1	B2	B3	B4	B5	B6	C1	C2	C3	C4	D1	D2	D3	D4	D5	D6	D7	D8	E1	Comments
Cadmium	0817		0714	0914	0914	0914	0914	0418	0518																			Draft doc for May 2018 meeting
Dioxane, 1,4-	1214		0616	0616	1218	0417	0417	0417	0617	0617					1117					1118								Doc approved by CDW for consult.
Chromium	0709		1214	0616	1218	0417	0417	0417	1014	0518	NA	0216	1117	0518	1117	0915	1218	1215	1215	1116	0419	0916	1118	1217			0119	Doc CHE approved, to be finalized for posting
Dichlorophenoxyacetic acid; 2,4- (2,4 D)	0209							0418	0518																			
Lead	0418		0714	0914	0115	0416	0315	0418	0515	0615		0116		0118	0117	0317	0917	0917	0917	1117								Revised document and table of comments with CDW
Bromate	0419		0714	0614	1014	0416	1014	1014	1014	1214	NA	0316	0815	0715	1115	1018	0416	0416	0416	0516	0916	1016	0917				0518	Doc CHE approved, to be finalized for posting
Aluminum	0617								1014																			Activated
Manganese	0418		0615	0715	0815	0815	0915	1015	1115	1215	0316	0316	0316	0418	0818	0818	1018	1016	1016	1116	0317	0317	1017				0218	Doc CHE approved, to be finalized for posting
Boron	0616																											On hold
Cyanobacterial toxins	0112		0714	1214	0115	0315	0415	0418	0515	0615	1215	1215	1215	0118	0216	0416	0616	0916	0818	1018	0117	0217	0717				0618	CHE approved Feb 24th
Acrylamide									1119																			
THMs									1119																			
HAAs									1119																			
Glyphosate									1119																			

Status of Approvals

Name of parameter	Q1 April - June	Q2 July - September	Q3 October - December	Q4 January - March	Q1 April - June	Q2 July - September	Q3 October - December	Q4 January - March	Q1 April - June	Q2 July - September	Q3 October - December	Q4 January - March	Q1 April - June	Q2 July - September
				2018				2019				2020		
Chromium				January-F										
Bromate					June-F									
Cyanobacterial toxins					June-F									
Manganese				February-F										
Cadmium	CDW - F		CHE											
PFOS		CDW - F	CHE	March-F										
PFOA		CDW - F	CHE	March-F										
Lead			CDW - F	CHE										
Uranium		October-C			CDW - F	CHE								
Nitrates		October-C			CDW - F	CHE								
NMRA		October-C			CDW - F	CHE								
Copper			October-C				CDW - F	CHE						
Strontium	CDW - C		November-C				CDW - F	CHE						
Dioxane 1,4-	CDW - C		November-C				CDW - F	CHE						
Fluoroquinolones	CDW - C		December-C				CDW - F	CHE						
HAN			CDW - C						CDW - F	CHE				
Total Coliforms			CDW - C						CDW - F	CHE				
Barium			CDW - C						CDW - F	CHE				
Chloramines			CDW - C						CDW - F	CHE				
Cadmium					CDW - C						CDW - F	CHE		
1,4-D					CDW - C						CDW - F	CHE		
Lead							CDW - C						CDW - F	CHE
Aluminum							CDW - C						CDW - F	CHE
Bacteriological - HPC			CDW - F*				CDW - C						CDW - F	CHE
Waterborne pathogens									CDW - C					
Acrylamide											CDW - C			
THMs											CDW - C			
HAAs											CDW - C			
Glyphosate											CDW - C			
Antimony													CDW - C	
Arsenic													CDW - C	
Turbidity													CDW - C	
Taste and Odour														
CE														
Boil Water Advisories														
Operational														
Formaldehyde														
Zinc														
Perchlorate														
Iron														


Status file: Status at the last meeting
Coliforms
Barium
Chloramines
Strontium
Enterococci
NOM
1,4-dioxane
Viruses
Uranium
Lead
Cyanobacterial toxins
Manganese
PFOS
PFOA
Benzo(a)pyrene
A 1 2 3 4 5 6 7 8 B 1 2 3 4 5 6 C 1 2 3 4 D 1 2 3 4 5 6 7 8 E 1
2,4-D
Atrazine
QMRA
Copper
Protozoa
Bromate
Chromium
CDW Meeting November 2017
CDW Status
5


Status file: Current status
Cadmium
Aluminum
2,4-D
Strontium
Enterococci
1,4-dioxane
Viruses
Uranium
Protozoa
PFOS
PFOA
A 1 2 3 4 5 6 7 8 B 1 2 3 4 5 6 C 1 2 3 4 D 1 2 3 4 5 6 7 8 E 1
E. coli
Acrylamide
THMs
HAAs
Boron
Coliforms
Barium
Chloramines
NOM
QMRA
Copper
Lead
Chromium
Bromate
Manganese
Cyanobacterial
toxins
CDW Meeting November 2017
CDW Status
6

Priority list



1) Arsenic (May 2020)
2) Trihalomethanes (THMs) (Nov 2019)
3) Strontium (May 2017)
4) Chloramines (Nov 2017)
5) Dioxane, 1,4- (May 2017)
6) Haloacetic acids (HAAs) (Nov 2019)
7) Barium (Nov 2017)
8) Cadmium (May 2018)
9) Boron (on hold)
10) Aluminum (Nov 2018)
11) Acrylamide (Nov 2019)
12) Pentachlorophenol (PF Nov 2018)
13) Trichloroethylene (Nov 2020)
14) Zinc (May 2021)
15) Iron (Nov 2021)
16) Formaldehyde (May 2021)
17) Hydrocarbons, F2, F3, F4
18) Odour (Taste and odour) (Nov 2020)
19) Perchlorate (Nov 2021)
20) Asbestos (PF)

In red: Expected first draft to CDW
PF: Problem formulation

Item 3-A
Total coliform

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- Draft document summarizing literature review completed
- Review document has been peer-reviewed and peer-review comments have been incorporated into the document
- Review document and proposed updates to the 2012 guideline technical document have been provided to CDW prior to meeting
- Seeking CDW approval for public consultation

Review document

- Developed in same format as 2012 document
- Part I
  - Intended to be used as appendix to 2012 document (as final deliverable), executive summary and notice for Canada Gazette
  - Provides high level findings and future considerations
- Part II
  - Provides review of scientific literature
  - Highlights considerations likely to be addressed in future reviews of micro documents (not limited to total coliforms)

Part II highlights (1)

- Significance of total coliforms in drinking water
  - Impact of aquifer type, rainfall and well integrity on TC presence in groundwater sources
  - Factors affecting bacterial regrowth in the distribution system
  - Burden of illness attributable to groundwater sources and distribution system
  - Relationship between TCs and enteric pathogens, including opportunistic premise plumbing pathogens (OPPPs)

Part II highlights (2)

- Analytical methods
  - Comparison of culture-based methods, including false positive/negative rates
- Sampling
  - Impact of storage temperature and sample volume on recovery of TCs
  - Sampling considerations in the distribution system

Part II highlights (3)

- Treatment technology
  - Considerations for well owners
  - Distribution system (real-time) monitoring
- Risk assessment
  - U.S. EPA's revised the Total Coliform Rule (TCR)

Peer reviewers

- Kenneth Rotert
  - Physical Scientist, U.S. EPA
- Lesley D'Anglada
  - Senior Microbiologist, U.S. EPA
- Andrée Maheux
  - Researcher, Université Laval

Peer review comments

- Outlined additional situations in which TCs might be present in distribution system
- Asked for clarification related to disease burden discussion
- Requested additional information on distribution system sampling
- Provided list of additional references to consider
- Identified additional areas for future consideration

Response to peer review

- Overall, minor revisions:
  - Provided definitions (e.g., dolomite, small community water system)
  - Expanded burden of illness discussion
  - Added some text related to sampling frequencies in distribution system
  - Included suggested references

Discussion / next steps

- Seeking input regarding next steps and CDW approval for public consultation
- The final document will only include part I as an appendix. Should the consultation be conducted on:
  - the full document (parts I and II), or
  - only the high level findings (part I)

Item 3-B
Bacteriological - HPC

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- Current HPC guidance published in May 2013
- Scheduled for an update in the rolling revision of microbiological parameters
- Objective of current HPC guidance: to describe an operational tool to monitor "general bacteriological quality" in drinking water systems

Problem formulation

- There is new research available on monitoring and maintaining microbial quality in drinking water
- Should the scope of the current guidance be expanded to include additional tools for assessing and managing general microbial water quality in water distribution systems?

Methods

- **Data sources:** 3 bibliographic databases; non-government and government material
- Studies from 2007- 2017, 16 key word combinations repeated in 3 databases
- Focus on abstract review

Results

- 408 abstracts reviewed; 301 screened in
- A significant body of work is available on analytical methods: flow cytometry and ATP methods stand out
- Other key information: molecular tools, determining water quality in buildings, operational factors

CDW discussion

- Other issues beyond monitoring tools:
  - factors that contribute to microbial growth
  - approaches to maintaining microbial water quality
  - molecular / genomic survey information
- Potential overlap with other guidelines/ guidance (NOM, total coliforms, chloramines)

Next steps



- Recommendation:
  - revise the guidance and broaden it to include microbiological assessment tools in addition to HPC
  - limit the scope of the document to the practical assessment tools
- Next steps:
  - clearly define content (what specific tools and approaches will be included)
  - prepare a draft for peer review

Item 4-A
Chloramines

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- Guideline technical document has been peer-reviewed
- Peer-review comments have been incorporated into the document
- The document was provided to CDW prior to meeting
- Seeking CDW approval for public consultation

Refresher

- The current Canadian guideline for chloramines in drinking water is 3.0 mg/L (1995), based on:
  - HBV (1.8 mg/L) calculated from NOAEL (4.8 mg/kg bw per day) for monochloramine based on reduction of bw gain in rats – 2 yr study (NTP, 1992)
  - Practicability for small municipalities
  - Natural ammonia levels are higher during cold weather, and may lead to higher levels of chloramines – may present control problem if level is lower than 3 mg/L

CDW Meeting November 2017 Chloramines 3

Exposure

- Drinking water is the main source of exposure
- Multi-route exposure assessment
  - Exposure to chloramines via inhalation and dermal routes during showering or bathing is expected to be negligible (calculated)
  - Mono- and dichloramine are water soluble but not volatile (physico-chemical characteristics) so are unlikely to contribute to exposure via dermal or inhalation route
  - Trichloramine is very volatile but not soluble in water; it is relatively unstable in water, and formed at conditions unlikely to occur in treated drinking water (very high chlorine to ammonia ratios or low pH)

CDW Meeting November 2017 Chloramines 4

Levels in water

- Levels in drinking water across Canada are not well-characterized, information is limited
- Reported as chloramines, combined chlorine, total chlorine, or monochloramine
- Some P/Ts provided dichloramine, trichloramine data as well
- Generally combined chlorine below 3 mg/L
- Only two values exceeded 3 mg/L

Health effects

- Focused on monochloramine, as very limited data are available for di- and trichloramine
- Subchronic and chronic studies in animals show decreased body weight and/or bodyweight gain, decreased organ weights and alterations of blood parameters
  - 1997 paired water study shows that these effects are likely caused by decreased water consumption (taste aversion at higher doses) and not toxicity
  - Chronic: 2 year study in rats and mice (NTP, 1992) found marginal increase in mononuclear cell leukemia in Female rats: not relevant
- Mutagenicity
  - *in vitro*: some mutagenic potential
  - *In vivo*: no significant evidence
- Epidemiology: did not show any adverse health effects / limitations

Peer reviewers – health

- Kannan Krishnan, PhD, DABT, FATS
  - Senior Vice President, Chemical Risk Assessment, Risk Sciences International
- Lynne Haber, PhD, DABT
  - Senior Toxicologist/Adjunct Associate Professor, Department of Environmental Health, University of Cincinnati, College of Medicine

Peer review comments – health

- Agreed that:
  - a critical toxic endpoint cannot be established for monochloramine because of taste aversion
  - a guideline value of 3 mg/L based on aesthetic considerations or treatment would be protective for all forms of chloramines
- Suggested to:
  - include more information on methemoglobinemia even though not relevant route of exposure
  - include more studies on trichloramine: irritation and lung effects based on swimming pool exposure because of volatility
  - elaborate on some of the studies, endpoints and explanations

Peer reviewers – analytical and treatment

- Andrzej Wilczak, PhD, PE
  - recently retired, San Francisco (EBMUD)
- Two reviewers from the U.S. EPA National Risk Management Research Laboratory
  - David Wahman, PhD, PE
    - Expertise in biological drinking water treatment, distribution system nitrification and chloramine chemistry
  - Jonathan Pressman, PhD, PE
    - Expertise in disinfection and nitrification in drinking water distribution systems including minimum residuals
- Chad Seidel, PhD, PE
  - Corona Consulting, University of Colorado

Peer review comments – Application

- Comments generally positive
- Consensus on the suggested operational range:
  - Doses higher than 2 mg/L likely required to maintain appropriate residual of 1.5 mg/L throughout the distribution system
  - Residual goals should be specific to the system
- Most reviewers did not agree with establishing an upper limit based on aesthetic considerations
  - Operationally setting a target that protects public health and minimizes nitrification is the goal.

Peer review comments Monitoring and analytical

- Greater mention of nitrification monitoring plans needed
- Guidance on sampling should be more detailed
- Dedicated sampling taps, consumer taps should be identified as preferred sampling locations (as opposed to hydrants)
- The indophenol analytical method for monochloramine should be more prominent

Peer review comments: Treatment

- Information to add:
  - Use of free chlorine burn for short-term nitrification control
  - Temperature (cold water) effects for Canadian context
- Reviewers supported:
  - Recommendation that utilities conduct site-specific studies before switching to chloramines
  - Guidance on ammonia in source water

International considerations

- All are based on NTP (1992)
- U.S. EPA (1998):
  - Maximum residual disinfectant level – 4.0 mg/L
  - Maximum residual disinfectant level goal – 4.0 mg/L
- WHO (1993; 2003): Guideline – 3.0 mg/L
- Australia (2014): Guideline – 3.0 mg/L

Proposed guideline

- *It is not considered necessary to establish a guideline for chloramines in drinking water, based on the low toxicity of monochloramine at concentrations found in drinking water. Any measures taken to limit the concentration of chloramines or their by-products in drinking water supplies must not compromise the effectiveness of disinfection.*

CDW discussion / next steps



- Does CDW agree with the choice to not establish a health-based MAC
- Seeking CDW approval for a 2-month public consultation period

Item 4-B
Natural Organic Matter

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- Peer-reviewed draft guideline technical document was provided to CDW in May 2017
- CDW members voted for a guidance document and provided comments
- The revised document was shared with CDW prior to meeting
- Seeking CDW approval for public consultation

Refresher and update

- May 2016 CDW discussion
  - Agreement to develop as a guideline technical document then seek CDW decision on final format
- May 2017 CDW discussion
  - CDW asked to indicate format preference (guideline or guidance) and provide comments by September 1
- Vote results
  - Guidance – 9
  - Guideline – 1
  - No preference – 3

CDW comments

- Provide values for measurable parameters
- Strongly suggest UV transmittance monitoring
- Treatability studies should assess seasonal changes in NOM
- NOM concentrations in treated water should be ALARA
- Alternative disinfectants should be recommended with caution
  - First choice should be to improve NOM removal

International considerations

- U.S. EPA – treatment technique
  - Mandated percent TOC removal based on raw water quality
- WHO – operational parameter
  - Optimized NOM removal suggested to minimize biofilm
- EU – indicator parameter for supplies >10,000 m^3/d
  - TOC no abnormal change or oxidisability 5 mg/L O_2
  - France – treated water quality reference guideline of 2 mg/L TOC
  - Netherlands – AOC target of 10 µg/L
- Australia – guidance on understanding and controlling impact of NOM

Discussion / next steps

- Seeking CDW approval for 2 month public consultation period

Item 4-C
HAAs – Screening values for BCA and BDCA

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- Last assessment on haloacetic acids (HAAs) was finalized in 2008
  - Based on achievability
- Problem formulation for HAAs was initiated
  - Revisit science on all parameters
  - New science on bromochloroacetic acid (BCA) and bromodichloroacetic acid (BDCA) which are not part of the current guideline (HAA5)
- CDW decision
  - Develop screening values for these compounds

Background

- HAAs are formed during disinfection of drinking water.
  - Reaction between natural organic matter and chemical disinfectants produces a mixture of chlorinated and brominated HAAs
- 5 HAAs are included in the current guideline
  - Monochloroacetic acid (MCA), dichloroacetic acid (DCA), trichloroacetic acid (TCA), monobromoacetic acid (MBA), and dibromoacetic acid (DBA)
- Other brominated and chlorinated HAAs were not considered
  - Bromochloroacetic acid (BCA), bromodichloroacetic acid (BDCA), dibromochloroacetic acid (DBCA), and tribromoacetic acid (TBA)

CDW Meeting November 2017 HAAs - Screening values for BCA & BDCA 3

Exposure

- Primarily via ingestion of chlorinated / chloraminated drinking water
- Canadian exposure data is limited to results of the National Disinfection By-Product Survey
  - Occurrence of BCA and BDCA in drinking water is comparable to that of HAA5

	MCA	DCA	TCA	MBA	DBA	BCA	BDCA
Frequency detected (%)	32	69	66	<1	15	34	34
Median (µg/L)	2.4	12	9.4	1.4	1.5	2.2	1.9

- Multi-route exposure assessment - Contribution from inhalation and dermal exposure from drinking water is not significant

CDW Meeting November 2017 HAAs - Screening values for BCA & BDCA 4

Bromochloroacetic acid (BCA)

BCA
Health effects

- Rats and mice
  - Evidence of cancer at multiple sites, including liver, large intestine, and epithelium
  - Reproductive and developmental effects significant, including decreased sperm quality and decreased reproductive parameters
  - DNA damage: weak database, mixed results
- Human data don't exist; data on HAA5 are limited in relevance

BCA
Risk assessment - cancer

- Benchmark dose modeling was done for all cancer endpoints
- The lowest $BMDL_{10}$ was 7.07 mg/kg bw per day for hepatoblastomas in male mice (NTP, 2009) and was used as the point of departure
- An HBV of 4.75 µg/L was derived for cancer effects
  - Point of departure was adjusted for human exposure scenarios by allometric scaling
  - Corresponds to a drinking water concentration associated with 10^{-5} lifetime increased risk of developing cancer

BCA
Risk assessment – non-cancer

- Evidence of reproductive effects
- HBV could not be calculated due to high degree of uncertainty

Bromodichloroacetic acid (BDCA)

BDCA
Health effects

- Rats and mice
  - Evidence of cancer at multiple sites, including mammary gland, skin, epithelium and liver
  - Evidence of non-cancer effects at multiple sites, including kidney, liver, bone marrow, spleen, and testes
  - DNA damage: weak database, mixed results
- Human data don't exist; data on HAA5 are limited in relevance

BDCA
Risk assessment - cancer

- Benchmark dose modeling was done for all cancer endpoints
- The lowest $BMDL_{10}$ was 3.32 mg/kg bw per day for mesotheliomas in all organs in male rats (NTP, 2015) and was used as the point of departure
- An HBV of 4.12 µg/L was derived for cancer effects
  - Point of departure was adjusted for human exposure scenarios by allometric scaling
  - Corresponds to a drinking water concentration associated with 10^{-5} lifetime increased risk of developing cancer

BDCA
Risk assessment – non-cancer

- Benchmark dose modeling was done for all non-cancer effects following 2 year exposure to BDCA in drinking water
- The lowest $BMDL_{10}$ was 4.03 mg/kg bw per day for bone marrow hyperplasia in female rats (NTP, 2015) and was used as the point of departure
- An HBV of 150 µg/L was derived for non-cancer effects
  - Composite uncertainty factor = 1000
  - Allocation factor = 0.8
  - Body weight and drinking water intake = 70 kg and 1.5 L/day

Drinking water screening values

- BCA: 0.005 mg/L (5 µg/L), based on cancer effects, but protective of both cancer and non-cancer effects
- BDCA: 0.004 mg/L (4 µg/L), based on cancer effects, but protective of both cancer and non-cancer effects

International considerations

- The current Canadian risk-managed guideline is 0.08 mg/L (80 µg/L) for the sum of the concentrations of HAA5 (MCA, DCA, TCA, MBA, DBA), with DCA as the driver (HBV of 0.01 mg/L)
- No international jurisdiction has developed a drinking water standard or guideline for either BCA or BDCA
  - The U.S. EPA has an MCL of 60 µg/L for the sum of the HAA5; BCA and BDCA are monitored as part of HAA9
  - The International Agency for Research on Cancer (IARC) has classified BCA as possibly carcinogenic to humans (Group 2B) (2013)

Options

Option 1

Keep current MAC for HAA5 = 80 µg/L (risk managed)

	HBV (µg/L)
MCA	100
DCA	10
TCA	300
MBA	-
DBA	2
BCA	5
BDCA	4
DBCA	-
TBA	-

Option 2

HAA5 + BCA = 80 µg/L

Option 3

HAA5 + HAA4 = 80 µg/L

CDW Meeting November 2017 HAAs - Screening values for BCA & BDCA 15

CDW discussion Path forward

- Option 1 – Status Quo
  - Document the scientific review and reaffirm the existing guideline
- Option 2 – Include BCA as part of the MAC
  - BCA often routinely measured with HAA5, but would result in a more stringent MAC
  - Need to update the whole document to incorporate new science
- Option 3 – Include BCA and BDCA as part of the MAC
  - Would result in additional analytical costs and a more stringent MAC
  - Need to update the whole document to incorporate new science

CDW Meeting November 2017 HAAs - Screening values for BCA & BDCA 16

Item 4-D
PFNA- Screening value

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- Perfluorononanoic acid (PFNA) is a perfluoroalkylated acid with nine carbon chain length
- CDW members expressed interest in new science about PFNA
- Drinking water screening value calculated – waiting for peer review comments

Background

- Member of class of perfluoroalkylated substances (PFAS) - man-made chemicals used in a variety of industrial and commercial applications
- Regulations prohibit the use, manufacture, sale, and import of products containing PFNA and its salts (with certain exemptions – e.g., aqueous film-forming foams)

Sources

- PFNA is not manufactured in Canada
- Largest point source of PFNA (and other PFAS) release in Canada is through the use of products with the potential to degrade into PFAS (e.g., aqueous film-forming foams)

Exposure

- Primarily via food and consumer products
  - For individuals in areas with contaminated drinking water, the proportion of exposure from drinking water increases
- Limited data exist on food and water sources; levels appear to be lower than levels of PFOA
- Biomonitoring findings
  - Blood, breast milk, amniotic fluid, placenta, and cord blood
- Multi-route exposure assessment
  - exposure to PFNA via inhalation and dermal routes during showering or bathing is expected to be negligible

Health considerations

Health effects	LOAELs
Liver toxicity – hypertrophy	≥0.025 mg/kg bw per day S-111-S-WB* in adult rats and offspring
Liver toxicity – necrosis	≥0.025 mg/kg bw per day S-111-S-WB* in adult rats
Reduced survival of offspring	≥1.1 mg/kg bw per day PFNA in mice
Reduced body weight of offspring	≥3 mg/kg bw per day PFNA in mice
Delayed eye opening in offspring	≥2 mg/kg bw per day PFNA in mice

*S-111-S-WB is a mixture of PFAS; PFNA makes up 74% of the content

- Mode of action
  - Not well-characterized; no endpoint could be eliminated based on relevance to humans

Health considerations

- Toxicokinetics
  - Similar to PFOA: absorption, distribution, metabolism, elimination
  - Human ½ life is estimated to be up to 2.7-fold longer than PFOA's ½ life [but key issues exist in these calculations]
- Approach to account for human-to-rodent differences
  - Default approach is not sufficiently protective
  - No PBPK or PK models have been described for PFNA
  - Chemical-specific adjustment factor (CSAF) approach
    - Incorporates species- and chemical-specific toxicokinetic data
    - Toxicokinetic values for humans not available; so propose to use PFNA:PFOA ratios. For example:

$$\text{Serum half-life}_{(PFNA)} = \frac{\text{Half-life}_{(PFNA)}}{\text{Half-life}_{(PFOA)}} \times \text{Serum half-life}_{(PFOA)}$$

Drinking water screening value

- Non-cancer risk assessment performed
  - Human equivalent POD calculated using CSAF approach
  - Uncertainty factor of 250 (2.5 x for interspecies variability, 10 x for intraspecies variability, and 3 x for database deficiency)
  - Allocation factor: 0.2
  - Body weight: 70 kg
  - Drinking water intake: 1.5 L/day
- Pending comments from peer reviewers, PFNA DWSV will be in the low ng/L range
  - Compared to PFOA at 200 ng/L

International considerations

- No international agency has established health-based values for PFNA in drinking water
- The State of New Jersey has established an MCL of 13 ng/L based on:
  - increased liver weight in pregnant mice exposed to PFNA
  - Uncertainty factor of 1000 (10 x for intraspecies variability, 3 x for interspecies variability, 10 x for duration of exposure, 3 x for incomplete database)
  - Relative source contribution = 50%
  - Interspecies differences accounted for by extrapolating from target blood serum concentration of PFOA x 2

Next steps

- Incorporate peer reviewer comments
- If approach is validated by peer-review, establish drinking water screening value

Item 4-F
Cadmium

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- For information only
- Scoping assessment completed
- Draft document expected for CDW review and approval for public consultation at spring 2018 meeting

Background

- Current MAC of 0.005 mg/L (5 µg/L) established in 1986, based on kidney toxicity
- Occurs in a number of salts, some of which are water-soluble (**chloride**, fluoride, iodide, nitrate, sulfate salts), but also as the free Cd^{+2} ion
- Sources include foods, cigarette smoke, smelting, burning of fossil fuels, galvanized pipes and some natural occurrence from soils
- Used in anticorrosion coatings, solders, welding, electrode material, batteries, in pigmentation and as a PVC stabilizer

CDW Meeting November 2017 Cadmium 3

Exposure

- Human exposure to cadmium is primarily from food (up to 90%), and tobacco in smokers
- Drinking water is a minor source of exposure
- CHMS data – highest levels of cadmium measured in blood and urine of Canadians aged 40–59
- Known to accumulate in the liver and kidney of animals, long half life

CDW Meeting November 2017 Cadmium 4

Levels in Canadian Water

- Environment Canada monitoring data indicates low levels of cadmium in freshwater sampled across Canada from 2000-2016:
  - Average concentration of 0.07 µg/L, median of 0.01 µg/L
  - A max value of 95 µg/L was reported in the Arctic Coast
- CDW exposure data received to date show very low levels of cadmium (< 1 µg/L) in source and treated water
- Levels of Cd at the tap may be more elevated due to leaching from drinking water materials

Health considerations

- **Kidney** is critical organ for toxicity in humans and animals
  - Renal dysfunction (impaired reabsorption and tubular injury) shown by the presence of low molecular weight proteins in urine
- Effects on bone and calcium metabolism
  - Inconsistent results from epidemiological studies
  - May be secondary to kidney effects
  - Considered premature to consider bone effects as the critical effect at present time
- Carcinogenicity
  - IARC classification of Group 1, carcinogenic to humans based on inhalation studies of exposed workers
  - Limited data on carcinogenicity via the oral route

Human health risk assessment

- Will closely follow a detailed risk assessment conducted by Heath Canada for cadmium in foods (2018)
- Joint FAO/WHO Expert Committee on Food Additives (JECFA) established tolerable monthly intake of 25 µg/kg (based on daily intake of 0.8 µg/kg)
  - Meta analysis of 35 epidemiological studies
  - Based on a cadmium concentration in the kidney at which histopathological changes are first observed
  - Metabolic model used to estimate exposure level that could result in this concentration

Potential HBV

- Based on effects in the kidney identified by Health Canada and JECFA
- **Could range from 3 µg/L to 8 µg/L**, pending a thorough review of available literature, including:
  - Health Canada's recent assessment for cadmium in foods
  - JECFA report
  - EFSA report
  - Analysis of uncertainty

Analytical methods

- Approved methods
  - U.S. EPA; Standard methods
    - ICP-MS, GFAAS and ICP-AES
    - MDLs ranged from 0.05 µg/L to 1.0 µg/L
- Current U.S. EPA (1991) PQL of 2 µg/L
- P/T data ranges from 0.01 to 1 µg/L

Treatment technologies-municipal scale

- Limited information — no full scale data available
  - Pilot scale
    - Conventional coagulation – variable results
    - Lime softening – below 2 µg/L
  - Ion exchange
    - SAC resins may be effective
    - Chelating resin show high selectivity for cadmium

Distribution system considerations

- Galvanized pipes, cement-based material, potential leaching from brass fitting are potential sources of cadmium in drinking water
- Cadmium may accumulate in distribution system scales
- NSF/ANSI Standard 60 established single product allowable concentration (SPAC) of 0.0005 mg/L (0.5 µg/L)

Treatment technologies-residential scale

- Certified residential treatment devices are available for reduction to 5 µg/L or less
- Applicable standards are:
  - NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems
  - NSF/ANSI Standard 62: Drinking Water Distillation Systems

International considerations

Agency	Publication Date	Value (µg/L)	Basis
Health Canada	1986	5	Provisional tolerable weekly intake established by the WHO/FAO – renal effects
U.S. EPA	1987/1991? IRIS?	5	Kidney damage
Australia	1996 Endorsed	2	Cadmium in the body will be kept below the critical amount of 200 mg/kg renal cortex tissue (JEFCA 2000)
WHO	2011 updated	3	Levels of cadmium in the renal cortex (JEFCA 2000)
California EPA PHG	2006	0.04	Kidney toxicity
Minnesota Department of Health	2015	0.5	Low molecular weight proteinuria, Risk for osteoporosis

Next steps

- Complete the risk assessment
- Internal and external peer review
- CDW approval to be sought in spring 2018 for a 2-month public consultation

Item 4-G
Barium

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- Guideline technical document has been peer-reviewed and peer-review comments have been incorporated into the document
- Guideline technical document has been provided to CDW prior to meeting
- Seeking CDW approval for public consultation

Refresher

- The current guideline (1990) for barium in drinking water in Canada is 1.0 mg/L (1000 µg/L):
  - based on an absence of adverse effects on blood pressure and no observed increase in the prevalence of cardiovascular disease in a population ingesting water containing a mean level of 7.3 mg/L barium and
  - 7.3 mg/L / 10 (intraspecies variation) = 0.7 mg/L; however a MAC of 1.0 mg/L was retained from the previous 1978 guideline

Exposure

- Main sources of exposure are food and drinking water:
  - food is the principal source; levels highly variable: estimated intake of 5.1–10.1 µg/kg bw per day for adults; and
  - drinking water represents a lesser but significant source; an estimated intake of 2 µg/kg bw per day for adults based on averaging of mean levels in treated drinking water
- Exposure from other media (air, consumer products, soil) is expected to be negligible
- Multi-route exposure: negligible contribution from dermal and inhalation exposure routes during showering and bathing.

Levels in water

- From provinces and territories:
  - Treated water: mean levels range 0.02 – 0.29 mg/L
  - Treated water: maximum levels range 0.12 – 11 mg/L
  - Raw water: mean levels range 0.02 – 0.13 mg/L
  - Raw water: maximum levels range 0.12 – 4.9 mg/L
  - Groundwater sources generally contain higher levels of barium
- National drinking water survey data:
  - mean treated levels range 0.024 – 0.105 mg/L
  - maximum levels range 0.12 – 0.51 mg/L

Health effects

- Acute effects in humans:
  - hypokalemia-related: hyper-/hypotension, muscle weakness, paralysis
  - high doses: vomiting, cramps, diarrhea
- Chronic effects in humans:
  - weak evidence of cardiovascular disease
  - single studies: weak association with hearing loss, autism spectrum disorder, body mass index
- Effects in animals:
  - Renal toxicity most sensitive endpoint
  - weak evidence of hypertension (possibly influenced by diet)
  - no tumors.

Peer reviewers - health

- Lynne Haber, Ph.D, DABT, Senior Toxicologist/Adjunct Associate Professor, University of Cincinnati.
- Jamie Strong, U.S. EPA, Office of Water.
- Kannan Krishnan, PhD, DABT, FATS:
  - Senior Vice President, Chemical Risk Assessment, Risk Sciences International
- Health Canada reviewers:
  - Existing Substances and Risk Assessment Bureau (ESRAB)
  - Health Products and Foods Branch (HPFB)
  - National Biomonitoring Program

CDW Meeting November 2017 Barium 7

Peer review comments Health

- Source allocation for drinking water - 20% vs 50%:
  - based on available Canadian exposure data, 20% most appropriate
- Database deficiencies UF - 3 vs 10:
  - 3 most appropriate; 10 overly conservative; lack of data in children accounted for by intraspecies UF
- Why does the $BMDL_5$ differ from the U.S. EPA $BMDL_5$ for the same study and health endpoint?
  - Health Canada used 2-year nephropathy incidence data only as reported by the NTP (1994); the EPA included nephropathy data and other kidney lesions (differing between males and females) from both the 15 month interim and 2-year data.

CDW Meeting November 2017 Barium 8

Peer reviewers – analytical and treatment

- Tony Myers - Civil & Environment Engineer
  - Water Technology Director - CH2M Hill
- Dr. Dennis Clifford – Ph.D., P.E.
  - Department of Civil and Environmental Engineering, Gullen College of Engineering, University of Houston

Peer review comments - analytical and treatment

- Document provides appropriate treatment technologies for barium removal and guidance for distribution system monitoring
- Suggested quarterly monitoring of treated water
- Suggested developing a correlation between hardness and barium concentrations in treated water.
- Minor clarification
  - Added study on barium removal by sodium carbonate

Proposed TDI

$$TDI = \frac{58 \text{ mg/kg bw per day}}{300}$$

$$= 0.19 \text{ mg/kg bw per day}$$

where:

- 58 mg/kg bw per day is the $BMDL_5$ for increased incidence of nephropathy in male mice (NTP, 1994); and
- 300 is the uncertainty factor (x10 for interspecies variability, x10 for intraspecies variability, x3 for database deficiencies).

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Proposed HBV

$$HBV = \frac{0.19 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L per day}}$$

$$= 2.0 \text{ mg/L (2000 µg/L)}$$

where:

- 0.19 mg/kg bw per day is the TDI;
- 70 kg is the average body weight of an adult;
- 0.2 is the allocation factor for drinking water; and
- 1.5 L per day is the estimated daily volume of tap water consumed by an adult (negligible dermal/inhalation exposure).

Proposed MAC = 2.0 mg/L (2000 µg/L)

CDW Meeting November 2017 Barium 12

International considerations

- The U.S. EPA established a MCL of 2.0 mg/L based on hypertension in humans in 1995
- WHO (2016) established a drinking water guideline value of 1.3 mg/L based on nephropathy in mice
- Australia has established a drinking water guideline of 2.0 mg/L based on hypertension and kidney disease in humans.

CDW discussion / next steps

- Seeking CDW approval for a 2-month public consultation period
- No need for impact statements from members (proposed MAC higher than current guideline)

Item 4-H
Lead

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- Public consultation ended March 15th, 2017
- Document was revised to address relevant consultation comments
- Document was sent to CDW 2 months prior to meeting, along with table of consultation comments and responses
- Seeking CDW approval for final posting

Refresher

- Current guideline statement (1992):
  - *The maximum acceptable concentration (MAC) for lead in drinking water is 0.010 mg/L (10 µg/L). It is recommended that faucets be flushed before water is taken for analysis or consumption*
- Main changes from 1992 document include:
  - Reduced MAC of 0.005 mg/L (5 µg/L)
  - No longer recommend flushing of faucet before sampling; Exposure-based sampling recommended
  - ALARA statement

CDW Meeting May 2017 Protozoa 3

Proposed guideline statement

- *The maximum acceptable concentration (MAC) for total lead in drinking water is 0.005 mg/L (5 µg/L), based on a sample of water taken at the tap and using the appropriate protocol for the type of building being sampled. Every effort should be made to maintain lead levels in drinking water as low as reasonably achievable (or ALARA)*

CDW Meeting November 2017 Lead 4

Consultation comments Overview

- Most comments in agreement with reduction of MAC (10 µg/L to 5 µg/L), exposure-based sampling (i.e., no flushing) and ALARA statement
- Most comments related to implementation and application of the guideline
- Few health comments; mainly related to use of a cancer approach for a non-cancer endpoint
- Comments on the need to update corrosion control guidance document
  - Document is being considered for an update

CDW Meeting November 2017 Lead 5

Consultation comments Health (1)

- Multiple comments on the use of a non-threshold approach for a non-cancer endpoint:
  - HC still supports the use of a non-threshold approach to estimate the risk of neurodevelopmental effects at low levels of exposure since a threshold BLL for adverse effects has not been identified
- Multiple comments on the choice of 10^{-4} to 10^{-5} as an acceptable level of risk for the HBV calculation for non-cancer endpoint:
  - A major revision of Section 10.2 (as shared with CDW at the last meeting) replaced the derivation of a HBV with estimated additional cases of Mild Intellectual Disability (MID) associated with various levels of lead in drinking water

CDW Meeting November 2017 Lead 6

Consultation comments Health (2)

- Better justification needed on choice of BLL indices used from key study (concurrent vs maximum vs lifetime average vs early-childhood BLL):
  - Text added in section 10.2 indicating that a comparative analysis by Lanphear et al. (2005) found that concurrent BLL explained the greatest variance in IQ compared to the other indices, which supports the use of concurrent BLL

Consultation comments Health (3)

- The age used in HBV calculation should be reconsidered, since intake per kg body weight is greater in infants:
  - the risk assessment for lead is based on children aged 5-11 since the relationship between IQ and BLLs in this age group can be characterized with greatest certainty due to the large database of relevant information
  - HC agrees that bottle fed infants might be at higher risk. A statement was added in section 3.0 to recommend not using tap water with any detectable lead to reconstitute infant formula
  - Note: bottle-fed infants have reduced exposure to lead from soil/dust ingestion thus reducing the number of sources of exposure in comparison to older children

Consultation comments Monitoring

- Need to clarify the use of other sampling protocols and sample volumes
  - Examples on the use of fully flushed protocol in Québec added to section 3.1
  - Table added in section 5.1 outlining different types of sampling, protocols and objectives of sampling
  - Information on differences for volume draw in different buildings added to section 5.1
- Questions on distribution system-wide sampling instead of sampling in high risk zones
  - Clarified differences for sampling to identify high risk zones (i.e., distribution system) and sampling in high risk zones (investigate and mitigate)

CDW Meeting November 2017 Lead 9

Consultation comments Analytical

- PQL is not representative of current laboratory capability in Canada
  - Added text that recognizes ability of Canadian laboratories to analyse well below the PQL
- Need laboratories to be accredited
  - Added recommendation for laboratory accreditation
- Hot digestion not required for all samples
  - Clarified conditions for sample preservation/digestion steps

CDW Meeting November 2017 Lead 10

Consultation comments Treatment

- Full lead service line removal should be prioritized
  - Strengthened statement regarding Health Canada's recommendation of full LSL removal
  - Clarified that mitigation measures are needed to reduce risks associated with lead exposure as partial LSL removal will still occur
- Request for additional details on several mitigation measures
  - Added details on corrosion inhibitors (orthophosphate), CSMR and point of use filters
- Need to expand information on private wells
  - Information on private wells and lead sources added to section 7.2

International considerations

- The U.S. EPA's Lead and Copper Rule is a treatment based rule which established an action level of 0.015 mg/L (15 µg/L) for lead in drinking water (90th percentile). It has not established a maximum contaminant level but rather, a maximum contaminant level goal of zero.
- WHO reconfirmed 10 µg/L in 2011; considered provisional on the basis of treatment performance and analytical achievability.
- CalEPA established a public health goal of 0.2 µg/L based on neurobehavioural deficits reported by Lanphear et al. (2005).

CDW discussion / next steps

- Seeking CDW approval for final posting
- Next step:
  - CHE approval

Item 5-B
CNPHI update

FPT Committee on Drinking Water

61st Meeting / November 7, 8 & 9, 2017

Ottawa, Ontario

Status

- Drinking Water Advisories Application (DWA) now approaching 10,000 drinking water advisory records
- Participation planned or underway in 9 of 13 P/T jurisdictions
- Health Canada FNIHB close to national coverage with 5 of 6 Regions implemented

Refresher

- Use of DWA is flexible:
  - Live use for alerting and communications
  - Information sharing – contributing to the national picture and using analytical/reporting tools
- Water Systems Manager
  - Information management tool for drinking water systems – now supports identification, source to tap and compliance related information
  - Captures service relationships between systems

Water monitoring data management tool

- To be completed this fiscal year
- Supports design, scheduling and compliance for sampling plans from source to tap
- Includes querying and reporting tools
- Provides flexibility for manual entry, batch uploads, laboratory linkage and mobile technologies
- Supports routine, survey or novel data collection for various waters

CNPHI on the go project

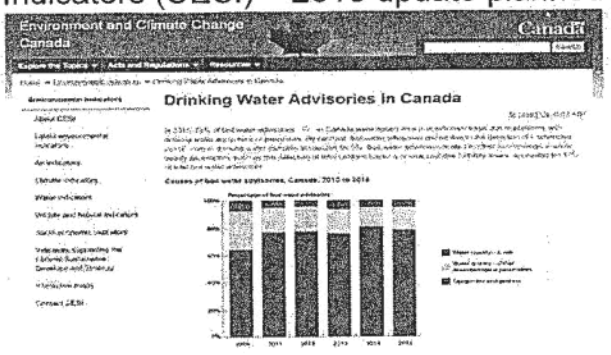
- Integration of mobile technologies with existing CNPHI applications
- Funded by National Defence Research and Development (Canadian Safety and Security Program) – led by CNPHI
- Mobile application pilots completed for field collection of drinking water monitoring data, event management and swine flu surveillance

Context

- DWA is helping to inform sustainable safe drinking water in Canada
  - Needs of small community water supplies
  - Appropriate emphasis on infrastructure and operations to inform future investments
- Improved intelligence on drinking water advisories
  - Illustrating root causes to a broader audience
  - Supporting confidence in drinking water oversight

CESI indicator

- Canadian Environmental Sustainability Indicators (CESI) – 2018 update planned



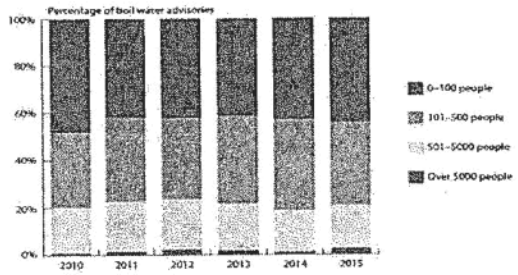
2018 CESI update

- 2018 update will focus on the same themes

Community size and drinking water advisories

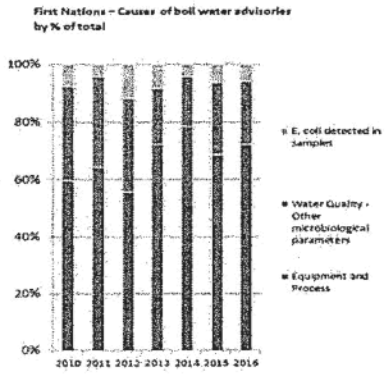
In 2015, 75% of boil water advisories were issued for drinking water systems serving 500 people or consistent with that observed from 2010 to 2014.

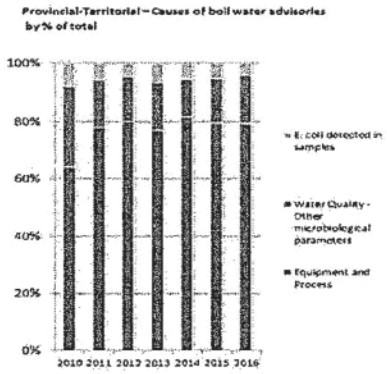
Boil water advisories by community size, Canada, 2010 to 2015



Comparative analysis First Nations focus (1)

- Causes





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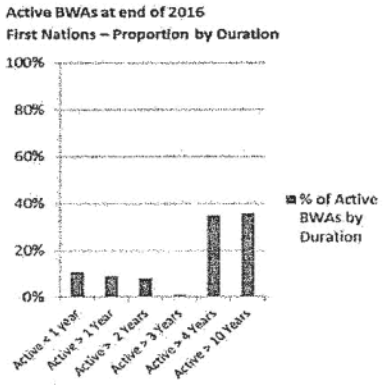
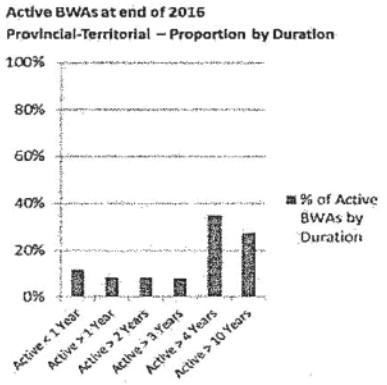
Comparative analysis First Nations focus (2)

- Duration





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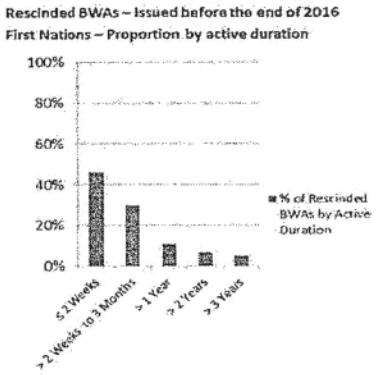
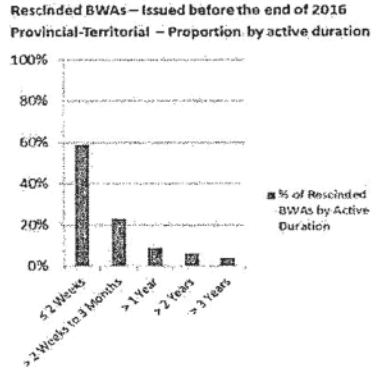
Comparative analysis First Nations focus (3)

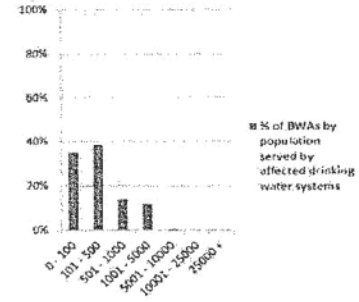
- Rescinded BWAs

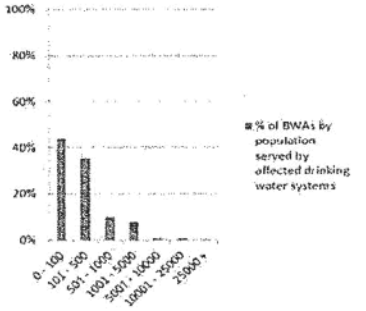




Comparative analysis First Nations focus (4)

- Population served





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Radium-228
A Natural Radionuclide
Commonly Found in Drinking Water

Jing Chen

Radiation Protection Bureau, Health Canada



Background Information

- Naturally occurring mineral deposits of uranium and thorium in the ground are predominantly responsible for the localization of radiological content in drinking water.
- Canada's uranium resources are the fourth largest in the world, after those of Australia, Kazakhstan and Russia.
- Thorium is about as common as lead in the Earth's crust and several times more abundant in Earth's crust than all isotopes of uranium combined.
- In drinking water, commonly found natural radionuclides are U-238, U-234, Ra-226 and Pb-210 from the uranium decay series, and Th-232 and Ra-228 from the thorium decay series



Common natural radionuclides listed in WHO DW Guidelines

Table 9.2 Guidance levels for common[a] natural and artificial radionuclides for members of the public

Category	Radionuclide	Dose coefficient (Sv/Bq)	Guidance level[b] (Bq/l)
Naturally occurring radioactive isotope that starts the uranium decay series[c]	Uranium-238	4.5×10^{-8}	10
Naturally occurring radioactive isotopes belonging to the uranium decay series	Uranium-234	4.9×10^{-8}	1
	Thorium-230	2.1×10^{-7}	1
	Radium-226	2.8×10^{-7}	1
	Lead-210	6.9×10^{-7}	0.1
	Polonium-210	1.2×10^{-6}	0.1
Naturally occurring radioactive isotope that starts the thorium decay series	Thorium-232	2.3×10^{-7}	1
Naturally occurring radioactive isotopes belonging to the thorium decay series	Radium-228	6.9×10^{-7}	0.1
	Thorium-228	7.2×10^{-8}	1



Issues in Canadian DW Guidelines

Short list of most commonly detected radionuclides:

Natural radionuclides	*MAC*	*Artificial radionuclides*	*MAC*
Total uranium[1]	*0.02 mg/L*	*Tritium (^{3}H)*	*7000 Bq/L*
Lead-210 (^{210}Pb)	*0.2 Bq/L*[3]	*Strontium-90 (^{90}Sr)*	*5 Bq/L*
Radium-226 (^{226}Ra)	*0.5 Bq/L*	*Iodine-131 (^{131}I)*	*6 Bq/L*
		Cesium-137 (^{137}Cs)	*10 Bq/L*

The main radionuclide from the thorium decay series, Ra-228, is missing from the above summary table.



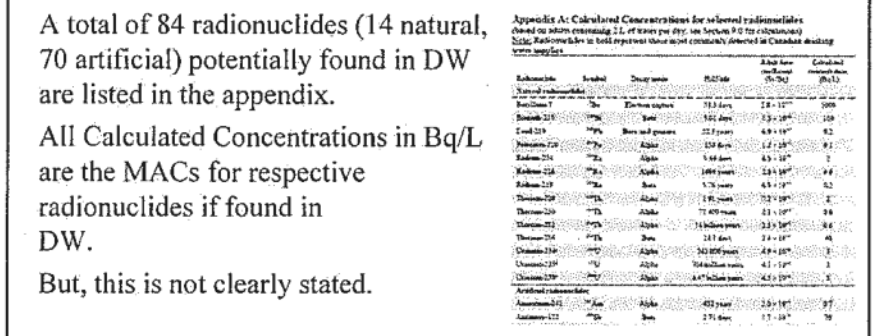


Issues in Canadian DW Guidelines

A total of 84 radionuclides (14 natural, 70 artificial) potentially found in DW are listed in the appendix.

All Calculated Concentrations in Bq/L are the MACs for respective radionuclides if found in DW.

But, this is not clearly stated.



Contribution of Ra-228

- The Canadian Radiological Monitoring Network (CRMN) operated by Radiation Protection Bureau, Health Canada, has continuously monitored natural radioactivity in drinking water for Regina, Elliot Lake and Port Hope since 1975.
- Activity concentrations of Ra-228 in drinking water of Regina, Elliot Lake and Port Hope for the recent 5 years are summarized below.

Location	2012	2013	2014	2015	2016
Regina	0.015 (<DL, 0.026)	<DL	0.002 (<DL, 0.008)	0.002 (<DL, 0.005)	0.008 (<DL, 0.019)
Elliot Lake	0.013 (<DL, 0.043)	<DL	0.002 (<DL, 0.008)	0.008 (<DL, 0.019)	0.009 (<DL, 0.028)
Port Hope	0.084 (0.035, 0.199)	0.081 (<DL, 0.242)	0.007 (<DL, 0.017)	0.010 (<DL, 0.031)	0.015 (0.002, 0.026)
Mean ± SD	0.037±0.040	0.027±0.047	0.004±0.003	0.006±0.004	0.011±0.004
Population-weighted mean	0.018	0.004	0.002	0.002	0.009

The population-weighted 5-year mean Ra-228 concentration is 0.007 Bq/L, well below the MAC of 0.2 Bq/L for Ra-228.

Contribution of Ra-228

- Drinking water quality data were recently reviewed for 24 metropolitan areas and cities which cover more than 64% of the total Canadian population.
- The population-weighted average levels are 0.0017 Bq/L for Ra-226, 0.0068 Bq/L for Pb-210, and 0.23 µg/L (0.0058 Bq/L) for total uranium.
- Ingestion radiation dose from radionuclides in DW:

Natural radionuclides	MAC	Dose coefficient Sv/Bq	Concentration	Annual Dose mSv	Contribution %
Total uranium (U)	20 µg/L		0.23 µg/L		2.6%
Uranium-238 (U-238)	3 Bq/L	4.5×10^{-8}	0.0028 Bq/L	0.000092	
Uranium-235 (U-235)	4 Bq/L	4.7×10^{-8}	0.00013 Bq/L	0.0000045	
Uranium-234 (U-234)	3 Bq/L	4.9×10^{-8}	0.00287 Bq/L	0.000103	
Lead-210 (Pb-210)	0.2 Bq/L	6.9×10^{-7}	0.0072 Bq/L	0.00363	47.0%
Radium-226 (Ra-226)	0.5 Bq/L	2.8×10^{-7}	0.0018 Bq/L	0.000368	4.8%
Radium-228 (Ra-228)	0.2 Bq/L	6.9×10^{-7}	0.007 Bq/L	0.00353	45.7%

Ra-228 contributes about half of the annual radiation dose resulting from natural radionuclides in drinking water.

Final Remark

The total annual effective dose due to natural radionuclides in drinking water including Ra-228 is 7.7 µSv for the above example, a relatively small contribution to the typical annual effective dose due to natural background radiation which is in the range of 1 – 10 mSv with 2.4 mSv (2400 µSv) being the central estimate

Data for Ra-228 in drinking water are very limited. The above estimate may not be representative for all of Canada.

However, it demonstrates that Ra-228 is a common radionuclide and should be considered in routine monitoring programs for drinking water quality.

Canadian drinking water is generally at high quality in radiological aspect.

Thanks for your attention !



Jing.chen2@canada.ca

Health Canada Santé Canada

Your health and safety... our priority. Votre santé et votre sécurité... notre priorité.

Report of the WHO Document

"MANAGEMENT OF RADIOACTIVITY IN DRINKING WATER"

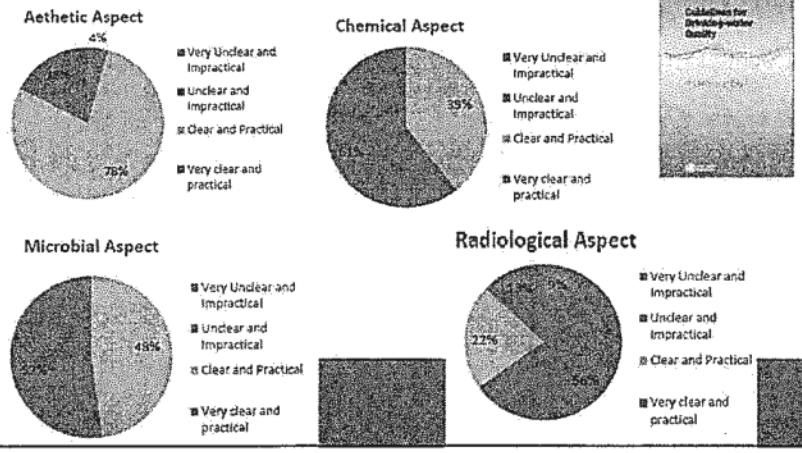
Jing Chen

Radiation Protection Bureau, Health Canada



THE ISSUE

Results of a WHO survey on clarity and practicality of drinking water guidelines:



Why radiological parameters can be hard to understand

- Difference in health risks
  The health risks associated with the presence of radionuclides in drinking-water are generally very low compared to those from micro-organisms and some chemicals. Any health risks from radionuclides in drinking-water will not be acute or immediate.
- Reference level of 0.1mSv/year is only a small fraction of background radiation
  People typically receive a radiation dose of about 0.3 mSv each year due to radionuclides of natural origin in their diet; of this about 0.01 mSv (about 5%) comes from drinking-water. A dose of 0.3 mSv is less than 15% of the average annual radiation dose from all natural sources of radiation (cosmic rays, soil, building materials, radon, diet) received by an individual which is about 2.4 mSv.



More challenges for understanding

- *The MACs are based on a reference dose of 0.1 mSv/year, representing < 5% of the annual dose from natural background radiation.*

  However, many people see MACs as the limit for safe or unsafe.
- *When radiological parameters are exceeded in a single sample, the reference dose level (0.1 mSv) would be exceeded **only if** exposure to the same measured concentration were continued for a full year.*

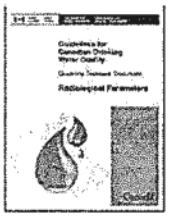
  However, sum > 1 for a single sample often causes concern on the safety of drinking water.



Issues and Challenges in Canada

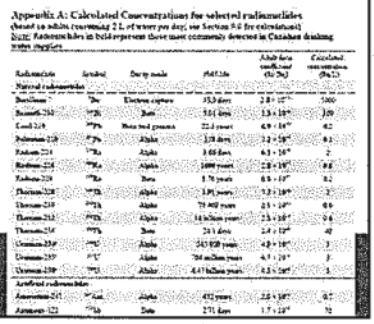
Short list of most commonly detected radionuclides:

Natural radionuclides	*MAC*	*Artificial radionuclides*	*MAC*
Total uranium[1]	*0.02 mg/L*	*Tritium (^{3}H)*	*7000 Bq/L*
Lead-210 (^{210}Pb)	*0.2 Bq/L*[b]	*Strontium-90 (^{90}Sr)*	*5 Bq/L*
Radium-226 (^{226}Ra)	*0.5 Bq/L*	*Iodine-131 (^{131}I)*	*6 Bq/L*
		Cesium-137 (^{137}Cs)	*10 Bq/L*



A total of 84 radionuclides (14 natural, 70 artificial) potentially found in DW are listed in the appendix.

Calculated Concentrations in Bq/L are the MACs for respective radionuclides if found in DW.
But, this is not clearly stated.


Appendix A: Calculated Concentrations for selected radionuclides

Note: Radionuclides in bold represent those most commonly detected in Canadian drinking water supplies

Radionuclide	Symbol	Decay mode	Half-life	Adult dose coefficient (Sv/Bq)	Calculated concentration (Bq/L)
Natural radionuclides					
Beryllium-7	^{7}Be	Electron capture	53.3 days	2.8×10^{-11}	1000
Bismuth-210	^{210}Bi	Beta	5.01 days	1.3×10^{-9}	20
Lead-210	^{210}Pb	Beta and gamma	22.6 years	6.9×10^{-7}	0.2
Polonium-210	^{210}Po	Alpha	138 days	1.2×10^{-6}	0.1
Radium-224	^{224}Ra	Alpha	3.66 days	6.3×10^{-8}	2
Radium-226	^{226}Ra	Alpha	1600 years	2.8×10^{-7}	0.5
Radium-228	^{228}Ra	Beta	5.76 years	6.9×10^{-7}	0.2
Thorium-228	^{228}Th	Alpha	1.91 years	7.2×10^{-8}	2
Thorium-230	^{230}Th	Alpha	75 400 years	2.1×10^{-7}	0.5
Thorium-232	^{232}Th	Alpha	14 billion years	2.3×10^{-7}	0.4
Thorium-234	^{234}Th	Beta	24.1 days	2.4×10^{-9}	40
Uranium-234	^{234}U	Alpha	245 000 years	4.9×10^{-8}	3
Uranium-235	^{235}U	Alpha	704 million years	4.7×10^{-8}	3
Uranium-238	^{238}U	Alpha	4.47 billion years	4.5×10^{-8}	3
Artificial radionuclides					
Americium-241	^{241}Am	Alpha	432 years	2.0×10^{-7}	0.7
Americium-243	^{243}Am	Beta	2.71 days	1.7×10^{-9}	30



Issues and Challenges in Canada



9.1 Summation formula

The radiological effects of two or more radionuclides in the same drinking water source are assumed to be additive. Thus, the following summation formula should be satisfied in order to demonstrate compliance with the guidelines:

$$\sum_{i} \frac{C_i}{MAC_i} \leq 1$$

where C_i and MAC_i are the observed and maximum acceptable concentrations, respectively, for each contributing radionuclide. Only those radionuclides that are detected with at least 95% confidence should be included in the summation. Detection limits of undetected radionuclides should not be substituted for the concentrations C_i. Otherwise, a situation could arise where a sample fails the summation criterion even though no radionuclides are present.

- *Some misinterpretation of the meaning of "observed concentration";*
- *Detection Limits (DLs) for radionuclides are often incorrectly substituted for measurements < DLs.*



Issues and Challenges in Canada

Water samples may be initially analysed for the presence of radioactivity using gross alpha and gross beta screening rather than measurements of individual radionuclides.

The screening levels are 0.5 Bq/L for gross alpha
1.0 Bq/L for gross beta

Why "may be"? This needs to be clearly explained.

- Like different chemicals, different radionuclides have different radiological toxicity. Levels of gross activity measurements cannot serve as guideline levels.
- Measurements of individual radionuclides are normally expensive and time consuming. However, for drinking water sources, individual radionuclide analyses should be carried out initially. Then the screening measurements can be used as a convenient way to monitor potential changes in the radiological characteristics of drinking water sources.

New Document of the WHO

World Health Organization (WHO) established an expert group to develop additional guidance for radiological parameters

with the title
"Management of Radioactivity in Drinking Water"
in the format of Q&As.

Some key Q&As are summarised below:



WHO APPROACH: Qs & As

Q: What is the purpose of the WHO Guidelines for Drinking Water Quality (GDWQ)?

The GDWQ provide the recommendations of WHO for managing the risk from hazards that may compromise the safety of drinking-water, including radionuclides.

The assessment and management of health risks from radionuclides need to be considered in the context of other potential health risks from the water supply, (namely microbial and chemical risks), the availability of other water supplies and available resources.



WHO APPROACH: Qs & As

Q: Are the Radiological Criteria in the WHO Guidelines for Drinking-water Quality mandatory?

No. The GDWQ is international guidance designed to help countries develop national standards and regulations. Countries should consider their specific situations in the adoption of the GDWQ, including the criteria to use (ie whether to adopt the IDC, screening levels and guidance levels without change).

Q: Should naturally occurring radionuclides and human-made radionuclides present in drinking-water be managed differently?

No. A radiation dose associated with the intake of a radionuclide into the body from drinking-water does not depend on its source.

However, in terms of risk management, there is a difference because human-made radionuclides are often controllable at the point at which they enter the water supply. Naturally occurring radionuclides, in contrast, which enter the water supply at its source are often less amenable to control. This may influence the actions that are taken in the event that the criteria in the GDWQ are exceeded.

WHO APPROACH: Qs & As

Q: What is the individual dose criterion (IDC) of 0.1 mSv/year?

- The IDC is a criterion in the GDWQ for assessing health risks from prolonged exposure to radionuclides in drinking-water.
- The IDC of 0.1 mSv/year represents a very low level of health risk.
- The IDC is for one year's consumption of drinking-water regardless of whether the radionuclides are naturally occurring or human-made.

The IDC should not be interpreted as a limit indicating that the drinking-water is unsafe for consumption. Drinking-water is a fundamental requirement of life and the risks of not having a drinking-water supply are likely to be much higher than consuming drinking-water that does not meet the IDC.



WHO APPROACH: Qs & As

Q: What are the screening levels for and how should they be used?

The screening levels are operational criteria, expressed as total alpha and beta activity concentrations, below which no further action is required.

Screening levels enable water suppliers and regulators to assess the total radioactivity in drinking-water in a resource- and cost-efficient manner. In most situations, activity concentrations in drinking-water are very low and detailed analysis is not normally justified for routine monitoring.

However, there are a few radionuclides that cannot be measured using these screening methods.

There are a few natural radionuclides (notably Ra-228 and Po-210) where the 0.1 mSv per year could be exceeded, even if the screening levels are not exceeded, in some situations.

WHO APPROACH: Qs & As

Q: If a screening level is exceeded for one or a few drinking-water samples, does this mean that the radiation dose will be greater than the IDC of 0.1 mSv?

No. The IDC is an annual criterion and so if the gross activity screening levels are exceeded for a short time in an individual drinking-water sample or even a few samples, this does not necessarily imply that the IDC will be exceeded.

Q: What do I do next if either of the screening levels is exceeded for a drinking-water sample?

If either of the screening levels is exceeded, the first task is to confirm the validity of the result by repeating the measurement.

Once the initial measurement has been confirmed, the next step is to carry out further measurements. These are needed to assess the situation and whether it is varying with time.

Naturally occurring radionuclides in drinking-water from groundwater sources are most likely to lead to the screening levels being exceeded.

WHO APPROACH: Qs & As

Q: If a screening level is exceeded for one or a few drinking-water samples, does this mean that the radiation dose will be greater than the IDC of 0.1 mSv?

Continue ...

If further measurements made over an agreed period following the initial measurement fall below the screening level, then no further intervention is required.

If there is a consistent exceedance of the screening level(s), the radionuclides that are present in the water need to be identified. Radionuclide specific analyses are required to both determine if a radionuclide is present and, if it is, what the activity concentration in the drinking-water is. Potential sources of radionuclides should be studied and a specific analytical strategy developed.



WHO APPROACH: Qs & As

Q: What is the 1 mSv/year reference level and its relationship with the 0.1 mSv/year IDC for drinking water?

The International Radiation Basic Safety Standards (BSS) recommend a reference level for the radiation dose due to consumption of drinking-water of approximately 1 mSv/year. A reference level represents the level of dose or risk above which it is judged to be inappropriate to plan to allow exposures to occur and below which optimization of protective actions should be planned in order to keep doses as low as reasonable achievable

The IDC of 0.1 mSv/year represents a very low level of health risk. The majority of water supplies comply with this criterion.

In cases where 0.1 mSv/year is not achievable, regulatory authorities may establish a specific reference level for radionuclides in drinking-water higher than 0.1 mSv/year, but generally less than the BSS reference level of 1 mSv/year, depending on the circumstance.

Thanks for your attention !

The Canadian Radiological Monitoring Network (CRMN) operated by Radiation Protection Bureau, Health Canada, has continuously monitored natural radioactivity in drinking water for Regina, Elliot Lake and Port Hope since 1975.

The average effective dose resulting from natural radionuclides in drinking water would be 0.008 mSv/year. This is a very small contribution to the typical annual effective dose due to natural background radiation which is in the range of 1 – 10 mSv with 2.4 mSv being the central estimate.

From a radiological perspective,
Canadian drinking water is generally of excellent quality.



jing.chen2@canada.ca

Item 6-B
Certification bodies report

FPT Committee on Drinking Water

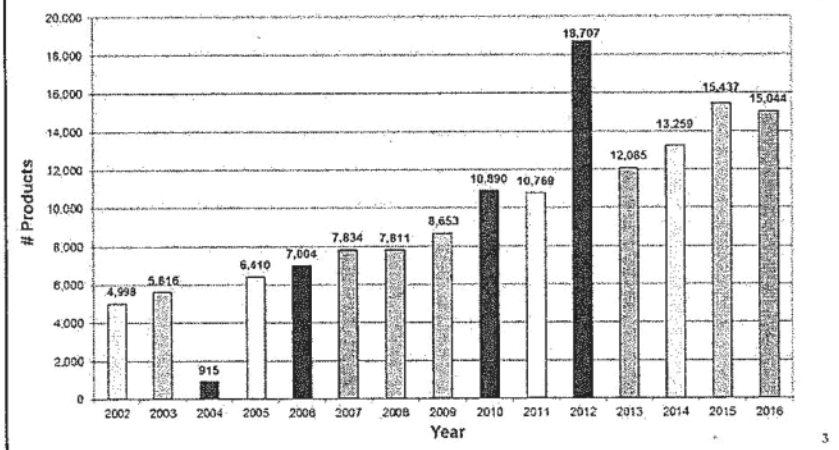
61th Meeting / November 7-9, 2017

Ottawa, Ontario

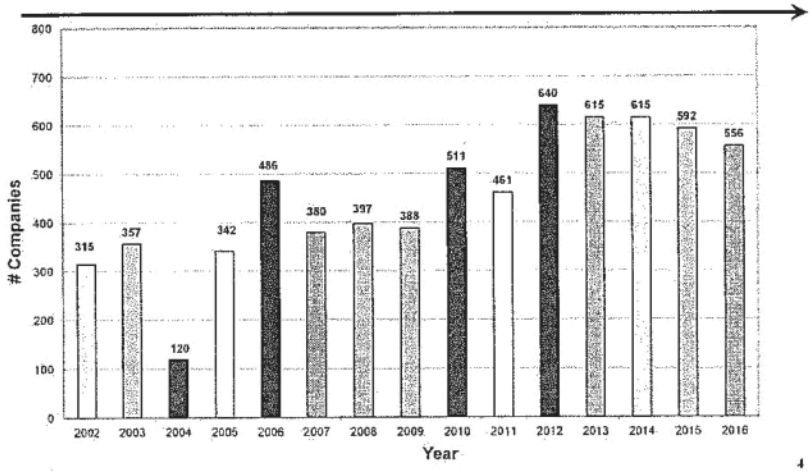
Major updates to NSF DWTU Standards

- NSF 53
  - Added a test protocol for evaluating the removal of perchlorate
- NSF 55
  - Revised formula for determining the time for a UV system to enter into shut-off mode during the UV alarm performance testing
- NSF 58
  - Modified influent cyst challenge concentration
  - New language to allow turbidity and cyst reduction tests to run simultaneously
- NSF 401: Emerging compounds/incidental contaminants – 2014
  - New standard to establish minimum requirements (materials, performance, etc.) of drinking water treatment systems designed to reduce emerging compounds in public or private water supplies (i.e., pharmaceutical, personal care products, endocrine disrupting compounds

DWTUs- Products 2002-2016



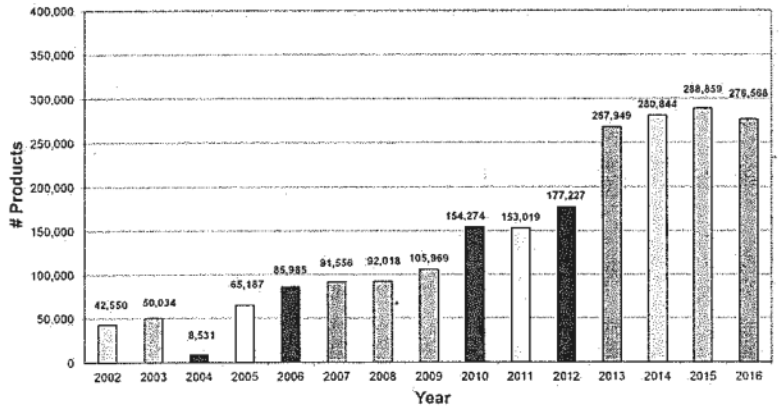
DWTUs - Companies 2002 - 2016



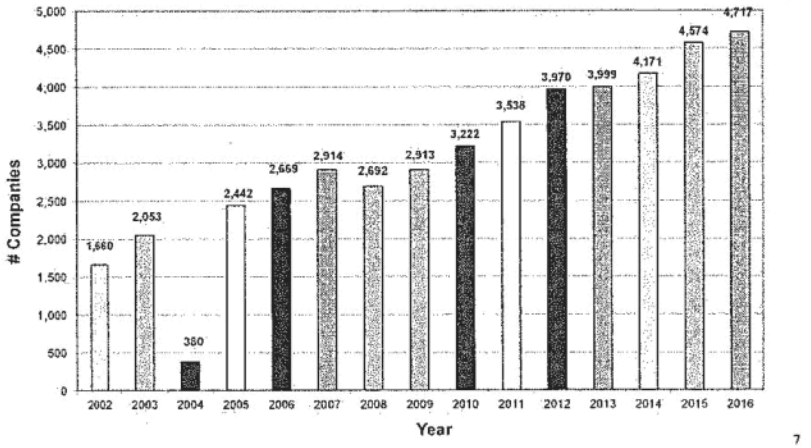
Major updates to NSF additive standards

- NSF 60
  - Reduced SPAC for bromate and removed low-bromate option
  - Corrected SPAC for chlorate
  - Addressed use of natural polymers in water well construction and remediation
  - Updated and combined tables from Annexes D and E (drinking water criteria)
- NSF 61
  - Removed the 2 square inch restriction and reference to Annex G
  - Eliminated the 2-L sample size requirement for POE systems
  - Added material-specific analyses
  - Updated and combined tables from Annexes D and E (drinking water criteria)
  - Incorporated minimum sample size (in-line devices)
  - Limited maximum lead release allowed for individual units (in-line devices)

Products – 60, 61 and 372 2002 - 2016



Companies – 60, 61 and 372 2002 - 2016



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CDW Meeting October 2017 Certification bodies report

Low lead: 61 and 372 (combined)

	CSA	IAPMO	NSF	UL	WQA	Trusdail	Total
# Products 2016	14,000	25,000	29,911	6,733	734	247	76,625

Separate data not available for NSF 372 only certification

CDW Meeting October 2017 Certification bodies report 8

Health Canada
Healthy Environments and Consumer Safety Branch

Santé Canada
Direction générale, Santé environnementale et sécurité des consommateurs

Your file Votre référence

Our file Notre référence

Federal-Provincial-Territorial Committee on Drinking Water Technical Secretariat
269 Laurier Avenue West (AL 4903D)
OTTAWA, Ontario K1A 0K9

Secrétariat technique du Comité fédéral-provincial-territorial sur l'eau potable
269 ave Laurier ouest (ia 4903D)
Ottawa (Ontario) K1A 0K9

October 12th, 2017

DISTRIBUTION

FEDERAL-PROVINCIAL-TERRITORIAL COMMITTEE ON DRINKING WATER

Enclosed you will find information for the next meeting of the Federal-Provincial-Territorial Committee on Drinking Water (CDW).

The CDW meeting will be held November 7, 8 & 9, 2017 at 269 Laurier Ave W., Ottawa, Ontario. The meeting will be held in room 7-086 and will start at 9:00 am on each day.

If you have any questions, please contact me at (613) 957-3130.

le 12 octobre 2017

DISTRIBUTION

COMITÉ FÉDÉRAL-PROVINCIAL-TERRITORIAL SUR L'EAU POTABLE

Vous trouverez ci-inclus l'information concernant la prochaine réunion du Comité fédéral-provincial-territorial sur l'eau potable (CEP).

La réunion du CEP aura lieu les 7, 8 et 9 novembre 2017, au 269 ave Laurier ouest, Ottawa (Ontario). La réunion se déroulera dans la salle 7-086 et débutera à 9h00 chaque jour.

Pour de plus amples renseignements, veuillez communiquer avec moi au (613) 957-3130.

Anne Vézina
Committee Coordinator / Coordonnatrice du comité

Canada

Federal Provincial Territorial Committee on Drinking Water

Sixty-first Meeting
November 7, 8 & 9, 2017
Ottawa, ON

AGENDA PACKAGE

Federal Provincial Territorial Committee on Drinking Water
Sixty-first meeting – November 7, 8 & 9, 2017
Ottawa, ON
AGENDA PACKAGE

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1 Opening

Reference/Action:

- Introduce CDW members and observers
- Attached, October 2017 CDW membership list
- Members to update the membership list

Notes:

CDW MEMBERSHIP LIST - LISTE DES MEMBRES DU CEP

VOTING MEMBERS – MEMBRES VOTANTS

Jurisdiction Compétence	***Member & Affiliation*** Membre & Affiliation	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* / NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Newfoundland and Labrador / Terre-Neuve et Labrador	Mr. Haseen Khan, P. Eng., Director, Water Resources Management Division Department of Municipal Affairs and Environment	P.O. Box 8700 St. John's, NL A1B 4J6	Phone: 709 729-2563 Fax: 709 729-0320	Emergencies: 709 729-3703 / 709 772-2083 NEEC: 709 772-7745	Email: hkhan@gov.nl.ca Website: www.gov.nl.ca/env/water
Prince Edward Island / Île-du-Prince-Édouard	Mr. George Somers, Manager Drinking Water and Wastewater Management Environment Division Department of Communities, Land and Environment	11 Kent Street, 4th Floor P.O. Box 2000 Charlottetown, PEI C1A 7N8	Phone: 902 368-5046 Fax: 902 368-5830	Emergencies: 902 426-6030 NEEC: 902 426-6200	Email: ghsomers@gov.pe.ca Website: www.gov.pe.ca/infopei/Environment_and_Land/Water_Resources/Drinking_Water/
New Brunswick / Nouveau-Brunswick	Mr. Kevin Gould, P.Eng (Vice-Chair) Public Health Engineer, Healthy Environments Branch Office of the Chief Medical Officer of Health New Brunswick Department of Health	520 King Street, 2nd Floor, HSBC Place Fredericton, NB E3B 5G8	Phone: 506 444-4096 Fax: 506 453-8702	Emergencies: 506 453-2133 NEEC: 902 426-6200	Email: kevin.gould@gnb.ca Website: http://www.gnb.ca/health
Nova Scotia / Nouvelle-Écosse	Ms. Angelina Polegato, Supervisor Drinking Water Management Unit, Science Division Nova Scotia Environment	1894 Barrington Street, Suite 1800 P. O. Box 442 Halifax, NS B3J 2P8	Phone: 902 471-1494 Fax: 902 424-0501	Emergencies: 902 426-6030 NEEC: 902 426-6200	Email: angelina.polegato@novascotia.ca Website: http://www.gov.ns.ca/nse/water/drinking.water.asp
Quebec / Québec	Ms. Caroline Robert (Chairperson), Directrice Direction de l'eau potable et des eaux souterraines Ministère du Développement durable, de l'Environnement et de la Lutte aux Changements Climatiques	Édifice Marie Guyart, 8e Étage 675 blvd René-Lévesque Est Québec, QC G1R 5V7	Phone : 418 521-3885 (ext 4938) Fax : 418 644-2003	Emergencies: 866 694-5454 / 418 643-4595 NEEC: 866 283-2333 / 418 317-0513	Email: caroline.robert@mddelcc.gouv.qc.ca Website: www.mddelcc.gouv.qc.ca/eau/potable/

Jurisdiction Compétence	**Member & Affiliation** Membre & Affiliation	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* / NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Ontario	Dr. Satish Deshpande, Team Leader, Water Standards Section Standards Development Branch, Ministry of the Environment and Climate Change	40 St. Clair Ave W, 9th Floor Toronto, ON M4V 1M2	Phone: 416-327-4689 Fax: 416-327-2936	Emergencies: 800 268-6060 NEEC: 416 994-2126	Email: Satish.Deshpande@ontario.ca Website: www.ene.gov.on.ca
Manitoba	Ms. Kim Philip, Director Office of Drinking Water Manitoba Sustainable Development	1007 Century Street Winnipeg, MB R3H 0W4	Phone: 204 945-7010 Fax: 204 945-1365	Emergencies: 204 944-4888 NEEC: 819 997-3742	Email: Kim.Philip@gov.mb.ca Website: www.manitoba.ca/drinkingwater/
Saskatchewan	Mr. Sam Ferris Executive Director Environmental & Municipal Management Services Division Saskatchewan Water Security Agency	420, 2365 Albert Street Regina, SK S4P 4K1	Phone: 306 787-6193 Fax: 306 787-0197	Emergencies: 800 667-7525 NEEC: 306 536-9991	Email: sam.ferris@wsask.ca Website: www.saskh2o.ca/browser.htm
Alberta	Dr. Donald Reid Drinking-water Quality Regulator Drinking-water and Wastewater Section Provincial Programs Branch Operations Division, Environment and Parks Alberta Environment	1504, 15th Floor, 9820-106 Street Edmonton, AB T5K 2J6	Phone: 780 644-8061 Fax : 780 422-4086	Emergencies: 800 222-6514 NEEC: 780 977-1559	Email: donald.reid@gov.ab.ca Website: www.environment.gov.ab.ca
British Columbia / Colombie Britannique	Mr. David Fishwick Drinking Water Manager, Ministry of Health Province of British Columbia	4-2, 1515 Blanshard Street Victoria, BC V8W 9P1	Phone: 250 952-1110 Fax: 250 952-1713	Emergencies: 800 663-3456 NEEC: 604 666-6100	Email: david.fishwick@gov.bc.ca Website: www2.gov.bc.ca/
Yukon	Ms. Patricia Brooks, Drinking Water Program Coordinator Health and Social Services, Government of Yukon	2 Hospital Road Whitehorse, YT Y1A 3H8	Phone: 867 667-8351 Fax: 867 667-8322	Emergencies: 867 667-7244 NEEC: 867 667-7244	Email: pat.brooks@gov.yk.ca
Northwest Territories / Territoires du Nord-Ouest	Mr. Peter Workman, Chief Environmental Health Officer Department of Health & Social Services Government of the Northwest Territories	5015 - 49th Street, 5th Floor - NGB P.O. Box 1320 Yellowknife, NT. X1A 2L9	Phone: 867 767-9066 ext. 49260 Fax: 867 669-7517	Emergencies: 867 920-8130 NEEC: 867 920-8130 Health Line: 867-920-8646	Email: peter_workman@gov.nt.ca Website: www.hss.gov.nt.ca

Jurisdiction Compétence	**Member & Affiliation** Membre & Affiliation	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* / NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Nunavut	Ms. Michele LeBlanc-Havard, Environmental Health Specialist Department of Health Government of Nunavut	Box 1000 Station 1000; 1107 Sivummut Bldg. Iqaluit, NU X0A 0H0	Phone: 867 975-5943 Fax: 867 975-5755	Emergencies: 867 222-0256 NEEC: 867 222-0256	Email: mleblanc-havard@gov.nu.ca Website: www.gov.nu.ca
Canada	Greg Carreau, Director Water & Air Quality Bureau Safe Environments Directorate Healthy Environments & Consumer Safety Branch, Health Canada	269 Laurier Ave West A.L. 4903D Ottawa, ON K1A 0K9	Phone: 613 948-2568 Fax: 613 952-2574	Emergencies: 613 954-6651	Email: greg.carreau@canada.ca Website: http://www.hc-sc.gc.ca/ewh-semt/water-eau/index_e.htm

**Telephone number for emergencies ONLY that may impact drinking water quality (e.g., toxic chemical spill into source water). Numéro de téléphone à utiliser SEULEMENT pour les urgences pouvant avoir des répercussions sur la qualité de l'eau potable (p.ex. déversement de substances toxiques dans une eau d'approvisionnement).*
*** NEEC - Environment Canada's National Environmental Emergencies Centre. CNUE – Centre National des Urgences Environnementales.*

CDW LIAISONS MEMBERS – MEMBRES LIAISONS DU CEP

Liaison	**Member & Affiliation**	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* /NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Environment and Climate Change Canada Environnement et changement climatique Canada	Philippa Cureton Science & Risk Assessment Directorate Emerging Priorities Division National Guidelines and Standards Office Environment and Climate Change Canada	6th Floor Place Vincent Massey Annex 351 St-Joseph Blvd Gatineau, QC	Phone: 819 938-5078	NEEC:	Email: philippa.cureton@canada.ca

Liaison	Member & Affiliation	Address Adresse	Phone / FAX / Téléphone / Télécopieur	Emergencies* /NEEC** (24hr) Urgences* / CNUE (24 hres)	Email / Website Courriel / Site Web
CHE Committee Comité CSE	Mr. Peter Workman, Chief Environmental Health Officer Department of Health & Social Services Government of the Northwest Territories	5015 - 49th Street, 5th Floor - NGB P.O. Box 1320 Yellowknife, NT. X1A 2L9	Phone: 867 767-9066 ext. 49260 Fax: 867 669-7517	Emergencies: 867 920-8130 NEEC: 867 920-8130 Health Line: 867-920-8646	Email: peter_workman@gov.nt.ca Website: www.hss.gov.nt.ca
FNIHB (HC) DGSPNI (SC)	Ms. G. Kristina Taracha, Manager Public Health Engineering Section Environmental Public Health Division Drinking Water Safety Program First Nations and Inuit Health Branch, Health Canada	Jeanne-Mance Building, A.L. 1919D Tunney's Pasture Ottawa, ON K1A 0K9	Phone: 613 323-6447 Fax: 613 952-8639	N/A	Email: kristina.taracha@hc-sc.gc.ca
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2 Agenda/Minutes

2-A Adoption of agenda

Reference/Action:

- Tentative meeting agenda
- Attached, schedule for tentative meeting agenda
- CDW to approve agenda

Notes:

Draft Agenda

FPT Committee on Drinking Water – November 2017 (269 Laurier West, Ottawa, Ontario)			
	Tuesday November 7th, 2017	**Wednesday November 8th, 2017**	**Thursday November 9th, 2017**
9:00 am	1 Opening 2-A Adoption of agenda 2-B Approval of minutes 2-C CDW status/checklist 2-D Prioritization process 2-E Terms of Reference 2-F Guideline development process 2-G Withdrawal of old guidelines	4-E Boron 4-F Cadmium 4-G Barium	6-G INAC update 4-H Lead (continued) - Presentations from ON, QC and AB - Updates from other P/Ts
10:30 am	Break	Break	Break
11:00 am	6-A CRCP/CACP report 6-B Certification body reports 3-A Total coliforms	5-B CNPHI update 5-C BWA in small water supplies 5-D Parliamentary business 5-E Update on GRC conference on DBPs	4-H Lead (continued) - Plenary discussion
12:00 pm	Lunch	Lunch	Lunch
1:00 pm	3-B Bacteriological - HPC 3-C Other microbiological 4-A Chloramines	4-H Lead 4-I Other chemical 5-F National drinking water conference 5-G Sampling integrity	7 Member's reports 8 Future meetings
2:30 pm	Break	Break	End of meeting
3:00 pm	5-A CHMS cycle 4 results 4-B NOM 4-C HAAs - Screening values for BCA & BDCA 4-D PFNA – Screening value	5-H Ra-228 5-I Radiological Qs/As – WHO document 5-J Research group update 6-C CHE report 6-D WHO report 6-E CCME report 6-F FNIHB report	
5:00 pm	End of day	End of day	
NB: Meeting will be held in room 7-086 and will run from 9:00 a.m. to Noon and from 1:00 p.m. to 5:00 p.m. on Tuesday and Wednesday. Meeting will end at 2:30 p.m. on Thursday. The social dinner will be held on Wednesday evening.			

2 Agenda/Meeting

2-B Approval of minutes

Reference/Action:

- Attached, draft May 2017 meeting minutes
- CDW to approve the minutes

Notes:

Federal-Provincial-Territorial Committee on Drinking Water

Sixtieth Meeting
May 3-4, 2017
Ottawa, ON

Draft Minutes

Draft minutes prepared by J. A. MacDonald, May 2017
Draft minutes revised by A. Vezina and V. Morisset, October, 2017
Minutes finalized, ? 2017

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FEDERAL-PROVINCIAL-TERRITORIAL COMMITTEE ON DRINKING WATER – 60th MEETING

May 3-4, 2017
Ottawa, Ontario

Members Present

Ms. C. Robert, Québec – Chair
Mr. K. Gould, New Brunswick – Vice Chair
Mr. G. Carreau, Health Canada
Mr. P. Workman, Northwest Territories
Mr. D. Fishwick, British Columbia
Ms. K. Philip, Manitoba
Ms. M. Leblanc-Havard, Nunavut
Mr. H. Khan, Newfoundland and Labrador
Dr. D. Reid, Alberta
Dr. S. Deshpande, Ontario
Mr. G. Somers, Prince Edward Island
Ms. P. Brooks, Yukon
Mr. S. Ferris, Saskatchewan (phone)
Ms. P. Cureton, Environment Canada

Secretariat

Mr. R. Carrier, Health Canada
Ms. F. Lemieux, Health Canada
Ms. V. Morisset, Health Canada
Ms. K. Taracha, Health Canada (First Nations)
Mr. X. Redhead, Health Canada (First Nations)
Ms. A. Vezina, Health Canada (Coordinator)
Ms. S. McFadyen, Health Canada
Dr. A-M. Tugulea, Health Canada (Research)
Dr. R-A. Rodriguez, Health Canada (Research)
Dr. B. Koudjonou, Health Canada (Research)
Water quality staff, Health Canada
Ms. J. MacDonald, Health Canada (Reporter)

Guests

Mr. K. Carisse, INAC
Mr. N. Ferguson, INAC
Ms. E. Ducharme, Health Canada (First Nations)
Dr. J. Cooper, Health Canada (May 3 only)

Regrets

Ms. A. Polegato, Nova Scotia
Ms. M. Giddings, Health Canada

1 Opening

The Chair called the 60th meeting to order and welcomed everyone to Ottawa. Members, guests and staff introduced themselves. The Coordinator reviewed administrative details. The membership list was circulated for updating.

Decision/Action:

- **Members to update the membership list.**

2 Agenda/Meeting

2-A Adoption of agenda

The Coordinator noted that two additional items have been added to the agenda – guideline development process (see item 2G) and an update on the access to information (ATI) request for the national drinking water survey data (covered under item 4J). C. Robert asked if there will be an update on the national drinking water conference as outlined in the minutes from the last meeting (covered under item 3-D). C. Robert asked if the guideline development process is the same thing as the Committee Terms of Reference discussed at the last meeting. The Coordinator indicated they are two separate items; she noted that the Committee Terms of Reference are on the work plan but no progress has been made yet. The meeting agenda was approved as amended.

Decision/Action:

- **Members approved the meeting agenda as amended.**

2-B Approval of minutes

K. Philip noted that in section 4E, the reference to lead and copper "exposure" should be changed to "monitoring and sampling collection methods". The meeting minutes were approved as amended.

Decision/Action:

- **Members approved the minutes as amended.**

2-C CDW status/checklist

The Coordinator reviewed the status of documents. Bromate, cyanobacterial toxins and manganese have been approved by CHE and are being prepared for posting on the website. Viruses and uranium are in the internal approval process to be posted for public consultation. QMRA and copper are being prepared to send for internal approval to post for public consultation. The final guideline technical document for benzo(a)pyrene has been posted on the Health Canada website. The top ten parameters on the priority list are being worked on and work has been initiated on the 11th parameter. For arsenic, staff is monitoring the status of the IRIS assessment. D. Reid indicated that arsenic is a significant concern. He asked if the health-based value will go up or down. The Coordinator indicated that this can't be predicted at this time. The Coordinator noted that pentachlorophenol was previously removed from the priority list because of low detects but it may become a priority again (see items 2-E and 2-F). The Coordinator reviewed the Committee Checklist of action items and re-iterated that the item related to the Terms of Reference remains to be completed.

Decision/Action:

- **For information.**

2-D Bill C-326

V. Morisset discussed the Private Member's Bill introduced in the House of Commons on December 5, 2016. The Bill would require the Minister of Health to conduct a review of the drinking water standards in member countries in the previous calendar year and prepare an annual report to be tabled in both Houses of Parliament. This report would be required to include recommendations from the Minister for specific guidelines to be updated. In order to address some of the concerns highlighted by this Bill, Health Canada is working to improve openness and transparency. The program is seeking to publish notices for draft and final documents in the Canada Gazette (Part I). P. Cureton asked for clarification on what would be published. V. Morisset indicated that the public notice in the Gazette would include the guideline statement, executive summary and international considerations. J. Cooper noted that the Canada Gazette process is expected to reach additional stakeholders and improve transparency. D. Reid raised concerns that the Bill will drive guideline values to be lower. He indicated that the two major drinking water tragedies in North America (Walkerton and Flint) would not have been prevented by the Bill as drafted. S. Deshpande noted that documents are peer reviewed by international experts and Health Canada is part of the international community. He questioned whether the Bill will achieve additional benefits. C. Robert raised concerns with the wording used in the French translation.

Decision/Action:

- **For information.**

2-E CDW priority list

The Coordinator indicated that the Secretariat is finalizing the list of parameters for the consultant, for their comprehensive review of the health effects. The contract is to be completed by March 2018. Once parameters are identified from a health perspective, another consultant will conduct a review of the top 10–20 health priorities from an analytical/treatment perspective. Input from PTs will be requested in the spring/summer of 2018. The Coordinator noted that large groups of chemicals (e.g., endocrine disrupters) cannot be considered for guideline development. She also noted that operational parameters will be considered at a later date for prioritization. D. Reid asked if the consultant could be requested to provide a high level opinion on endocrine disrupters. It was noted that the CEPA annual report may discuss the prioritization process. C. Robert asked what the expected timeline is. V. Morisset indicated the consultant's report is to be completed by March 31, 2018 then treatment will consider the top 20 parameters and provinces/territories will be requested for input. She indicated that members should expect a discussion on the priority list at the fall 2018 meeting.

Decision/Action:

- **For information.**

2-F Withdrawal of old guidelines

R. Charron noted that the rationale document for withdrawing some old guidelines is being prepared. It is currently on hold pending the work being done to initiate the consultant review of the priority list (see item 2-E). Pentachlorophenol was specifically identified as a parameter that is being re-considered. It was previously identified for withdrawal but is one of the top ten pesticides used in Canada. The document is scheduled to be presented to the Committee for approval to consult at the November 2017 meeting. C. Robert asked S. Deshpande to explain how Ontario withdrew standards for a number of pesticides. S. Deshpande noted that a public

consultation was completed through the Environmental Bill of Rights website to withdraw standards for 13 pesticides. Ontario chose to introduce one number (100 ng/L) for all pesticides. If concentrations are above this value, an adverse water quality event must be reported and an investigation initiated within one month. A discussion ensued on coordination issues that have since arisen and which parameters are analysed. S. Deshpande noted that the pesticide scan includes 420 compounds and about 30 are typically detected. He noted that more adverse water quality events have been reported. K. Gould asked what is done when an exceedance is reported. S. Deshpande noted that typically a CAS number is provided with the exceedance. K. Philip noted that colleagues have raised concerns that the information in the old pesticide guideline documents will no longer be available. J. Cooper clarified that the information will be archived and a screening value should be requested for pesticides that are detected. V. Morisset added that the guideline information is outdated and a screening value would be more applicable. R. Charron re-iterated that screening values should be requested because the science has changed since the old guidelines were developed. S. Deshpande asked that the rationale document outline why a pesticide is being recommended for withdrawal. R. Charron gave a brief overview of what is to be included in the document.

Decision/Action:

- **For information.**

2-G Guideline development process

G. Carreau noted that a working group has been formed to review the guideline development process and assess opportunities for efficiencies that maintain the robustness of the science but streamline the length of documents and the internal approvals process so that the objective of five guidelines per year can be met. He indicated that additional details would follow at the fall meeting and asked members for their feedback. K. Philip indicated that all sections are important and valuable. P. Brooks indicated that jurisdictions, particularly the smaller ones, need access to the experts at Health Canada and the treatment applications that are used as these become the basis for provincial/territorial standards. M. Leblanc-Havard indicated that support from Health Canada is critical as drinking water is very important and the jurisdictions have very limited capacity. D. Reid noted that it is difficult for members to attend meetings and that under the existing Terms of Reference, Health Canada is to provide funding to support the Committee's activities. He also noted that he is hopeful the Canada Gazette process will help get information out faster so that the objective of five guidelines per year can be met. K. Gould expressed concern with the use of the word "efficiency". He questioned the goal of five guidelines per year if it compromises the quality of the documents. He noted that the timelines for the lead guideline were not typical. D. Reid indicated that looking at performance measurements for analytical methods, instead of specific methods, might save time. S. McFadyen noted that this initiative is staff-driven with the objective to do the best job possible. F. Lemieux re-iterated this point and indicated that the treatment group will complete a scoping exercise to assess what is critical for treatment and analytical considerations. H. Khan noted that the work done by this Committee is extremely important, especially for the small jurisdictions. He asked if a white paper would be prepared. G. Carreau clarified that the process is not intended to affect the scientific integrity of documents and that if the review finds that five guidelines per year cannot be met, the goal may need to be re-visited. K. Philip noted that Manitoba cannot use the analytical performance method suggested by Alberta. She indicated that efficiencies could be achieved by grouping parameters, for example, PFOS and PFOA should have been one document. Also, metals could

be grouped and other compounds that co-occur could be grouped. She suggested the use of less text and more tables. R. Charron indicated that some efficiencies have already been implemented, for example, the health sections are focused on the science and mode of action data that supports the key health endpoint on which the health-based value is based while only summarizing the science that doesn't directly support the key health endpoint. He indicated that the scoping assessment is another key step to help focus and streamline the health component of guideline technical documents early in the process. C. Robert indicated that this is not the first time this issue has been discussed. She indicated that the original goal was to reduce the length of pesticide guidelines but 2,4-D and atrazine are on hold so the Committee hasn't seen these documents yet. She noted that jurisdictions identify impacts after consultation documents are prepared, which can delay the process, and that jurisdictions need the health-based value earlier in the process to assess impact. She also indicated that sometimes the discussion on whether a guideline is needed is done too late in the process, after a lot of work has been done. S. Ferris indicated that support from Health Canada is vital and guideline development work is not the only support provided. He described a spill situation that occurred in Saskatchewan that shut down the water supplies for three cities. He indicated that the assistance provided by F. Lemieux and V. Morisset was very helpful. G. Carreau re-iterated that the expected outcome of the review is tweaks to the internal approval process while maintaining robust documents that meet the needs of members. He indicated water quality staff requested the review to ensure the sustainability of the program. K. Taracha asked if it is possible to get approved guidelines or documents out earlier. V. Morisset indicated that final documents are not published or considered final until Health Canada approvals are secured. G. Carreau indicated the review would confirm whether ministerial approval is necessary to publish guideline technical documents. K. Gould thanked G. Carreau for clarifying the intent of the review. He re-iterated that anything that can be done to get information to members sooner would be helpful. A discussion ensued on the role of CHE. G. Carreau encouraged members to forward any other suggestions.

Decision/Action:

- **Members to forward any other suggestions.**

3 Parameters: Microbiological

3-A Protozoa

T. Brooks and J. MacDonald gave a presentation. K. Gould noted that the text in the sample collection section has been changed to within the timeframe described by the method. He asked if the method provides a range. T. Brooks noted that the method does not specify 24 hours hence it was changed. C. Robert noted that the method specifies 72 hours. K. Philip asked whether sample collection was part of the analytical method. J. MacDonald indicated that sample collection requires clear communication between the lab and water utilities regarding how much water to sample, what filter to use, and other required steps. K. Philip asked whether lab accreditation includes sample collection. J. MacDonald indicated that labs generally do not take responsibility for sample collection and some labs will note when samples do not meet temperature specifications so that clients are aware that results may be compromised. A-M. Tugulea indicated that labs are not accredited for sample collection as there is no way to do it. J. MacDonald noted that it is the responsibility of the sampler and utility to understand how and where to collect the sample; utilities that choose to sample for protozoa are typically aware of sampling requirements. D. Reid noted that sampling is not included under a lab's scope of

accreditation. He indicated that anything to improve training and handling would be useful. K. Philip asked if labs provide the sampling methodology to clients. J. MacDonald indicated that information is provided if requested by the client and re-iterated that good communication between the lab, sampler and utility is required. K. Philip noted that the discussion regarding other protozoa of interest in the appendix indicates they are removed because of their size. She asked what happens when UV disinfection is used. J. MacDonald noted that the required UV dose to inactivate these microorganisms will need to be verified. C. Robert requested that the text regarding "subsurface sources", "groundwater" and "GUDI" be verified since, in some cases, "groundwater" was used where "GUDI" was expected. J. MacDonald noted that some studies did not indicate whether the sources had been assessed as secure groundwater or GUDI. It was suggested it might be better to use "subsurface sources" for these studies. C. Robert indicated that the document does not explain why microscopic particulate analysis (MPA) should be used and questioned whether this information was needed. J. MacDonald noted that chlorophyll-containing algae would be found through an MPA, so the text was drafted to ensure that jurisdictions using MPA considered chlorophyll-containing algae. C. Robert asked for the text to explain the relevance of MPA or to be deleted as it doesn't add useful information. J. MacDonald asked how chlorophyll-containing algae should be addressed as they provide unequivocal evidence of surface water influence. K. Gould asked if MPA should be done. P. Brooks indicated that the Yukon requires it as part of the GUDI assessment. C. Robert noted that Québec decided not to use MPA as it didn't provide additional information to their assessment process. J. MacDonald noted that an MPA test should never be done without completing the first two steps of a GUDI assessment hence the use of the text "for those jurisdictions using MPA". F. Lemieux suggested that text be added to explain that some jurisdictions may use MPA as part of a GUDI assessment. K. Taracha asked if the recommendations in section 5 regarding raw water analysis for *E. coli* and total coliforms had changed. T. Brooks answered in the negative. C. Robert asked for clarification regarding recovery in section 6.5. She noted that some publications indicate it is not good to correct for recovery. S. McFadyen noted that accounting for recovery is being encouraged, although she acknowledged that it is not always feasible to determine recovery for every sample. She further noted that if recovery isn't taken into consideration, concentrations of protozoa may be greatly underestimated. C. Robert suggested that the text be amended to say that "if you choose to account for recovery, the method should be recorded". S. McFadyen indicated this would be acceptable. C. Robert indicated that some corrections are needed for Québec data in Table 4. D. Reid noted that, with some areas considering recycling to potable water (direct potable water reuse), it may be necessary to consider monitoring protozoa in treated water in order to determine actual log reductions for a system.

Decision/Action:

- **C. Robert to provide corrected Québec data.**
- **Members approved the final document with changes.**

3-B Total coliforms

D. Medeiros gave a presentation. S. McFadyen noted that this update will not change the guideline statement. C. Robert asked for clarification on the public consultation process. V. Morisset indicated that the Secretariat is in process of clarifying what is required with the new Canada Gazette publication process. G. Carreau indicated that the annex will undergo a 60 day public consultation. D. Reid suggested that the updated information be an annex to the existing guideline technical document so it is clear that the two documents should be reviewed together.

Decision/Action:

- **For information.**

3-C Enterococci

G. Yasvinski gave a presentation. K. Philip asked if the false positives are related to all bacteriological methods or just enterococci methods. She also noted that there is no quantification of the false positives but the false negatives are quantified and labs are implicated in text. G. Yasvinski indicated he would verify the information and ensure a balanced discussion on the false-positive rates for enterococci and *E. coli*/total coliforms. S. Deshpande indicated the document needs a clear statement on how monitoring for enterococci is useful and whether it is a better indicator than *E. coli*. G. Yasvinski noted that this can be challenging because there are advantages and disadvantages. He indicated it is too early to say it is a better indicator. S. Deshpande indicated chlorine residual remains a good indicator. S. McFadyen noted that the body of evidence suggests that enterococci is beneficial for groundwater supplies but there is no demonstratable health argument to use it instead of *E. coli* hence the use of a guidance document format. K. Gould suggested highlighting the benefits regarding better survival and as a distribution system indicator. D. Reid indicated that *E. coli* and enterococci are universal indicators and they should complement each other not replace each other. He noted that enterococci is widely used for recreational water and water re-use applications. S. Ferris indicated that wastewater is required to test for enterococci for recreational water impacts but *E. coli* is also required. H. Khan noted that at the last meeting it was agreed that the document should elaborate on the benefits of using enterococci and the circumstances under which testing would be helpful. G. Yasvinski indicated that the benefits are for groundwater supplies and distribution system vulnerability. K. Gould asked if routine monitoring methods are able to differentiate between naturalized enterococci and enterococci from faecal sources. G. Yasvinski indicated that methods cannot distinguish the source of the enterococci. However, when isolates undergo further testing, most are faecal species. G. Yasvinski noted that *E. coli* can also have naturalized species, particularly though wastewater treatment. K. Gould asked for clarification regarding the term "naturalized" on page 6 of the document. G. Yasvinski explained that certain strains have adapted to survive for lengthy periods and are becoming part of the natural flora. K. Gould indicated that New Brunswick uses the AWWA standard for the distribution system but the document is suggesting that enterococci may be more valuable. F. Lemieux indicated she would check with AWWA to determine if they have included any enterococci requirements in the distribution system standard. K. Philip noted that naturalization introduces doubt about *E. coli*. She asked if faecal specificity is more of an issue for *E. coli* or enterococci. G. Yasvinski indicated genetic changes are occurring for both *E. coli* and enterococci. S. McFadyen noted that the strengths and benefits of *E. coli* need to be identified and the *E. coli* document is scheduled to be updated. K. Philip noted that the false negatives seem to be high. S. McFadyen indicated this would be verified. C. Robert noted that there is repeated text in the last paragraph of section A. She also indicated that section 3.3 notes that if delays are anticipated, on-site testing can be considered. She requested that text be added to check with the jurisdiction regarding the acceptability of on-site testing. K. Gould asked for clarification regarding the requirements for on-site testing. G. Yasvinski noted that enterolert tests are available which are similar to colilert tests.

Decision/Action:

- **Members approved the document for public consultation with changes.**

3-D Other microbiological

S. McFadyen provided a verbal update. An initial meeting has been held with NSERC to consider *Legionella* and building water management issues. Information is being considered including BC's sampling protocols and the WRF workshop communication materials which are aimed at different audiences. A number of green building studies have identified water quality issues and generally concluded that energy efficiency and water quality should be considered together. Regarding the National Drinking Water Conference, a de-brief occurred with Dalhousie University. They found it was too much work for an organization that doesn't normally do conference administration. AWWA has been suggested as an alternative. The conference will be discussed in more detail at the fall meeting. Another ongoing project includes the Alberta water re-use group. The recreational water guidelines are being updated with the focus of revisions on indicators and cyanobacterial toxins. C. Robert asked who else is partnering on the WRF *Legionella* project. S. McFadyen noted that the U.S. EPA and CDC are also involved. D. Reid asked if possible conference locations will be restricted to Ottawa. A discussion ensued on travel restrictions.

Decision/Action:

- **For information.**

4 Parameters: Chemicals

4-A Natural organic matter

J. MacDonald, G. Yasvinski and S.J. Payne gave a presentation. K. Philip asked what monitoring should be conducted. S. Deshpande asked what tools can be used to monitor NOM. J. MacDonald indicated that UV absorbance and dissolved organic carbon can be measured and then SUVA (specific UV absorbance) can be calculated. In the distribution system, chlorine residual and its variability, corrosion indicators and biofilm growth rate can be used. S. Deshpande asked whether operators can do this monitoring. J. MacDonald indicated that this is standard monitoring; new components would include UV absorbance and calculating SUVA. For biological stability, additional requirements for biofilm growth rate and corrosion may be needed. S. Deshpande indicated that small systems may find UV absorbance challenging. J. MacDonald noted that bench-scale units are relatively inexpensive; they cost $1,500.00. Small utilities in Nova Scotia have UV absorbance monitors. J. MacDonald noted that NOM is like ammonia because both should be monitored due to indirect health impacts. D. Reid indicated that NOM is not comparable to ammonia because ammonia includes a statement on toxicity. He suggested the document would be more appropriate as a white paper to inform stakeholders and prepare industry for future guidelines, then work towards developing other guidelines like colour, SUVA, total organic carbon. D. Fishwick asked if the Dutch approach of using biologically stable water could be used as a means to not use chlorine. F. Lemieux indicated that a clean distribution system is needed. J. MacDonald noted that this is associated with the 10 µg/L assimilable organic carbon (AOC) target set by the Dutch; in the Netherlands, they starve the microorganisms so they don't grow. J. MacDonald added that studies show that increased microbial growth is associated with increased organic content. D. Reid indicated that the context of the Dutch situation needs to be properly considered; their distribution systems were constructed 60 years ago and they apply a lot treatment to avoid the use of chlorine. J. MacDonald asked how members want to move forward – have a conference call or discuss the document at the next meeting. C. Robert asked members how much time they require to provide

comments. V. Morisset indicated that it would be helpful to know members' preference on the document format before the next meeting. D. Reid suggested the first week of September to submit written comments and input on format preference. G. Somers asked if specific questions needed to be responded to in the comments. V. Morisset indicated that, at a minimum, members should provide an indication of their preference for a guideline or guidance document. K. Philip asked for an electronic copy of the document to be sent to members. C. Robert concluded by requesting that members send written comments by September 1, including input on whether the document should be in guideline or guidance format.

Decision/Action:

- **Secretariat to send an electronic copy of the document to members.**
- **Members to provide written comments by September 1, 2017 and indicate their preference for a guideline or guidance document format.**

4-B Lead

J. Bourdon-Lacombe and F. Lemieux provided a verbal update D. Reid indicated that the labs in Alberta can measure lower concentrations, and that lab representatives have offered to assist the guideline development process. D. Reid indicated that the length of time it took to get the document out for consultation was an issue. S. Deshpande indicated that Public Health Ontario would prefer to maintain the current MAC with an ALARA statement. S. Deshpande noted that he met with the Ontario Municipal Water Association (OMWA); their understanding of the document is that no level is safe but the proposed MAC is 5 µg/L. He indicated they want to know what position this puts them in with respect to Ontario's regulated standard of care. F. Lemieux indicated that arsenic is similar. S. Deshpande indicated that arsenic is different as the document provides a health-based value but sets the MAC at 10 µg/L based on treatment achievability. S. Deshpande indicated the new section 10.2 may help but OMWA's concerns are difficult to address. K. Gould indicated that the duty of care is complicated in that the MAC is set for the consumer's tap but utilities don't typically measure water quality at consumer's taps. D. Reid indicated that similar problems were experienced in the UK; if an investigation determined that the exceedance was on the customer's side of the service, no violation was deemed to occur but the customer was advised of the issue. F. Lemieux indicated that guidelines take a source-to-tap approach; utilities should be delivering non-corrosive water and removing lead service lines. S. Deshpande indicated that consumer update for lead service line replacement is low even when the utility pays 100% of the cost. K. Philip raised issues related to the variability in random daytime sampling, communities with no lead service lines asking to be exempt from monitoring, others asking if they can use their pipe-loop to monitor water quality. The utilities are also asking if they are responsible for lead concentrations or corrosion control. J. Cooper summarized that concerns are not just related to the MAC but also the sampling method and location. K. Philip noted that if a home has a lead service line and the utility does not have corrosion control, the homeowner should be advised to use a point-of-use treatment device regardless of whether the MAC is 5 or 10 µg/L. K. Gould indicated that it is difficult to determine what is compliance – corrosion control or something else – and the economic impacts are unknown. He indicated utilities are asking who will pay for this. D. Reid indicated that random daytime sampling should not be used to determine household lead issues; for households, sequential first draw sampling is needed. F. Lemieux indicated that random daytime sampling helps characterize the system. A discussion ensued on how the responsibility to meet the lead guideline is shared between the utility and homeowner. A discussion ensued on the various sampling protocols and which ones

assess exposure to lead. S. Ferris indicated that Saskatchewan has been pushing the corrosion control document rather than the lead guideline. He indicated the focus has been on sampling at the tap but most small communities don't have lead service lines. S. Deshpande indicated that it is not clear what Table 10.1 in the new section 10.2 is trying to convey. He suggested adding the blood lead concentration and the reduced number of gifted children. G. Somers indicated that implementation is a provincial jurisdiction. K. Gould indicated that CDW can't endorse something that can't be implemented. K. Philip asked if compliance can be achieved by adding orthophosphate. A discussion ensued and it was concluded that lead service line replacement is preferred. H. Khan indicated that implementation concerns were raised during the public consultation. C. Robert agreed and noted that this was the first time Québec received calls from municipalities during a public consultation. C. Robert indicated that the sampling method is too prescriptive and requested more flexibility. K. Gould asked how lead sampling compared to copper. F. Lemieux indicated sampling protocols are similar but samples should be collected at different locations. K. Gould indicated that the lead and copper documents should be linked. K. Philip asked if all metals require random daytime sampling at the tap. F. Lemieux indicated that wording is being added to guideline technical documents where appropriate. J. Cooper asked if the text is flexible enough for jurisdictions. F. Lemieux indicated that the document specifies different sampling protocols depending on the objective of sampling. C. Robert indicated that the Québec approach is to identify lead service lines rather than exposure. F. Lemieux indicated that the document currently discusses two options for determining exposure, and identifies other methods for different objectives. She indicated she would follow up with C. Robert to ensure her concerns are addressed. G. Carreau asked how the Committee wants to move forward on the implementation issue. G. Somers suggested better describing the objective of the various sampling protocols. K. Gould indicated that New Brunswick is looking for a specific sampling protocol with recommendations on what to do to measure exposure and for a follow-up investigation. D. Reid suggested a regulators forum at a future meeting to discuss implementation issues. A discussion ensued and it was agreed that a half-day session would be scheduled at the next meeting to allow members to discuss lead sampling and implementation issues. C. Robert noted that Health Canada staff should also attend. K. Philip indicated that the issues go beyond implementation. She requested advice to answer questions related to who is responsible for sampling at a consumer's tap, particularly daycares, and whether communities that don't have lead service lines can be exempted for sampling. It was agreed that the fall meeting would include an extended session to discuss lead sampling/implementation issues, and that the lead document would be sent to members by early September. J. Cooper asked members to stay in touch with their CHE representatives.

Decision/Action:

- **Secretariat to send the revised document to members by early September.**
- **Secretariat to schedule a forum to discuss lead sampling/implementation issues as part of the next meeting.**

4-C PFOS/PFOA

S. Labib and N. Martinova gave a presentation. S. Deshpande raised concerns with the guideline and indicated he preferred the U.S. EPA approach. S. Labib noted that the U.S. EPA health advisory was reviewed, and that their approach includes a lot of uncertainty; in particular, the modelling assumed linearity and therefore accepted more uncertainty. S. Deshpande noted that the half-lives in humans are 3.5 and 5.5 years but 30 days in rodents. S. Labib noted that Health

Canada used modeling to account for this and that the highest half-life was used in the model. S. Labib noted that the contaminated sites group had a consultation document prepared and it included new science about PFNA. She indicated that the committee could consider this later. S. Deshpande indicated that he prefers to proceed with the U.S. EPA guideline of 70 ng/L for total PFAS due to uncertainty and the possibility that many of these substances may be present. S. Labib indicated that this was considered but there was no overwhelming reason to measure the other compounds at this time. S. Deshpande indicated that the hazard index approach considers contaminant mixtures due to spills otherwise the uncertainty isn't taken into account. He requested that the committee step back and acknowledge that other contaminants would be present because of a spill situation. J. Cooper noted that Canada is the only jurisdictions that will have a formal guideline therefore it is difficult to compare it to the U.S. EPA health advisory. He indicated that DND and Transport Canada have sites across Canada where PFOS and PFOA are likely to be found, and recommended that the committee move forward now on PFOS/PFOA while acknowledging that the science is evolving for other PFAS. He noted that guidelines are updated as new science becomes available. S. Deshpande indicated that due to the likelihood of finding a mixture of contaminants when PFOS/PFOA are detected, GAC treatment should be in place and monitoring should be done. F. Lemieux raised concerns with this suggestion. S. Deshpande re-iterated his concern that a contaminant mixture will be present when PFOS and PFOA are detected and his preference for one number for total PFAS. C. Robert indicated that her colleagues support the new section on additivity, however, she requested that the section titles be reviewed. C. Robert indicated that two references need to be fixed. The Chair asked whether members approve the final document. S. Deshpande responded that Ontario requires additional time to submit comments and requested another two months.

Decision/Action:

- **Ontario requires additional time to consider the document, and will provide comments to the Technical Secretariat within the next two months.**

4-D 1,4-Dioxane

S. Labib and A. Cherry gave a presentation. K. Gould asked why 1,4-dioxane is found in landfill leachate. A. Cherry indicated that it is present in consumer products and hazardous waste. S. Deshpande indicated past practices may also result in it being present. D. Reid asked that information on life stages be added. S. Labib indicated this has been done. A-M. Tugulea indicated that a national survey was completed on landfills. K. Taracha asked if the health-based value is based on life-time exposure. S. Labib answered in the affirmative. S. Deshpande requested clarification on the benchmark dose and asked what the impact would be of using the NOAEL. S. Labib indicated the health-based value would increase. S. Ferris asked if 1,4-dioxane is on the domestic substances list. S. Labib answered in the affirmative and indicated that a Chemicals Management Plan assessment was conducted in 2010. Members were requested to submit impact statements.

Decision/Action:

- **Members approved the document for public consultation.**
- **Members to submit impact statements.**
- **S. Labib to follow-up with A-M. Tugulea for the survey on landfills information.**

4-E Chloramines

M. Loos, S.J. Payne and G. Yasvinski gave a presentation. The document is scheduled to be presented to the committee for approval for consultation at the November 2017 meeting. C. Robert asked what the health-based value will be. M. Loos indicated it is likely to remain around 3 mg/L. D. Reid indicated that the document needs to link to precursors and NOM removal. He noted that water age can be upwards of 60 to 70 days in some locations and that re-chlorination can be challenging. A-M. Tugulea indicated that the research group has water quality data. C. Robert indicated that when chloramination is unintentional, larger tri-chloramine formation occurs. A discussion ensued on the need to consider tri-chloramine formation, its volatility in showers and chemistry impacts. A-M. Tugulea indicated that there are numerous locations where unintentional chloramination occurs in Canada. F. Lemieux indicated that the ammonia guideline technical document discusses this issue. A-M. Tugulea indicated that iodo- and brominated-disinfection by-products can be a concern with unintentional chloramination. C. Robert asked that it be clarified that chloramination is applicable when long distribution system retention times occur. F. Lemieux indicated this would be clarified. S. Ferris indicated there is a large number of systems with natural ammonia and other disinfection by-products. Members were reminded to submit water quality data if they have not done so already.

Decision/Action:

- **Members should submit water quality data if they have not done so already.**

4-F Barium

P. Hamel and N. Martinova gave a presentation. The document is scheduled to be presented to the committee for approval to consult at the November 2017 meeting. C. Robert asked what the health-based value would be and P. Hamel indicated that it is likely to go up. C. Robert asked why residential-scale drinking water treatment units are not certified to the existing guideline of 1 mg/L. F. Lemieux indicated that certification agencies were awaiting the outcome of the risk assessment. Members were reminded to submit water quality data if they have not done so already.

Decision/Action:

- **Members should submit water quality data if they have not done so already.**

4-G 2,4-D and atrazine

R. Charron provided a verbal update. He indicated that 2,4-D continues to be on hold and the forecast for publication of the PMRA risk assessment is sometime this year. Members were reminded that Norway prohibited the use of 2,4-D in 2000. S. Deshpande indicated that some additives may impact biodegradation. He asked if the risk assessment considers only the active ingredient or the adjuvant as well. F. Lemieux indicated that, based on her past experience at PMRA, they also consider the formulants, not just the active ingredient. J. MacDonald noted that the literature reports that 2,4-D is biodegradable and biological filtration will be included as a treatment option. A-M. Tugulea indicated that once the 2,4-D formulation is in water, 2,4-D separates from the surfactants and the volume of conditioning formulants is much higher than the active ingredient. A discussion ensued on how toxicity and environmental fate are considered by PMRA. It was agreed that R. Charron would contact PMRA to confirm how formulants are considered. C. Robert indicated that Québec received a request from PMRA for water quality data. She asked if other members received the same request. G. Somers and A-M. Tugulea noted that they received the same request. With respect to atrazine, R. Charron indicated that the risk

assessment remains on-hold pending the completion of PMRA's special review. He indicated that it is unknown when this review will be finalized.

Decision/Action:

- **For information.**

4-H Strontium

P. Hamel and N. Martinova gave a presentation. D. Fishwick indicated that the water quality data for British Columbia needs to be confirmed. P. Brooks asked how the MAC compares to the previously developed screening value. P. Hamel indicated that the MAC is higher. D. Reid indicated that more discussion is needed on the allocation factor. C. Robert noted that a 50% allocation factor is used for formula-fed infants but in section 5.2, tap water is discussed. She requested that this be clarified. C. Robert indicated that France has a strontium guideline of 18 mg/L (dated 2013) and this should be included in the international considerations. S. Ferris asked if northern diets were considered. He indicated young individuals can have calcium deficient diets. P. Hamel indicated that adolescents were considered but sub-populations such as northern youth were not specifically considered. A. Vezina asked if data is available. A discussion ensued on what information could be used to consider northern diets. M. Leblanc-Harvard offered to provide vitamin D data which could be linked to calcium deficiency. It was agreed that this information could be added at a later date. P. Hamel clarified that the key study used had low calcium consumption, so this would have been considered. S. Deshpande indicated that Public Health Ontario prepared a fact sheet on strontium. Members were requested to submit impact statements.

Decision/Action:

- **D. Fishwick to confirm British Columbia water quality data.**
- **M. Leblanc-Havard to provide Vitamin D data.**
- **Members approved the document for public consultation with changes.**
- **Members to provide impact statements.**

4-I Microcystins (recreational)

R. Charron provided a verbal update. The review of recreational water quality guideline has been initiated mainly to align it with the updated drinking water quality guideline on cyanobacterial toxins. A new working group has been established. C. Robert asked what the expected timeline is. T. Brooks indicated that the working group should have considered cyanobacterial toxins and indicators by sometime this fall. She indicated a staged approach is being taken to update the document. R. Charron noted that the U.S. EPA draft is currently out for consultation.

Decision/Action:

- **For information.**

4-J Other chemical

R. Carrier gave a verbal update. The following parameters are being worked on: boron, cadmium, aluminum and acrylamide. For THMs and HAAs, the problem formulation process confirmed that a full re-assessment is not necessary at this time. However, new science is available for HAAs. A mode of action analysis is being completed by I. Moffat for DCA and S. Labib is working on screening values for BCA and BDCA. D. Reid requested an update regarding the ATI request for the national drinking water survey (new agenda item). B. Koudjonou outlined that the water quality results from the 2009/2010 survey were provided to

municipalities and provinces and there has since been numerous ATI requests for the data. He indicated that municipalities and provinces were advised as part of the survey that location details would not be disclosed. His group has advised the ATI office that any details that would link test results to specific locations could not be disclosed unless they obtained permission from the affected municipalities and provinces. The ATI request has since been put on-hold pending clarification. B. Koudjonou requested permission from members to contact the participating municipalities regarding the possible publication of the water quality data. D. Reid asked for clarification. A discussion ensued and it was agreed that the original letters sent by the research team to seek permission to collect samples would be re-sent to members through the Coordinator.

Decision/Action:

- **Health Canada Research Group to send letters to the Coordinator.**
- **Coordinator to send letters to members.**

5 Secretariat projects

5-A Guidance for well owners

D. Medeiros gave a verbal update. She noted that members had sent her a variety of well-related resource materials and asked members whether they were aware of the resources available from other jurisdictions. She offered to share the compiled material and asked members for feedback. K. Philip indicated that it would be helpful to clarify how the recommended 4 log virus reduction applies to private well owners. K. Gould indicated that a guidance document, written at an appropriate reading level, that outlines sampling requirements and frequencies for microbial and inorganic requirements would be helpful; information on viruses would also be helpful. He indicated the document should holistically address the question – I have a well, what should I do? H. Khan asked what the objective and scope of the document is. D. Medeiros indicated this is the feedback she needs from members and that she would share the information collected. D. Reid also asked that discussions be held on what constitutes a small system in Canada. G. Somers indicated that this is a policy issue established by provinces/territories depending on what regulatory requirements apply to different sized systems. P. Brooks asked if any jurisdiction has a regulatory program for private wells. K. Taracha indicated that there are semi-public supplies that use private wells. G. Somers indicated that PEI has testing requirements for semi-public supplies. A discussion ensued on private wells. It was agreed that the information collected should be compiled, circulated and discussed at the next meeting. S. McFadyen noted that it would also be helpful to identify gaps and outline some questions for members. D. Reid suggested New Zealand's information was worth reviewing. K. Gould, C. Robert and D. Fishwick offered to help by providing the contact information for some of their staff.

Decision/Action:

- **Secretariat to compile and circulate information to members.**
- **K. Gould, C. Robert and D. Fishwick to assist as needed.**

5-B Research group update

B. Koudjonou provided a verbal update. It was noted that the research group tries to align its programs to the needs of the committee. Surveys and monitoring projects are now finished. Analytical methods for approximately 37 disinfection by-products have been updated in the past year, particularly nitrogenated-DBPs and iodo-DBPs. Other lab updates include the implementation of high resolution GC-MS and the resolution of situations where natural water

interferes with the analysis, such as for nitrosamines. A-M. Tugulea noted that the lab is exploring bio-analytical methods, as well as the analysis of complex mixtures. She indicated the lab is also taking steps to collaborate with scientists in the United States on a Water Research Foundation proposal on bromide, iodide and disinfection by-products. She indicated that she may be in touch with Québec and Alberta for potential sites for the proposal. B. Koudjonou and A-M. Tugulea thanked members for their support in the past. C. Robert asked if the national water quality survey results have been presented in any way. B. Koudjonou noted that it was decided at the time of the survey that no report would be prepared because scientists would publish articles. A-M. Tugulea noted that aggregate data has been shared on demand with provinces and other Health Canada groups and that an article is in preparation. B. Koudjonou indicated that the research group is now considering making the data available in a report. The survey measured more than 100 compounds some of which have no toxicological data. A discussion ensued on a study conducted by Alberta and whether it measured brominated-DBPs. D. Reid agreed to share the Alberta study.

Decision/Action:

- **D. Reid to share Alberta water quality survey results.**

5-C INAC update

K. Carisse gave a verbal update. The Act came into effect in 2013. Activities are currently on-hold pending a review of the legislation. A discussion ensued on progress and timing.

Decision/Action:

- **For information.**

6 Committee Liaison Reports

6-A First Nations and Inuit Health Branch report

K. Taracha provided a verbal update. FNIHB is planning to develop harmonized national risk communication materials when THMs exceedances are reported, including a pamphlet targeting community residents and a template notifying letter. A question and answer document is also being developed. FNIHB is updating its lead monitoring protocols for drinking water in schools and children's facilities in First Nations communities with input from water quality staff to ensure consistency in methodology and approach. Sampling is scheduled to begin next spring if the lead guideline is approved. Members were thanked for the assistance provided to help FNIHB develop policy options for monitoring lead in individual homes in First Nation communities. K. Philip noted that Manitoba is coordinating with FNIHB regarding THMs and lead.

Decision/Action:

- **For information.**

6-B World Health Organization report

R. Carrier provided a verbal update. The Chemical Aspects Working Group is considering specific chemicals that need to be updated. Manganese will be updated using Health Canada's recent assessment as the main source of information. The United Kingdom will lead the update and Health Canada will provide support. Chromium will be updated using Health Canada's 2015 assessment and the European Food Safety Authority (EFSA) 2014 information. With respect to PFOS/PFOA, the WHO review will consider the approaches used by Health Canada and U.S. EPA. For bromate, Health Canada used a non-threshold approach but there is more evidence to

go with a threshold approach. A mode of action study has been funded that would allow a threshold cancer approach to be used. TCE is based on Health Canada's 2003 guideline. Italy will lead the update using more recent evidence from the U.S. EPA. Italy will lead the update on tetrachloroethylene, using the approaches from both Health Canada and the U.S. EPA. C. Robert asked what the timeline is. R. Carrier indicated that manganese and chromium are expected this fall while bromate will await the mode of action publication.

Decision/Action:

- **For information.**

6-C CHE report

P. Workman reported that the CHE Terms of Reference are being updated. The next meeting is tentatively scheduled for June but it may be deferred to the fall. A discussion ensued on the proposed Terms of Reference and CHE's mandate. It was agreed that P. Workman, G. Carreau and V. Morisset would discuss the concerns raised by CDW and clarify the CDW-CHE relationship for the CHE Terms of Reference.

Decision/Action:

- **P. Workman, G. Carreau and V. Morisset to discuss the CHE Terms of Reference update and concerns raised by CDW.**

6-D CCME report

P. Cureton provided a verbal update. She noted that Environment Canada develops guidelines for two areas: 1) federally to support chemical management plan risk assessment/management and for contaminated sites; and 2) to support the CCME water management committee and the soil quality task group. Water priorities include improving water quality and water quantity management and adaptation to climate change. A new initiative of both the water and soil management groups is to streamline guideline development and publication processes to improve timelines. Substances being reviewed for water quality guidelines include carbamazepine and zinc; both are awaiting publication of the final technical document. Manganese has undergone peer review and comments are being addressed. Guidance for the application of the groundwater sustainability approach has been published. Guidance for alternate water quality parameter assessment where no CCME guideline exists is awaiting publication. To support this exercise, the 2012 database of guidelines has been updated. Over 11,000 entries from 38 jurisdictions for 11 media (air; surface water – fresh, brackish and marine; groundwater; sediment – freshwater, marine; soil; soil solution; soil vapour; wildlife tissue) have been verified. Changes are in translation. Soil quality task group activities are geared to increase jurisdictional capacity to manage contaminated sites. When groundwater is contaminated, the guideline value is taken directly from the Guidelines for Canadian Drinking Water Quality. With respect to soil quality guidelines, methanol, zinc and PFOS are undergoing internal review. Soil vapour guidelines are under development using 2015 protocols. Guidance for soils includes the national classification system which was published in February 2017. Guidance for ecological risk assessment is in the queue for translation. Guidance for the management of contaminated sites located in permafrost is being prepared in phases. Phases 1 and 2 are completed and awaiting publication. Phase 3 involves a request for proposal phase to assess the applicability of environmental quality guidelines in permafrost given differences in transport mechanisms. Guidance is also being developed for the re-use of excess or treated soil. Phase 1 and 2 involves a literature review and

best management practices. Phase 3 involves stakeholder consultation to develop consistent guidance.

Decision/Action:

- **For information.**

7 Members' Reports

Each jurisdiction provided a report on its program and legislative activities, training and outreach programs, publications and current key issues. Written reports were provided by Ontario, Québec and Saskatchewan. The Nova Scotia member provided a written report by email for the minutes.

Alberta

D. Reid indicated that joint regulations were out for public consultation in 2015 but Health has decided to proceed with its own regulations.

British Columbia

D. Fishwick provided an update on activities.

Manitoba

K. Philip indicated that requirements for system assessments have been revised to include checklists and/or work to be completed by qualified persons. The HAAs guideline has been adopted. The province is assessing how to manage lead and a working group is looking at monitoring requirements.

New Brunswick

K. Gould indicated that day-to-day activities are proceeding as usual and no new activities have been initiated.

Newfoundland and Labrador

H. Khan indicated that the environmental assessment process is being reviewed and the climate change action plan is being updated. The drinking water safety annual report was released. New water use fees are being implemented. The government announced a new structure on February 22 and the Department of Environment and Conservation has been combined with Municipal Affairs.

Northwest Territories

P. Workman indicated that a database of microbial and chemical water quality results has been developed for internal use and data can be provided to the public upon request. The database also allows problems to be identified more quickly. Automatic data harvesting will be considered later.

Nova Scotia

On April 27th, Executive Council approved the changes to the Water and Wastewater Facilities and Pubic Drinking Water Supplies regulations to amend the definition of a public drinking water supply to address a loophole. More changes to the definition are proposed for 2018 to address several additional issues raised during internal consultation (e.g. the requirement for workplaces and waterline associations to register as a public drinking water supply). Nova Scotia

Environment (NSE) is planning a targeted consultation with water testing labs in June to determine the potential impact of requiring labs to report exceedances of health-related parameters at public drinking water supplies to NSE. NSE also plans to add a requirement that all public drinking water supplies must have their water tested at an accredited lab that meets the Policy on Acceptable Certification of Labs. This requirement is currently referenced in guidelines but NSE lacks the regulatory authority to enforce it. NSE is in the process of revising the Guidelines for Monitoring Public Drinking Water Supplies. Some changes include: revising the process for issuing a boil advisory at municipal systems to no longer require a boil advisory for a single presence of *E.coli* in the absence of any treatment or distribution system failure; and revising the process for removing a boil advisory to no longer require two samples separated by a minimum of 24 hours showing the absence of total coliform/*E.coli* bacteria, if the advisory is not issued due to the presence of bacteria. For registered systems, we are revising the process for issuing do not consume advisories to no longer automatically issue an advisory for an exceedance of a health-based guideline without input from the provincial Medical Officers of Health (MOH). In July, we are returning to our Executive Policy Committee (EPC) to get direction on a strategy to align treatment at registered supplies based on risk of waterborne disease. From our last EPC meeting on the topic, we have piloted the business impact assessment tool with the Office of Regulatory Affairs and Service Effectiveness, conducted a pros and cons analysis of non-regulatory policy options and gathered additional evidence to support the need for treatment. Regarding lead, we prepared the business case to have Dalhousie University's Centre for Water Resource Studies perform lead sampling at several municipal facilities throughout the province. This has been submitted to the Deputy Minister for approval. NSE continues to work with municipal utilities on the protection of their source water. The 26th protected water area in Nova Scotia was designated (the Davidson Lake Watershed Protected Water Area) with associated regulations in April. Several other protected water area regulations were also revised. NSE and the Department of Natural Resources (DNR) collaborated on the development of a private wells drought risk map. NSE also participated on the CCME Groundwater, Surface Water Science Integration/Awareness Project.

Nunavut

M. Leblanc-Havard indicated that work continues on the Public Health Act and drinking water continues to be a priority. Preliminary activities include revising the drinking water program with Dalhousie University. More complex water treatment plants are being constructed so a curriculum for operator training is being developed. The "hedgehog" system has been implemented for the inspection program.

Ontario

S. Deshpande noted that the first Great Lakes progress report outlines some of the key accomplishments achieved to date under Ontario's Great Lakes Strategy and highlights important new scientific research that points to the vulnerability of the Great Lakes and the need to continue to invest in science and monitoring. Continued commitment to Great Lakes research includes assessing contaminants and monitoring algal blooms. Ontario is working with First Nation communities and the federal government to help deliver on the federal commitment to eliminate long-term drinking water advisories on reserves within five years. A new office (Indigenous Drinking Water Projects Office) has been created. Beginning December 16, 2016, Ontario has put in place a two-year moratorium on new or expanded water takings from

groundwater by bottling companies, as well as stricter rules for renewals of existing permits. Ontario is consulting on: new standards for toluene, ethylbenzene and xylenes; updating the standards for selenium and tetrachloroethylene; and, revoking a redundant standard for nitrate+nitrite. A new approach for assessing pesticides in treated water was introduced (see item 2-F). The "Open Data" initiative to ensure public access to data has been launched.

Prince Edward Island
G. Somers indicated that the draft Water Act has undergone extensive public consultation and it may be announced next week in the House. The draft Act proposes that water be a collective, common good. If approved, the focus will move to existing and new regulations, and policies.

Québec
C. Robert indicated a Bill was adopted at the end of March for the modernization of the Environment Quality Act. One of the key features is a reform of the authorization scheme, simplifying and modulating the authorization process based on environmental risks. It is expected to reduce substantially the number of authorizations delivered and, for projects considered at low risk for the environment, replacing authorizations with a declaration of compliance. Low risk projects include extensions of distribution systems. It could eventually mean less work for the ministry. The ministry has one year to implement the changes which involves modifying many regulations, all tools, and creating a new public registry. In the recent provincial budget, $37 M was announced for municipalities over the next five years to support their work related to source water vulnerability assessments, and to compensate farmers affected by protection measures around wells, required by a recent regulation. Also, $9 M was announced over the next five years to develop knowledge regarding groundwater resources. Previous projects had developed knowledge for around 75% of southern Quebec, the goal is to have the remaining 25% covered. It will also probably include some special projects, one on Magdelen Islands and one in northern Quebec. The ministry is about to publish a best practice manual on how to determine well protection zones and their vulnerability level, as well as a guidance manual on what to include in a hydrogeological study for a well.

Saskatchewan
Saskatchewan continues with implementation of *The Waterworks and Sewage Works Regulations* that took effect in Saskatchewan on June 1, 2015. Progress to inform waterworks upgrading to meet the various Canadian guidelines adopted as standards by the provincial regulations is being made. Some effort to re-examine the opportunities for regional waterworks is also getting underway within the province based on efforts between the Saskatchewan Water Security Agency, Saskatchewan Ministry of Government Relations and SaskWater (a provincial Crown Corporation that provides drinking water and wastewater related services). Saskatchewan is currently undertaking a review of its 2002 Long-Term Safe Drinking Water Strategy as a means to inform what revisions or updates may be appropriate given that 15 years has elapsed since the strategy was released in early April 2002. We will also be integrating any recommended drinking water related key actions and initiatives within the second round of the provincial 25 Year Water Security Plan expected later this year. As a result, updates to the provincial regulatory framework for drinking water could proceed to conclusion within the next two years.

Yukon
P. Brooks indicated that the Yukon is receiving feedback on revised regulations for small drinking water systems. Work continues on other initiatives and regular inspection.

Decision/Action:
- **For information.**

8 Meetings

8-A Future Meetings
Members discussed future meeting dates.
Decision/Action:
- **Fall 2017: November 7-9, 2017**
- **Spring 2018: May 1-3, 2018**
- **Fall 2018: November 6-8, 2018**

The next meeting is expected to include a focused session on lead with presentations from Ontario and Québec on their lead sampling/implementation programs. An update on the CNPHI advisory tool was also requested. The Coordinator reminded members that if they have an urgent request, to please copy V. Morisset and G. Carreau.

The meeting adjourned at 3:45 p.m. on May 4, 2017.

2 Agenda/Meeting

2-C CDW status/checklist

Reference/Action:

- Oral presentation on the status of guideline/guidance documents
- Verbal update on the record of decision and checklist of action items
- Attached, record of decision sorted by subject
- Attached, checklist of action items from the May 2017 meeting
- Provided at meeting, CDW parameters status list
- For information only

Notes:

CDW Date	Subject	Decision
2017-05	1,4-Dioxane	Members approved the document for public consultation.
2011-05	Ammonia	• Secretariat to make links between the ammonia document and the nitrate/nitrite document • Operational considerations to be removed from the guideline statement • Public consultation to be done at the same time as the nitrate/nitrite document
2013-05	Ammonia	• Members approved final document
2010-05	Bacteriological	• Secretariat to set up a working group meeting for June 2010.
2012-02	Bacteriological - *E. coli* & total coliforms	• Members approved by consensus e.coli and total coliforms documents with discussed changes on a conference call, Feb 14th, 2012
2010-11	Bacteriological - *E.coli*	• Members agreed to go forward with enzyme-based methods are 'recommended' and see what feedback comes back. • Members approved the E.coli document for public consultation.
2011-05	Bacteriological - Emerging	• Members approved the document in principle for consultation with minor adjustments to text to be made by Secretariat.
2016-10	Bacteriological - Enterococci	Members approved moving forward as a guidance document.
2010-05	Bacteriological - HPC	• Members approved document for a two month public consultation. • Secretariat to add a note in the consultation package asking participants to copy their comments to their provincial CDW rep.
2011-11	Bacteriological - HPC	• Members approved document with discussed changes
2016-10	Bacteriological - QMRA	Members approved the document for public consultation.
2010-11	Bacteriological - Total coliforms	• Members approved the document for public consultation in principle. The Secretariat to make changes and circulate the document for final approval.
2015-05	Bacteriological - Total coliforms	• Members approved moving forward with a guideline technical document for total coliforms with a MAC.
2016-10	Bacteriological - Total coliforms	Members approved moving forward with re-affirmation and targeted consultation.
2012-10	Bacteriological - WBP	• Members approved document in principle, awaiting confirmation from Quebec. The approval from Qc was received one month after the meeting by email (Nov 2012).
2013-11	Benzo(a)pyrene	• Members approved the document for consultation with the modified purpose of consultation
2014-05	Benzo(a)pyrene	• Members approved the document in principle with proposed changes for public consultation.
2015-11	Benzo(a)pyrene	• Members approved the final document.
2013-11	Boil Water Advisories	• Members approved the document, amended as discussed, for consultation. Secretariat to work with C Robert on wording changes.
2014-10	Boil Water Advisories	• Members approved the document in principle for publication.

CDW Date	Subject	Decision
2014-10	Bromate	• Members approved the document in principle for public consultation.
2016-05	Bromate	• Members approved the final document with minor corrections noted in the meeting
2010-05	Carbon Tetrachloride	• Members agreed to approve the document for publication.
2013-05	CDW Administration	• Members agreed to contribute to the cost of providing light refreshments at meetings.
2014-05	CDW Administration	• Secretariat to maintain the collaboration centre on CNPHI for CDW use
2012-05	CDW collaborating centre	• Members agreed to try using CNPHI as a tool for CDW communication, especially as an archive and a place for approved documents. Alternates and CHE reps will have access, as will working group members who are not CDW members (to appropriate sections only).
2010-11	CDW Stuff	• Members agreed that the conference is a venue for presentations. The committee is a
2014-10	Chromium	• Members approved the document in principle for public consultation.
2015-11	Chromium	• Secretariat to circulate the document for final CDW approval when ready. A conference call will be convened, if needed, to obtain final CDW approval
2016-01	Chromium	• Members approved the final document via email (11 of 13 jurisdictions responded)
2016-10	Copper	Members approved the document for public consultation with minor changes.
2011-11	Cyanobacterial Toxins	• Members agreed to rolling revision of the guideline technical document • Secretariat to draft letter to jurisdictions alerting them to the need to review the guideline and that in the meantime, the recommendation is to test for total microcystins
2015-05	Cyanobacterial Toxins	• Members approved the document for public consultation in principle, subject to the changes noted at the meeting.
2016-10	Cyanobacterial Toxins	Members approved the final document subject to minor changes
2011-05	DBPs publication	• Members agreed on need to develop a plan of action to address false or misleading clains regarding Guidelines
2010-11	DCM	• Members approved the guideline with a MAC of 0.05 mg/L.
2012-05	Dichloroethane 1,2-	• Members approved the document for a two month consultation. • Members agreed that no impact paragraphs are needed since the proposed guideline value
2013-11	Dichloroethane 1,2-	• Members approved the guideline for publication.
2016-10	Dioxane, 1,4-	Members approved moving forward with a guideline document.
2010-05	Election of Chair and Vice-Chair	• Members elected J. MacDonald as Chair and C. Robert as Vice-Chair.
2014-05	Election of Chair and Vice-Chair	• Members elected S.Ferris as Chair and C.Robert as Vice-Chair.

CDW Date	Subject	Decision
2016-05	Election of Chair and Vice-Chair	• Members elected C. Robert as Chair and K. Gould as Vice-Chair.
2010-11	Enteric Viruses	• Secretariat to send revised document with highlighted changes to members. • Members to review the changes in the document by email.
2016-05	Enteric Viruses	• Members approved the document for public consultation in principle, subject to revisions.
2016-10	Enteric Viruses	Members approved the document for public consultation subject to the requested changes being made.
2013-11	Enterococcus	• Members asked Secretariat to pursue option 2 (develop more formal guidance on the use of
2015-05	*Enterococcus*	• Members approved moving forward with a guideline technical document for *enterococcus*.
2017-05	Enterococcus	Members approved the document for public consultation with changes.
2010-11	Fluoride	• Members approved the document.
2010-05	Future meetings	• 2010 Fall - Saskatoon, Nov 3,4,5 (National Conference Oct 30 - Nov 2) • 2011 Spring - Ottawa, May 4,5,6
2012-05	Future meetings	• Next meeting in Kelowna - October 2012 • May 2013 - Ottawa
2013-11	Future meetings	• April 30 - May 2, 2014 Ottawa • Oct 30 – 31, 2014 Ottawa (after National Conference) – members requested to start the
2014-05	Future meetings	• Spring 2015: May 6-8, 2015 in Ottawa
2014-10	Future meetings	• Spring 2015: May 6-8, 2015 in Ottawa, Fall 2015: November 4-6, 2015 in Ottawa
2015-05	Future meetings	• Fall 2015: November 4-6, 2015 in Ottawa; • Spring 2016: May 4-6, 2016 in Ottawa with possible workshop
2015-11	Future meetings	• Spring 2016: May 4-6, 2016 in Ottawa with possible lab or treatment plant tour; • Fall 2016: October 19-20, 2016 (conference October 16-18, 2016); • Spring 2017: May 3-5, 2017
2016-05	Future meetings	• Fall 2016: October 19-20, 2016 (conference October 16-18, 2016); • Spring 2017: May 3-5, 2017; • Fall 2017: November 8-9, 2017
2016-10	Future meetings	Spring 2017: May 3-5, 2017;
2017-05	Future meetings	Fall 2017: November 7-9, 2017; Spring 2018: May 1-3, 2018; Fall 2018: November 6-8, 2018
2012-05	Guideline booklet	• Members agreed the guideline booklet should be published as a companion to the summary table.
2016-10	Guideline development process	Members agreed to begin discussing economic impacts as early as possible in the guideline
2015-11	HAAs	• Secretariat to draft problem formulation
2015-05	Hydraulic fracturing	• Hydraulic fracturing to remain as a standing item on the agenda.
2015-05	Lead	• Members approved the document in principle for public consultation, subject to the above noted changes being made.
2015-11	Manganese	• Members approved the document for public consultation subject to discussed changes
2016-11	Manganese	Members approved the document (by email) for posting
2014-10	Minutes	• Members approved changing the name of the "notes" to "minutes". Members agreed with the
2010-05	Monitoring Framework	• Members to provide comments on the monitoring framework by May 31. P Brooks to provide
2010-05	National Drinking Water	• The next National Drinking Water Conference is Oct 30 to Nov 2, 2010.
2013-05	National Drinking Water Conference	• Members agreed to change location of next conference to Ottawa
2010-11	NDMA	• Members approved the document in principle, with the understanding that members will see Appendix 2 before it is posted.
2011-05	Nitrate / Nitrite	• Members approved the document for public consultation in principle, subject to the
2011-07	Nitrate / Nitrite	• Members approved document in principle for public consultation with discussed changes on
2011-09	Nitrate / Nitrite	• Members approved document for public consultation with discussed changes on a conference call, Sept 21st
2012-05	Nitrate / Nitrite	• Members approved the document in principle for consultation.
2013-05	Nitrate / Nitrite	• Members approved final document pending minor changes
2015-11	Old guidelines	• Secretariat will move forward with the proposed approach for the path forward for old guidelines and will prepare a draft consultation document for the May 2016 meeting
2012-10	Other Chemical / Radiological	• Members agreed the Technical Secretariat should develop the benzo(a)pyrene guideline technical document (even if lower on priority list)
2014-10	Other Chemical / Radiological	• The members approved the following parameters for the priority list: strontium, chloramines, 1,4-dioxane, barium and cadmium.
2013-01	Overarching microbiological document	• Conference call Jan 15th: Members approved the document in principle with discussed changes
2014-10	Pentachlorophenol	• Members approved withdrawing the guideline and removing it from the priority list.

CDW Date	Subject	Decision
2015-11	PFOS and PFOA	• Members approved the PFOS and PFOA documents for public consultation
2017-05	PFOS and PFOA	Ontario requires additional time to consider the document, and will provide comments to the Technical Secretariat within the next two months.
2014-05	pH	• Members approved the document in principle with proposed changes for public consultation.
2015-05	pH	Members approved the document in principle for publication, subject to the above noted
2010-05	Priority List	• (B)TEX to be listed as one document/one priority. • Members agreed on the following priority list:
2011-05	Priority List	• Members declined to put sodium higher on the priority list
2014-05	Priority list	• Members approved the priority list.
2014-10	Priority List	Members approved waiting for the IRIS assessment before beginning work on arsenic.
2015-05	Priority List	Members agreed switching the priority of aluminum and cadmium.
2015-11	Priority List	s-metolachlor will be included in the next prioritization exercise
2011-11	Protozoa	• Members approved the document by concensus
2015-11	Protozoa	• Members approved the document for public consultation
2017-05	Protozoa	Members approved the final document with changes.
2014-10	Regulatory Frameworks	• Sub-committee to scope the discussion for a special meeting in May 2015 to compare
2014-05	Safe Drinking Water for First	• Safe Drinking Water for First Nations Act is to be kept as a standing agenda item for CDW
2012-10	Selenium	• Members agreed that the guideline should be for total selenium • Members approved the document for public consultation, with the changes discussed.
2013-11	Selenium	• Members approved the document in principle if MAC value remains as proposed. Secretariat
2017-05	Strontium	Members approved the document for public consultation with changes.
2011-11	Summary table	• Members agreed that the new summary table should replace the summary table currently on
2012-10	Tetrachloroethylene	• Members approved approach taken to develop the guideline.
2013-06	Tetrachloroethylene	• Conference call June 18th: Members approved the document for consultation in principle
2014-10	Tetrachloroethylene	Members approved the document in principle for publication.
2012-10	TEX	• Members agreed the Technical Secretariat should proceed with developing the document as
2013-06	TEX	• Conference call June 18th: Members approved the document for consultation in principle
2014-05	TEX	• Members approved the final document.
2014-10	Trihalomethanes	• Members approved the amended document in principle.
2015-11	Trihalomethanes	• Secretariat to draft problem formulation by May 2016
2010-05	Turbidity	• Secretariat to make links to turbidity in the distribution system more prominent, provide
2010-06	Turbidity	• Members approved the document for public consultation on a conference call.
2012-05	Turbidity	• Members agreed to use the wording "health-based treatment limits" rather than MAC since turbidity is not measured as a concentration. Secretariat to revise document accordingly.
2012-09	Turbidity	• Members approved by consensus the document on turbidity with discussed changes for final posting on a conference call, September 18th, 2012
2016-05	Uranium	• Members approved the document for public consultation.
2016-10	Uranium	Members approved the guideline technical document for public consultation, re-affirming the
2011-11	Vinyl chloride	• Members agreed with including ALARA in the guideline statement • Secretariat to add consideration about age of pipes in distribution system to the document

CDW meeting May 2017 - action items

Item	Action Item	Status/comment
1 Opening	Members to update the membership list	Done
2-B Minutes	K. Philip noted that in section 4E, the reference to lead and copper "exposure" should be changed to "monitoring and sampling collection methods".	Done
2-G Guideline development process	Members to forward any other suggestions on potential efficiencies in the guideline development process.	Done
3-A Protozoa	C. Robert to provide corrected Québec data.	Done
4-A Natural organic matter	Secretariat to send an electronic copy of the document to members.	Done
	Members to provide written comments by September 1, 2017 and indicate their preference for a guideline or guidance document format.	Done
4-B Lead	Health Canada staff to address public consultation comments.	Done
	Secretariat to send the revised document to members by early September.	Done
4-C PFOS/PFOA	Ontario requires additional time to consider the document, and will provide comments to the Technical Secretariat within the next two months.	Done
4-D 1,4-Dioxane	Members to submit impact statements.	Done
	S. Labib to follow-up with A-M. Tugulea for the survey on landfills information.	Done
4-E Chloramines	Members should submit water quality data if they have not done so already.	Done
4-F Barium	Members should submit water quality data if they have not done so already.	Done
4-H Strontium	D. Fishwick to confirm British Columbia water quality data.	Done
	M. Leblanc-Havard to provide Vitamin D data.	Done
	Members to provide impact statements	Done
4-J Other chemical	Health Canada Research Group to send letters to the Coordinator.	Done
	Coordinator to send letters to members.	Done
5-A Guidance for well owners	Secretariat to compile and circulate information to members.	Done
	K. Gould, C. Robert and D. Fishwick to assist as needed.	On-going
5-B Research group update	D. Reid to share Alberta water quality survey results.	Done
6-C CHE report	P. Workman, G. Carreau and V. Morisset to discuss the CHE Terms of Reference update and concerns raised by CDW.	Done

8-A Future Meetings	The next meeting is expected to include a focused session on lead with presentations from Ontario and Québec on their lead sampling/implementation programs.	On the agenda for fall meeting
	It was requested that Tim Beattie present on update on the CNPHI advisory tool.	On the agenda for fall meeting

2 Agenda/Meeting

2-D Prioritization process

Reference/Action:

- Verbal update on the prioritization process for guideline development that is underway
- Attached, prioritization process overview
- For information only

Notes:

October, 2017

Prioritization process overview

In Canada, the responsibility for ensuring the safety of drinking water supplies is shared by the various levels of government, with provinces and territories having primary responsibility. Health Canada works in collaboration with all provinces and territories, through the Federal-Provincial-Territorial Committee on Drinking Water (CDW), to develop the *Guidelines for Canadian Drinking Water Quality*. These guidelines are used by every jurisdiction in Canada as the basis to establish their drinking water quality requirements. There are over 100 guidelines already established, and work is on-going to develop new guidelines or update existing ones.

As microbiological contaminants may pose an immediate and acute risk to health, and because the science behind these guidelines is continuously evolving, the guidelines for these parameters are reviewed on a rolling, four-year cycle. For chemical, physical and radiological parameters, priorities for guideline development are determined by the CDW and take into consideration several factors.

Prioritization process (chemical, physical and radiological)

A comprehensive, systematic prioritization exercise is conducted approximately every 4 years (i.e., 2005, 2009, 2013, 2017). This multi-step process incorporates:

1. Establishing health-based priorities:
    a. Health Canada staff create an initial list of substances that need to be reviewed, using a variety of information sources. This includes substances for which the science is rapidly evolving (e.g., PFAS, arsenic, manganese, lead); contaminants with guideline/guidance older than 6 years unless an assessment is already underway, or for which screening values have been requested by more than one jurisdiction; relevant pesticides (i.e., that could be found in water), based on information from PMRA and international organizations; contaminants identified through CMP, ECCC environmental water quality data, new water health risk assessments (completed or on-going) from leading international organizations (e.g., WHO, U.S. EPA, EU and Australia); and substances identified by provinces, territories or other federal departments.
    b. The list is provided to an expert consultant under contract with Health Canada. Their role is to review the scientific literature and develop a comprehensive spreadsheet of the relevant information, focusing on any new or emerging science on health effects, and including international guidelines and standards for each substance. *In 2017, we provided a list of 145 substances to the consultant.*
    c. Health Canada staff uses the consultant's spreadsheet to identify the substances that would be the top health priorities for guideline development.

2. Establishing priorities based on treatment and analytical considerations:
    a. A list of the top 10–20 health priorities is provided to a different expert consultant specializing in water treatment, for their review and input related to analytical considerations and municipal and residential treatment options. *This is dependent on funding for the 2018-2019 fiscal year. As this work only occurs every 4 years, it is not part of our normal funding envelope...*
    b. Health Canada staff uses the consultant's review to identify the substances that would be the combined priorities for guideline development.

3. Establishing priorities for provinces and territories: Provinces and territories are asked to rank parameters based on exposure and needs for each jurisdiction.

4. Establishing the priority list:
    a. All the information gathered is used to create the draft priority list, which incorporates priority ratings for health, analytical/treatment, as well as needs and exposure for each province and territory.
    b. The list is shared with CDW prior to their meeting as the basis for the final priority-setting discussion for chemical, physical and radiological parameters. *For the current exercise, this would be discussed by CDW either in the fall of 2018, or the spring of 2019.*

Developing CDW's 5-year workplan

Finally, the newly identified chemical priorities and the microbiological priorities (based on their 4-year rolling revision) are combined to establish the priorities for guideline development and CDW's 5-year workplan.

In addition to this formal exercise, CDW discusses priorities at each of their bi-annual meetings in order to take into account emerging science and needs and may adjust its workplan to address an emerging issue.

Criteria for guideline development

In general, guidelines would only be established for chemical substances that may lead to adverse health effects at levels that could be found in drinking water and in a large number of drinking water supplies throughout Canada. Microbiological priorities are based on representative and indicator organisms.

2 Agenda/Meeting

2-E Terms of Reference

Reference/Action:

- Verbal update on the CDW Terms of Reference
- To be sent prior to meeting: Copy of the current CDW TOR, with proposed revisions highlighted
- CDW to discuss

Notes:

2 Agenda/Meeting

2-F Guideline development process

Reference/Action:

- Oral presentation on the proposed approach to improve the guideline development process
- For information only

Notes:

2 Agenda/Meeting

2-G Withdrawal of old guidelines

Reference/Action:

- Verbal update on the status of the withdrawal of old guidelines
- For information only

Notes:

3 Parameters - Microbiological

3-A Total coliforms

- Oral presentation on the draft appendix to the guideline technical document on total coliforms
- Status: The work on the total coliforms guideline technical document was initiated in August 2016 to update the science. The document is being updated through the creation of an appendix. The appendix went through internal and external peer-review processes in the summer of 2017. Comments from peer-reviewers were considered and the appendix revised accordingly.
- To be sent prior to meeting: Draft appendix to the guideline technical document on total coliforms
- For CDW approval

Notes:

3 Parameters - Microbiological

3-B Bacteriological - HPC

Reference/Action:

- Oral presentation on a problem formulation completed for the document on bacteriological – HPC.
- CDW to discuss

Notes:

3 Parameters - Microbiological

3-C Other microbiological

Reference/Action:

- Verbal update on other microbiological documents and review of other work in the area of water microbiology
- For information only

4 Parameters - Chemical

4-A Chloramines

Reference/Action:

- Status: The work on the chloramines document was initiated in November 2014. The document is drafted and went through internal and external peer-review processes in the summer of 2017. Comments from peer-reviewers were all considered and the document revised accordingly. The document is presented to CDW members for approval for a 2-month public consultation period.
- Attached: Draft guideline technical document on chloramines in drinking water.
- For CDW discussion/approval.

Notes:

Chloramines in Drinking Water

Document for Public Consultation

Prepared by the Federal-Provincial-Territorial Committee on Drinking Water

Consultation period ends
XXXXX, 2017

Chloramines in Drinking Water
Document for Public Consultation

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October 2017

Chloramines in Drinking Water

Purpose of consultation

The Federal-Provincial-Territorial Committee on Drinking Water (CDW) has assessed the available information on chloramines with the intent of updating the current drinking water guideline and the guideline technical document. The purpose of this consultation is to solicit comments on the proposed guideline, as well as to determine the availability of additional exposure data.

The existing guideline on chloramines, last updated in 1996, based its maximum acceptable concentration (MAC) of 3.0 mg/L (3000 µg/L) on the toxicity of monochloramine only, but applied to the sum of all three compounds. This reflects the facts that monochloramine is usually predominant in drinking water, and that information on the toxicity of dichloramine and trichloramine is insufficient to establish guidelines for these two compounds. The MAC was based on decreased body weight gain in rats and took into consideration limitations in analytical methodology and treatment technology. This new document re-assesses the risk of exposure to chloramines in drinking water and takes into consideration more recent science, which still supports that there is insufficient information to establish guidelines for dichloramine and trichloramine. As for monochloramine, recent studies continue to support a very low toxicity for monochloramine in drinking water and provide new evidence indicating that the reduction in body weight gains observed in earlier studies was in fact related to a decrease in water consumption in animal studies, owing to a taste aversion to monochloramine in drinking water. Based on these considerations, the document proposes that it is not considered necessary to establish a guideline for chloramines in drinking water.

The CDW has requested that this document be made available to the public and open for comment. Comments are appreciated, with accompanying rationale, where required. Comments can be sent to the CDW Secretariat via email at water_eau@hc-sc.gc.ca. If this is not feasible, comments may be sent by mail to the CDW Secretariat, Water and Air Quality Bureau, Health Canada, 3rd Floor, 269 Laurier Avenue West, A.L. 4903D, Ottawa, Ontario K1A 0K9. All comments must be received before Month day, year.

Comments received as part of this consultation will be shared with the appropriate CDW member, along with the name and affiliation of their author. Authors who do not want their name and affiliation shared with their CDW member should provide a statement to this effect along with their comments.

October 2017

Chloramines

Part I. Overview and Application

1.0 Proposed guideline

It is not considered necessary to establish a guideline for chloramines in drinking water, based on the low toxicity of monochloramine at concentrations found in drinking water. Any measures taken to limit the concentration of chloramines or their by-products in drinking water supplies must not compromise the effectiveness of disinfection.

2.0 Executive summary

The term "chloramines" refers to both inorganic and organic chloramines. This document focusses on inorganic chloramines, which consist of monochloramine, dichloramine and trichloramine. Unless specified otherwise, the term "chloramines" will refer to inorganic chloramines throughout the document.

Chloramines are found in drinking water mainly as a result of treatment, either intentionally as a disinfectant to kill or inactivate most microorganisms commonly found in water, or unintentionally as a by-product of the chlorination of drinking water in presence of natural ammonia. As monochloramine is more stable and provides longer-lasting disinfection, it is commonly used in the distribution system, whereas chlorine is more effective at disinfecting water in the treatment plant. Chloramines have also been used in the distribution system to help reduce formation of common disinfection by-products such as trihalomethanes and haloacetic acids. However, chloramines also react with natural organic matter to form other disinfection by-products.

All drinking water supplies should be disinfected, unless specifically exempted by the responsible authority. Disinfection is an essential component of public drinking water treatment; the health risks associated with disinfection by-products are much less than the risks from consuming water that has not been adequately disinfected. Most Canadian drinking water supplies maintain a chloramine residual below 4 mg/L in the distribution system.

This guideline technical document focuses on the health effects related to exposure to chloramines in drinking water supplies. It does not review the benefits or the processes of chloramination, nor does it assess the health risks related to exposure to by-products formed as a result of the chloramination process.

Health Canada recently completed its review of the health effects associated with chloramines in drinking water, also taking in consideration taste and odour concerns. Based on this review, the Federal-Provincial-Territorial Committee on Drinking Water does not consider it necessary to establish a guideline for chloramines in drinking water.

2.1 Health effects

The International Agency for Research on Cancer and the U.S. Environmental Protection Agency have classified monochloramine as "not classifiable as to its carcinogenicity to humans" based on inadequate evidence in animals and in humans. The information on dichloramine and

trichloramine is insufficient to establish any link with unwanted health effects in animals or in humans. These forms are also less frequently detected in drinking water. Studies have found no to minimal effects in humans and animals following ingestion of monochloramine in drinking water, with the most significant effect being decreased body weight gain in animals. However, this effect is due to reduced water consumption caused by taste aversion.

2.2 Exposure

Human exposure to chloramines primarily results from their presence in treated drinking water; monochloramine is usually the predominant chloramine. Intake of monochloramine and dichloramine from drinking water is not expected through either skin contact or inhalation. Intake of trichloramine from drinking water might be expected from inhalation, however it is relatively unstable in water and is only formed in specific conditions (at very high chlorine to ammonia ratios or under low pH), which are unlikely to occur in treated drinking water. Consequently, exposure to chloramines via inhalation and skin contact during showering or bathing is expected to be negligible.

2.3 Analysis and treatment

Although there are no U.S. EPA approved methods for the direct measurement of chloramines, there are several such methods for the measurement of total and free chlorine. The results from these methods can be used to calculate the levels of combined chlorine (or chloramines). However, it is also important to determine the levels of organic chloramines to avoid overestimating the disinfectant residual.

For municipal plants, a change in disinfectant such as changing the disinfectant residual to chloramine can impact water quality. When considering conversion to chloramine, utilities should assess the impacts on their water quality and system materials, including the potential for corrosion, nitrification and the formation of disinfection by-products.

Chloramines are not expected to be found in water in the treatment plant, as their formation would primarily occur in the distribution system. For consumers that find the taste of chloramines objectionable, there are residential drinking water treatment devices that can decrease concentrations of chloramines in drinking water. However, removal of the disinfectant residual is not recommended.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

Chloramines are formed when chlorine and ammonia are combined in water and comprise three chemical species: monochloramine (NH_2Cl), dichloramine ($NHCl_2$) and trichloramine (NCl_3). The relative amounts formed are dependent on numerous factors including pH, the ratio of chlorine:ammonia (Cl_2:NH_3), temperature and contact time. When chloramines are used as a disinfectant in drinking water systems, the desired species is monochloramine. When treatment processes are optimized for monochloramine stability (Cl_2:NH_3 weight ratio of 4.5:1 – 5:1, pH > 8.0), almost all of the chloramines are present as monochloramine. Since chloramines can also be formed when ammonia is present in source water, utilities should characterize their source water to assess the presence of and variability of ammonia levels. When utilities are considering conversion from chlorine to chloramine, they should assess the impacts on their water quality and system materials, including the potential for corrosion and nitrification.

Maintenance of adequate disinfectant residual will minimize bacterial regrowth in the distribution system and provide a measurable level of chloramine; therefore, a drop in monochloramine level, suggesting unexpected changes in water quality, can be more quickly detected. Specific requirements for chloramine residual concentrations are set by the regulatory authority and may vary among jurisdictions. Monochloramine, used as a secondary disinfectant, should be applied so as to maintain a stable residual concentration throughout the distribution system. The appropriate amount of disinfectant needed to maintain water quality in the distribution system will depend on (among other factors), the characteristics of the distribution system, the species of bacteria, the presence of biofilms, temperature, pH and the amount of biodegradable material present in the treated water. Water utilities should be aware that a minimum target chloramine residual of "detectable" will not be sufficient to effectively limit bacterial growth in the distribution system. Regular monitoring of distribution system water quality (e.g., disinfectant residual, microbial indicators, turbidity, pH) and having operations and maintenance programs in place (water mains cleaning, cross-connection control, replacements and repairs) are important for ensuring drinking water is transported to the consumer with minimum loss of quality

Depending on the water system, chloramine residual concentrations of >1.0 mg/L may be required to maintain lower heterotrophic bacterial counts, to reduce coliform occurrences and to control biofilm development. Some utilities may require monochloramine concentrations much higher than this to address their specific distribution system water quality. Nitrification in the distribution system is also a potential problem for municipal systems that chloraminate. The concerns for utilities from nitrification are the depletion of the disinfectant residual, increased bacterial growth and biofilm development in the distribution system as well as decreased pH which can result in corrosion issues. When used as part of a program for nitrification prevention and control, suggested best operational practices for a chloramine residual are 2 mg/L leaving the treatment plant and preferably greater than >1.5 mg/L at all monitoring points in the distribution system. Information on strategies for controlling nitrification can also be found in the guideline technical document for ammonia.

Most Canadian drinking water supplies maintain a chloramine residual range below 4 mg/L in the distribution system. At these concentrations, taste and odour related to chloramines are generally within the range of acceptability for most consumers. However, individual sensitivities in the population are widely variable but generally, taste and odour complaints resulted at levels of 3–3.7 mg/L monochloramine. Taste and odour concerns should be taken into account during the selection of operational and management strategies for the water treatment and distribution systems, although they do not make the water unsafe to consume. The protection of public health by maintaining the microbiological safety of the drinking water supply during distribution is the primary concern when using monochloramine for secondary disinfection.

Taste and odour issues can be indicators that operational changes may be required to address causal issues (i.e., water age, loss of monochloramine stability, formation of dichloramine, etc.). Utilities should establish operational targets for a disinfectant residual concentration appropriate for their system which allows them to meet their water quality objectives (i.e., microbial protection, minimizing the formation of disinfection by-products, nitrification prevention, biological stability and corrosion control).

Dialysis treatment providers at all levels (e.g., large facilities/hospitals, small community facilities, mobile units, providers for independent/home dialysis) should be notified that water is chloraminated.

3.1 Monitoring

Utilities using chloramine for secondary disinfection should monitor total chlorine residual daily, at minimum, in water leaving the treatment plant and throughout the distribution system. Disinfectant residual sampling should be conducted at the point of entry to (baseline) and throughout the distribution system. This ensures that the target chloramine level is being applied at all times and provides a comparison against residual levels observed throughout the distribution system. Sample locations should be chosen to represent all areas of the distribution system. Key points for sampling also include entry point to distribution system (baseline), storage facilities, up and downstream of booster stations, in areas of low flow or high water age, in areas of various system pressures, mixed zones (blended water) and with various sizes and types of pipe material. Some utilities should also consider increasing the frequency of sampling during warmer months. A larger number of sample sites will provide a more representative assessment of residual achieved. Dedicated sampling taps are an ideal for residual sampling and customer taps can be used as an alternative. In the absence of suitable tap access, hydrants can be used for residual sampling. However, taking a meaningful hydrant sample can be challenging. Additional samples can be added for investigative purposes.

Operational parameters including finished water pH, free chlorine, free ammonia, temperature, total organic carbon and alkalinity should be monitored at the treatment plant when using chloramines. It is also recommended that water leaving the treatment plant and throughout the distribution system be tested at least weekly for nitrite and ammonia. Nitrite should also be analysed weekly at storage facilities and in areas of low-flow and high water age to monitor for nitrification. Utilities should also monitor weekly for free ammonia at locations such as reservoir outlets and areas with long water detention times (e.g., dead ends). Changes in the trends of nitrification parameters in the distribution system (i.e., total chlorine residual, nitrite and nitrate) should trigger more frequent monitoring of free ammonia. Utilities that undertake comprehensive preventive measures and have baseline data that indicate nitrification does not occur in the system may conduct less frequent monitoring of free ammonia and nitrite. Heterotrophic plate count (HPC) monitoring on a monthly basis, at minimum, is also useful as a tool to assess system water quality.

More information on monitoring for nitrite, ammonia and HPC can be found in the guideline technical documents on nitrate and nitrite and on ammonia and in the guidance document on the use of heterotrophic plate counts in Canadian drinking water supplies.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Chloramines are oxidizing compounds containing one or more chlorine atoms attached to a nitrogen atom. In the literature, the term "chloramine" refers to both inorganic and organic chloramines. Health effects of organic chloramines are beyond the scope of the present document and will not be discussed. Throughout the document, the term "chloramines" will refer only to inorganic chloramines, unless otherwise specified.

Inorganic chloramines consist of 3 chemically related compounds: monochloramine, dichloramine and trichloramine. Only mono- and dichloramine are really soluble in water. The volatility varies depending on the compound, with trichloramine being the most volatile. Their physical properties are provided in the table below:

Table 1. Physical and chemical properties of inorganic chloramine compounds

Parameter	Inorganic chloramine compounds		
	Monochloramine	**Dichloramine**	**Trichloramine**
Synonym	Chloramide[d]	Chlorimide[d]	Nitrogen trichloride[b]
CAS No.	10599-90-3	3400-09-7	10025-85-1
Molecular formula	NH_2Cl	$NHCl_2$	NCl_3
Molecular weight[a]	51.48	85.92	120.37
Water solubility[a]	Soluble	Soluble	Limited to hydrophobic
Boiling point	486°C (predicted)[c]	494°C (predicted)[c]	NA
pK[a]	14±2	7±3	NA
Henry's Law constant - Kaw (estimated, at 25°C)[c]	0.00271	0.00703	1
Vapour pressure (at 25°C)	1.55×10^{-7} Pa[c]	8.84×10^{-8} Pa[c]	19.99 kPa[b]

[a] Environment Canada and Health Canada, 2001
[b] OSHA, 2007
[c] U.S. EPA, 2012
[d] Pubmed 2005a, 2005b
[e] U.S. EPA, 2017
NA = not available

Chloramines have been used for almost 90 years as disinfectants to treat drinking water. Although chloramines are less efficient than free chlorine in killing or inactivating pathogens, they generate less trihalomethanes (THMs) and haloacetic acids (HAAs). They are also more stable than free chlorine, thus providing longer disinfection contact time within the drinking water distribution system. Because of these properties, chloramines are mainly used as secondary disinfectants to maintain a disinfectant residual in the distribution system and are generally not used as primary disinfectants (White, 1992).

Of the three chloramines, monochloramine is the preferred chloramine species for use in disinfecting drinking water because of its biocidal properties and relative stability, and because it rarely causes taste and odour problems when compared to dichloramine and trichloramine (Kirmeyer et al., 2004).

As a secondary usage, monochloramine has been used for the organic synthesis of amines and substituted hydrazines used as pharmaceutical intermediates, while dichloramine has been used for the preparation of diazirine, a labelling reagent (Graham, 1965; Kirk-Othmer, 2004; El-

Dakdouki, 2014). Trichloramine gas was previously used in the food industry for bleaching flour (agene method), but the practice was discontinued in 1950 in the U.S. and the United Kingdom due to adverse health effects seen in animals (Shaw and Bains, 1998). Other uses have included paper manufacturing and as a fungicide on fruit (Kirk-Othmer, 2004).

Chloramines do not occur naturally (IARC, 1994). They may be intentionally produced or generated as by-products of drinking water chlorination including in ground water systems that undergo chlorination in the presence of natural ammonia as well as in chlorinated wastewater effluents (WHO, 2004; Hach, 2017).

For disinfection purposes, chloramines are formed through a process called chloramination (U.S. EPA, 1999). Chloramination involves the addition of ammonia (NH_3) to free aqueous chlorine (hypochlorous acid, HOCl). This mixture can lead to the formation of inorganic compounds, such as monochloramine, dichloramine, and trichloramine (NHMRC, 2011).

$NH_3 + HOCl \rightarrow NH_2Cl$ (monochloramine) $+ H_2O$
$NH_2Cl + HOCl \rightarrow NHCl_2$ (dichloramine) $+ H_2O$
$NHCl_2 + HOCl \rightarrow NCl_3$ (trichloramine) $+ H_2O$

Chloramine speciation mainly depends on the chlorine to ammonia ratio (Cl_2:NH_3) and pH, but also on the temperature and contact time (U.S. EPA, 1999). Cl_2:NH_3 ratios $\leq$ 5:1 by weight (equivalent to ratios $\leq$ 1:1 by mole) are optimum for monochloramine formation. The Cl_2:NH_3 ratio by weight is defined as the amount of chlorine added in proportion to the amount of ammonia added (in milligrams); all the Cl_2:NH_3 ratios presented in the following document are reported by weight. Ratios between 5:1 and 7.6:1 favour dichloramine production, whereas trichloramine is produced at higher ratios. Neutral to alkaline conditions (pH between 6.5 and 9.0) are optimum for monochloramine formation (monochloramine formation occurs most rapidly at pH=8.3), whereas acidic conditions are optimum for the formation of dichloramine (pH between 4.0 and 6.0) and trichloramine (pH <4.4) (Kirmeyer et al., 2004).

Under typical drinking water treatment conditions (pH ranging from 6.5 to 8.5) and with a Cl_2:NH_3 ratio of less than 5:1 (a ratio of 4:1 is typically accepted as optimal for chloramination), both monochloramine and dichloramine are formed with a much higher proportion of monochloramine (U.S. EPA, 1999). For example, when water is chlorinated with Cl_2:NH_3 ratio of 5:1 at 25°C and pH 7.0, the proportions of monochloramine and dichloramine are 88% and 12%, respectively (U.S. EPA, 1994a). For its part, trichloramine can be formed in drinking water at pH 7.0 and 8.0 but only if the Cl_2:NH_3 ratio is increased to 15:1 (Kirmeyer et al., 2004). Thus, under usual water treatment conditions, monochloramine is the principal chloramine encountered in drinking water. Elevated levels of dichloramine and trichloramine in drinking water may occur, but would be due to variations in the quality of the raw water (e.g., pH changes) or accidental changes in the Cl_2:NH_3ratio (Nakai et al., 2000; Valentine, 2007).

Chloramines (mono-, di- and trichloramines) can be found in media other than drinking water. In swimming pools, for example, they are DBPs incidentally formed from the decomposition, via chlorination, of organic-nitrogen precursors, such as urea, creatinine and amino acids, originating from human excretions (e.g., sweat, faeces, skin squama, urine) (Li and Blatchley, 2007; Blatchley and Cheng, 2010; Lian et al., 2014).

Chloramines are also formed when wastewater effluents or cooling waters are treated with chlorine (U.S. EPA, 1994a). In the food industry, they may result from the reaction between hypochlorite and nitrogen compounds coming from the proteins released by vegetables or animals

(Massin et al., 2007). At home, chloramine fumes, a combination of monochloramine and dichloramine that form a noxious gas, can be produced when bleach and ammonia are accidentally mixed for cleaning purposes (Gapany-Gapanavicius et al., 1982).

4.1 Environmental fate

Because chloramines are found mainly in the aqueous phase, their fate in the environment will be ruled by processes relevant to this media.

The decomposition (auto) of monochloramine in water is affected by many factors (Wilczak et al., 2003b); its rate will increase as the temperature and inorganic carbon increase, the CL_2:NH_3 ratio increases and the initial chloramine concentration, as well as the pH decreases. Vikesland et al. (2001), using decay experiments, reported that at pH 7.5, monochloramine has a half-life of over 300 hours at 4 °C, whereas it decreases to 75 hours at 35 °C. Autodecompositon of aqueous monochloramine to dichloramine will occur by one of two pathways: hydrolysis and acid-catalyzed disproportionation, both of which are described in Wilczak et al. (2003b).

When the pH is neutral, trichloramine in water will slowly decompose by autocatalysis to form ammonia and hypochlorous acid (U.S. EPA 1994). Trichloramine has limited solubility. Since it is extremely volatile, it will volatilize into air (U.S. EPA, 1994; Environment Canada and Health Canada, 2001). In contrast, according the physic-chemical properties listed in to Table 1, mono- and dichloramine are very soluble in water and not very volatile.

4.1.1 Impact of chloramines on aquatic life

Chloramines enter the Canadian aquatic environment primarily through municipal wastewater release (73%) and drinking water release (14%), along with other minor sources (Pasternak et al., 2003). Release of chloraminated water (total chlorine = 2.53 and 2.75 mg/L) as a result of a water main break reportedly caused two large fish kills in the Lower Fraser River watershed (Nikl and Nikl, 1992). To mitigate the impact of chlorine or chloramines, aquarium owners must ensure the use of proper aeration or chlorine/chloramine quenching (Roberts and Palmeiro, 2008).

4.2 Terminology

This section provides definitions for some relevant terms used in this document, as adapted from the American Water Works Association (AWWA, 1999; Symons et al., 2000):

- *Total chlorine*: all chemical species containing chlorine in an oxidized state. Usually the sum of free and combined chlorine concentrations present in water.
- *Free chlorine*: the amount of chlorine present in water as dissolved gas (Cl_2), hypochlorous acid (HOCl), and/or hypochlorite ion (OCl^-) that is not combined with ammonia or other compounds in water.
- *Combined chlorine*: the sum of the species resulting from the reaction of free chlorine with ammonia (NH_3), including inorganic chloramines: monochloramine (NH_2Cl), dichloramine ($NHCl_2$), and trichloramine (nitrogen trichloride, NCl_3).
- *Chlorine residual*: the concentration of chlorine species present in water after the oxidant demand has been satisfied.
- *Primary disinfection*: the application of a disinfectant at the drinking water treatment plant, with a primary objective to achieve the necessary microbial inactivation.
- *Secondary disinfection*: the subsequent application of a disinfectant, either at the exit of the treatment plant or in the distribution system, with the objective of ensuring that a disinfectant residual is present throughout the distribution system.

4.3 Chemistry in aqueous media

The objective of chloramination is to maximize monochloramine formation, to minimize free ammonia, and to prevent excess dichloramine formation and breakpoint chlorination. Chloramine formation is governed by reaction of ammonia (oxidized) and chlorine (reduced); its speciation is principally determined by pH and the Cl_2: NH_3 weight ratio. The reaction rate of monochloramine formation depends on pH, temperature and the Cl_2:NH_3 weight ratio. Ideally, a weight ratio of 4.5:1 – 5:1 will help minimize free ammonia and reduce the risk of nitrification (AWWA, 2006b).

The breakpoint chlorination curve can be used to illustrate the ideal weight ratio where monochloramine production can be maximized. For a utility wishing to produce monochloramine, the breakpoint ratio should be determined experimentally for each water supply (Hill and Arweiler, 2006). Figure 1 below shows an idealized breakpoint curve that occurs between pH 6.5 and 8.5 (Griffin and Chamberlin, 1941; Black and Veatch Corporation, 2010). Initially, monochloramine is formed, and once the Cl_2:NH_3 weight ratio is greater than 5:1, monochloramine formation decreases. Once the Cl_2:NH_3 weight ratio is greater than 5:1, no free ammonia is available to react with the free chlorine being added. The reaction of free chlorine with monochloramine leads to the formation of dichloramine. When high enough Cl_2:NH_3 weight ratios are achieved, breakpoint chlorination will occur. The breakpoint curve is characterised by the "hump and dip" shape (Figure 1). Dichloramine undergoes a series of decomposition and oxidation reactions to form nitrogen-containing products, including nitrogen, nitrate, nitrous oxide gas and nitric oxide (AWWA, 2006b). Trichloramine, or nitrogen trichloride, is an intermediate during the complete decomposition of chloramines. Its formation depends on pH and the Cl_2:NH_3 weight ratio and may appear after the breakpoint (Kirmeyer et al., 2004; Hill and Arweiler, 2006; Randtke, 2010).

After breakpoint, free chlorine is the predominant chlorine residual, not monochloramine. However, the reaction rate of breakpoint chlorination is determined by the formation of monochloramine and the formation and decay rates of dichloramine and trichloramine, reactions that are highly dependent on pH. The theoretical Cl_2:NH_3 weight ratio for breakpoint chlorination is 7.6:1 however, the actual Cl_2:NH_3 ratio varies from 8:1 to 10:1, depending on pH, temperature and the presence of reducing agents. The presence of iron, manganese, sulphide and organic compounds create a chlorine demand, i.e., compete with the free chlorine added, potentially limiting the chlorine available to react with ammonia (Kirmeyer et al., 2004; AWWA, 2006b; Muylwyk, 2009). It is therefore important that each utility generates a site-specific breakpoint curve, experimentally. Additionally, periodic switching to chlorine (breakpoint chlorination) for seasonal nitrification control has also been observed to increase disinfection by-products such as trihalomethanes (chloroform) (Vikesland et al., 2006; Rosenfeldt et al., 2009). However, Rosenfeldt et al. (2009) also observed that flushing was an effective mitigation strategy.

Automated systems can be used to monitor and maintain weight ratio. Hutcherson (2007) reported that the application of programmable logic control and human-to -machine interface, resulted in an intuitive and effective dosing control strategy for Newport Beach, California. The 5:1 ideal weight ratio was maintained and monitored 24 hours a day. At the time of the report, the system had been in use for two years of successful operation.

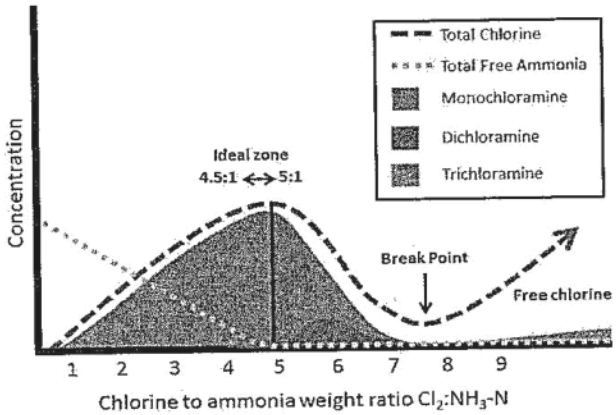

Figure 1: Idealized break point chlorination curve (modelled after Griffin and Chamberlin (1941) and Black and Veatch Corporation (2010))

4.4 Application to drinking water treatment

This document focuses on the health effects related to exposure to chloramine in drinking water supplies, whether formed intentionally as a secondary disinfectant, or unitentionally as a by-product of chlorination. It does not review the benefits or the processes of chloramination, nor does it assess the health risks related to exposure to by-products formed as a result of the chloramination process.

4.4.1 Chloramines in water treatment

The mechanisms by which monochloramine inactivates microbiological organisms are not fully understood (Jacangelo et al., 1991; Coburn et al., 2016). It is suggested that free chlorine and chloramines react with different functional groups in the cell membrane (LeChevallier and Au, 2004). The proposed mode of action of monochloramine is the inhibition of protein-mediated processes such as bacterial transport of substrates, respiration and substrate dehydrogenation (Jacangelo et al., 1991; Coburn et al., 2016). Experiments with bacteria indicated monochloramine was most reactive with sulfur-containing amino acids (LeChevallier and Au, 2004; Rose et al., 2007). Monochloramine did not severely damage the cell membrane or react strongly with nucleic acids. Monochloramine is a more selective reactant than free chlorine and seems to act in more subtle ways at drinking water concentrations (Jacangelo et al., 1991). Inactivation with monochloramine appears to require reactions at multiple sensitive sites (Jacangelo et al., 1991). More research is needed for a better understanding of the process behind chloramine disinfection.

4.4.2 Primary disinfection

Primary disinfection is the application of a disinfectant in the drinking water treatment plant, with a primary objective to achieve the necessary microbial inactivation.

Monochloramine is much less reactive than free chlorine, has lower disinfecting power and is generally not used as a primary disinfectant because it requires extremely high CT values[1] to achieve the same level of inactivation as free chlorine (Jacangelo et al., 1991, 2002; Taylor et al., 2000; Gagnon et al., 2004; LeChevallier and Au, 2004; Rose et al., 2007; Cromeans et al., 2010).

4.4.3 Secondary disinfection

Secondary disinfection may be applied to the treated water as it leaves the treatment plant or at rechlorination points throughout the distribution system, to introduce and maintain a disinfectant residual in the drinking water distribution system.

The main function of the residual is to protect against microbial regrowth (LeChevallier and Au, 2004). The disinfectant residual can also serve as a sentinel for water quality changes. A drop in residual concentration can provide an indication of treatment process malfunction, inadequate treatment or a break in the integrity of the distribution system (LeChevallier, 1998; Haas, 1999; Health Canada, 2012a, 2012b).

Monochloramine is slower to react and, in treated drinking water, can provide a more stable and longer-lasting disinfectant residual in the distribution system (Jacangelo et al., 1991; U.S. EPA, 1999; LeChevallier and Au, 2004, Cromeans et al., 2010). However, combined chlorine residuals are less functional as sentinels of potential post-treatment contamination events than free chlorine residuals. Declines in combined chlorine measurements may not always be large enough or rapid enough to alert utilities that a contamination problem has occurred within the distribution system (Snead, 1980; Wahman and Pressman, 2015). Also, a drop in residual may be due to nitrification and not post-treatment contamination (Wahman and Pressman, 2015). Disinfectant residual monitoring should be conducted alongside other parameters as part of broader programs for microbiological quality and nitrification.

Organic chloramines provide little to no disinfection (Feng, 1966; Donnermair and Blatchley, 2003). In bench scale experiments, Lee and Westerhoff (2009) demonstrated that organic chloramines comprise a greater proportion of the chlorine residual in systems where chloramines are formed by adding ammonia after a 10 minute contact time with free chlorine compared to pre-formed monochloramine. Organic chloramines formed more rapidly in the presence of free chlorine than in the presence of monochloramine. However, as it is common practice to provide short chlorine contact time followed by ammonia addition, the risk of generating organic chloramines is an important consideration.

4.4.4 Formation of chloraminated disinfection by-products

Chloramines are often used to meet DBP compliance based on HAAs and THMs; however, chloramines also react with natural organic matter (NOM) to form other DBPs such as iodinated disinfection by-products (I-DBPs) and nitrosamines (Richardson and Ternes, 2005; Charrois and Hrudey, 2007; Hua and Reckhow, 2007; Richardson et al., 2008; Nawrocki and

[1] A measure of a chemical's efficacy as a disinfectant and is the residual concentration of a disinfectant, measured in mg/L (C) multiplied by the disinfectant contact time, measured in minutes (T).

Andrzejewski, 2011). Hydrazine can also form as a result of abiotic reactions of ammonia and monochloramine (Najm et al., 2006).

I-DBPs are more readily formed in chloraminated systems. Monochloramine oxidizes iodide to hypoiodous acid quickly but the reaction with NOM is slow, allowing sufficient time for the formation of I-DBPs (Singer and Reckhow, 2011). Chlorine and ozone can also oxidize iodide to hypoiodous acid; however, the iodide is further oxidized to iodate, forming only trace to minimal amounts of I-DBPs (Hua and Reckhow, 2007). In bench-scale formation experiments using simulated raw water, Pan et al. (2016) found that chloraminated water formed more polar I-DBPs compared to water treated with either chlorine dioxide or chlorine. The authors also noted that as pH increased (from 6 to 9), the formation of polar I-DBPs decreased. Water quality factors such as pH and ratios of dissolved organic carbon (DOC), iodide (I^-) and bromide (Br^-) have been demonstrated to play an important role in determining the species and abundance of iodated trihalomethanes formed under drinking water conditions (Jones et al., 2012).

N-Nitrosodimethylamine (NDMA) is a nitrogen-containing disinfection by-product that may be formed during the treatment of drinking water, particularly during chloramination and, to a lesser extent, chlorination (Richardson and Ternes, 2005; Charrois and Hrudey, 2007; Nawrocki and Andrzejewski, 2011). The key to controlling the formation of NDMA lies in limiting its precursors, including dichloramine. As such, optimization and control of free ammonia are important elements in preventing NDMA formation (Health Canada, 2011). Additionally, Krasner et al. (2015) demonstrated that several pre-oxidation technologies were effective in destroying the watershed-derived NDMA precursors (ozone>chlorine>medium pressure UV>low pressure UV>permanganate). Uzen et al. (2016) observed that site specific factors such as upstream reservoirs, wastewater discharge, and mixing conditions can affect NDMA formation potential and should be characterized for each individual site. More detailed description of precursors and treatment options can be found in that report (Krasner et al., 2015; Uzen et al., 2016). Cationic polymers, containing diallyldimethylammonium chloride, used in water treatment can also act as a source of NDMA precursors (Wilczak et al., 2003a).

Under certain conditions, hydrazine can form through a reaction between ammonia and monochloramine. Najm et al. (2006) found that at low concentrations of free ammonia-nitrogen (< 0.5 mg/L) and pH < 9, less than 5 ng/L of hydrazine was formed but that increasing either ammonia concentrations or pH also increased hydrazine formation. Davis and Li (2008) obtained thirteen samples from six chloraminated drinking water utilities and found hydrazine above the detection limit of 0.5 ng/L in seven of the samples (0.53–2.5 ng/L). Hydrazine production was found to be greatest where treatment processes had high pH (i.e., lime softening). Several treatment practices were identified to minimize hydrazine production including delaying chloramination until the pH was adjusted (i.e., recarbonation step) and managing the chlorine to ammonia ratio to minimize the free ammonia concentration (Najm et al., 2011).

4.4.5 Taste and odour considerations

Chloramines are less readily detected in terms of their taste and odour in water than chlorine. The majority of the taste issues arise from the presence of dichloramine and trichloramine. Chloramines have been described with a flavour profile of chlorine-like, musty and/or chalky, ammonia, slat, soapy-slimy feel, sour, bitter, dry mouth. Interestingly, trichloramines have also been described as having a geranium-like odour (Krasner et al., 1985). Mackey et al. (2004) explored taste and odour thresholds for chlorine and chloramine treated water. In a test group of 93 American adults, the taste threshold for chloraminated water (dosed as monochloramine) was found to be 3.7 mg/L. Krasner and Barrett (1984) derived a taste threshold

of 0.48 mg/L by linear regression for detecting the presence of monochloramine at various concentrations. However the authors stated that monochloramine will likely not result in complaints about taste and odour at concentrations as high as 3 mg/L. White (1992) found that at concentration of 5 mg/L did not result in taste and odour complaints.

Odour is more closely related to the ratio of dichloramine to monochloramine than to their absolute concentrations. Problems with taste and odour may result when the concentration of dichloramine exceeds 20% of the monochloramine concentration (Mallevialle and Suffet, 1987). Taste and odour complaints should be monitored and tracked. Utilities can address taste and odor issues through a variety of operational strategies to address water age, disinfection demand, hydraulic issues such as dead-ends and low flow areas, bacteria growth, dosing issues, etc. (Kirmeyer, 2004).

5.0 Exposure

No environmental data were found for inorganic chloramines in sediments, soils, and ambient air (Environment Canada and Health Canada, 2001). As a result drinking water is considered the primary source of exposure for this assessment.

5.1 Water

Chloramines are usually measured as combined chlorine residuals, corresponding to the difference between total chlorine residual and free chlorine residual. This method has limitations, because the combined chlorine value does not determine the individual concentrations of mono- and dichloramines present in drinking water, and because the free chlorine measurement is not always accurate in the presence of high levels of chloramines. Individual chloramines can be differentiated using multi-stage procedures but interferences (e.g., organic chloramines) may, in some cases, result in misleading measurements (e.g., overestimation of monochloramine concentrations) (Lee et al., 2007; Ward, 2013)(see Sec. 6 for additional information).

Limited provincial data are reported in Table 2. Generally, levels of chloramines or combined chlorine are below 3 mg/L. Only a few values exceeding 3 mg/L were reported.

Table 2. Residual disinfectant levels in distribution systems across Canada

Province (Year)	# of sites	Range: min–max (# non-detects/total # of samples)						
		Chlorine			Chloramines			
		Total	Free	Combined	Chloramines	Mono-	Di-	Tri-
NS[e] (2008-2015)	39	---	---	---	<0.00002–1.75 mg/L (1/81)	<0.1–0.1 mg/L (0/9)	<0.1 (0/9)	<0.1–0.4 mg/L (0/9)
QC[f] (2013-2015)	3[a]	---	---	---	0.07–1.80 mg/L (0/7)	---	---	---
QC[f,j] (2013-2015)	5[b]	0.01–4.6 mg/L (0/3432)	0–4.2 mg/L (544/3432)	---	0–3.24 mg/L (9/3432)	---	---	---
QC[f] (2013-2015)	11[c]	0–7.05 mg/L (8/2924)	0–5.5 mg/L (239/2924)	---	0–2.47 mg/L (8/2924)	---	---	---
ON[g] (2012-2017)	108	---	----	0–2.64 mg/L (2/1500)	---	----	----	
SK[d,h,j] (2006-2015)	18	0.62–3.24 mg/L (0/25)	0.01 – 1.18 mg/L (0/24)	---	0.01–3.9 mg/L (0/28)	1.28–3.11 mg/L (0/24)	---	---
BC[i] (2015)	37	0.01–1.86 ppm (10/1923)	0–0.97 ppm (10/1918)	----	----	0.6–1.51 mg/L (0/51)	0–0.7 µg/L (4/51)	----
BC[i] (2016)	37	0.03–1.89 ppm (0/1931)	0–0.93 ppm (11/1929)	----	----	0–1.3 mg/L (1/51)	0–0.61 µg/L (2/50)	----

[a] Method not specified, reported as "chloramines"
[b] distribution system
[c] at extremity of distribution system
[d] SK: this data does not distinguish between chloramine residuals following intentional chloramination or chlorination of water containing background ammonia. In Saskatchewan, chloramines are allowed as a primary disinfectant for true groundwater, however it is not typically allowed as primary disinfectant for surface or groundwater under the direct influence of surface water systems (Saskatchewan Water Security Agency, 2017)
[e] Nova Scotia Environment (2017)
[f] Ministère du Développement durable, de l'Environnement et des Parcs du Québec (2017)

[g] Ontario Ministry of the Environment and Climate Change (2017)
[h] Saskatchewan Water Security Agency (2017)
[i] BC Ministry of Health (2017)
[j] only 1occurrence of exceedence was seen in the data set

5.2 Air

Chloramines may be encountered in the ambient air of food industry facilities that typically use large quantities of disinfecting products. For example, total concentrations of chloramines (mainly trichloramine) have been reported in the ambient air of green salad processing plants (e.g., 0.4 to 16 mg/m^3; Hery et al., 1998) and of turkey processing plants (e.g., 0.6 to 1 mg/m^3 - average concentrations; Kiefer et al., 2000).

5.3 Swimming pools and hot tubs

Chloramines are present in indoor swimming pools as disinfection by-products of chlorination. Due to its high volatility and low solubility, trichloramine is the predominant species present in the swimming pool atmosphere. Numerous papers report trichloramine concentrations in the atmosphere of indoor swimming pools (including water parks) with mean concentrations ranging from approximately 114 to 670 $\mu g/m^3$ (Carbonnelle et al., 2002; Thickett et al., 2002; Jacobs et al., 2007; Dang et al., 2010; Parrat et al., 2012). The levels of airborne trichloramine are influenced by several factors, such as the number of swimmers, organic compounds (mainly urine and sweat) introduced into the water by swimmers, air ventilation, as well as water temperature, circulation and movement (splashing, waves, etc.) (Carbonnelle et al., 2002; Jacobs et al., 2007; Parrat et al., 2012).

5.4 Multi-route exposure through drinking water

Mono- and dichloramine do not possess the physico-chemical characteristics to consider their contribution via the dermal or inhalation route, since both are water soluble but not volatile (see Table 1). Whereas trichloramine is very volatile, it is not soluble in water. In addition, trichloramine is relatively unstable in water and is only formed at very high chlorine to ammonia ratios or under low pH, conditions which are unlikely to occur in treated drinking water. Therefore under normal usage conditions, the ratio of trichloramine to total chloramines is very low and would not contribute significantly to the dermal or inhalation routes of exposure. Consequently, exposure to chloramines via inhalation and dermal routes during showering or bathing is expected to be negligible.

6.0 Analytical methods

There are no U.S. EPA approved methods for the direct measurement of chloramines. There are, however, several U.S. EPA approved methods for the measurement of total and free chlorine (Table 3). Free chlorine is the sum of chlorinated species that do not contain ammonia or organic nitrogen (i.e., Cl_2, HOCl, OCl^-, and Cl_3^-); whereas combined chlorine is the sum of chlorine species that are combined with ammonia (NH_2Cl, $NHCl_2$, and NCl_3) (Black and Veatch Corporation, 2010). Since total chlorine is often used an assumed proxy for combined chlorine (chloramines), it is important that free chlorine be measured to validate the assumption that none is present. Although there is no method for the direct measurement of chloramines, equation 1 below shows how chloramines can be determined by subtracting free chlorine from total chlorine:

Combined chlorine (chloramines) = Total chlorine – Free chlorine (1)

Table 3. U.S. EPA approved methods for total, free and combined chlorine measurement

Method (Reference)	Methodology	Residual measured (MDL)	Comments
ASTM D1253 (ASTM, 1986, 2003, 2008, 2014)	Amperometric Titration	Total, free, combined (NA)	Reaction is slower at pH > 8 and requires buffering to pH 7. A maximum concentration of 10 mg/L is recommended. Interferences: cupric, cuprous and silver ions; trichloramine; some N-chloro compounds; chlorine dioxide; dichloramine; ozone; peroxide; iodine; bromine; ferrate; Caro's acid.
SM 4500-Cl D (APHA et al., 1995, 1998, 2000, 2005, 2012)	Amperometric Titration	Total, free, combined (NA)	Dilutions are recommended for concentrations above 2 mg/L. Interferences: trichloramine, chlorine dioxide, free halogens, iodide, organic chloramines, copper, silver. Monochloramine can interfere with free chlorine, and dichloramine can interfere with monochloramine. Can also be used to characterise species (monochloramine and dichloramine)
SM 4500-Cl G (colorimetric) (APHA et al., 1995, 1998, 2000, 2005, 2012) SM 4500-Cl F (ferrous) (APHA et al., 1995, 1998, 2000, 2005, 2012)	N,N-diethyl-p-phenylenediamine (DPD)	Total, free, combined (10 µg/L) Total, free, combined (18 µg/L)	Interferences: oxidized manganese, copper, chromate, iodide, organic chloramines Can also be used to characterise species (monochloramine, dichloramine, and trichloramine) in a laboratory setting.
Hach 10260 Rev 1.0 (HACH, 2013)	DPD Chemkey	Total (0.04 mg/L), free (0.04 mg/L), combined (NA)	Interferences: acidity > 150 mg/L $CaCO_3$, alkalinity > 250 mg/L as $CaCO_3$ highly buffered or extreme pH samples, bromine, chlorine dioxide, iodine, ozone, organic chloramines, peroxides, oxidized manganese, oxidized chromium.

NA = not available

Although not approved by U.S. EPA for direct measurement of chloramine species, several methods (SM 4500 D, 4500 F, and 4500 G) have additional steps that can be used to distinguish between the various chloramine species (monochloramine, dichloramine, trichloramine). Both dichloramine and trichloramine are relatively unstable, and their formation reactions do not proceed to completion under typical drinking water conditions (Black and Veatch Corporation, 2010). Specific instructions for mitigating effects of interfering agents (including interference from other chlorine species), optimal analytical performance (including the use of reagent blanks), and reaction times for accurate sample readings are available in the method documents.

Organic chloramines are formed when dissolved organic nitrogen reacts with either free chlorine or inorganic chloramines (Lee and Westerhoff, 2009) and are known interfering agents for both the amperometric and the DPD methods (APHA et al., 2012). Wahman and Pressman (2015) highlighted that organic chloramines can provide false positives. Lee and Westerhoff (2009) estimated that utilities are likely to overestimate chloramine residuals by approximately 10% as a result of interference of organic chloramines. Similarly, in Gagnon et al. (2008), a pipe loop distribution system study identified that organic chloramines comprised approximately 10–20% of the total chlorine residual in a chloraminated system. The contribution of organic chloramines to the total chlorine residual can be calculated by subtracting the monochloramine concentration from the total chlorine residual. Although not approved by the U.S. EPA, the Hach 10241 U.S. EPA Indophenol method (Hach, 2017) can be used to measure monochloramine using a DPD method. This method could be used to help inform day-to-day operations by providing an approximation of organic chloramines.

6.1 Sampling considerations

Key points for sampling also include entry point to distribution system (baseline), storage facilities, up and downstream of booster stations, in areas of low flow or high water age, in areas of various system pressures, mixed zones (blended water), and with various sizes and types of pipe material. Dedicated sampling taps are an ideal for residual sampling (AWWA, 2013), and customer taps can be used as an alternative. In the absence of suitable tap access hydrants can be used for residual sampling. However, taking a meaningful hydrant sample can be challenging. The U.S. EPA (2016) has developed a hydrant sampling best practice manual that can be used to estimate the flush time required for a representative sample. Alexander (2017) recommended targeting remote locations of a distribution system, and suggested that it is preferable to target more locations with fewer samples at those locations vs. more samples at fewer locations and recommended taking additional investigative samples. An investigation of disinfectant residuals in Flint, Michigan, revealed that the previous number and location of sampling sites (10 sites) were insufficient because these locations demonstrated adequate disinfectant (chlorine) residual. However, upon expanding the number and location of sample sites to more representative locations (additional 24 sites), the disinfectant residual was revealed to be problematic (Pressman, 2017). Although, chloramine residuals are consumed less readily in the distribution system, it is still important to have an adequate and representative set of sampling sites.

Alexander (2017) highlighted the importance of proper field testing techniques. Sample vials can become scratched (during transportation in a truck) or dirty, leading to inaccurate readings. Additionally, plastic vials are prone to the formation of fine bubbles, which can be resolved with slow inversion of the sample. It is important that operators are aware of the challenges of disinfectant residual sampling.

Sampling programmes should be reviewed on an annual basis and the review should examine historical data, water use patterns/changes, as well as any changes in water treatment or distribution system operation (AWWA, 2013).

7.0 Treatment technology and distribution system considerations

As chloramines are added to drinking water to maintain a residual concentration in the distribution system, or are formed as a by-product of the chlorination of drinking water in presence of natural ammonia, they are only expected to be found in drinking water after it exits the treatment plant, in the distribution and plumbing systems.

7.1 Municipal scale

The literature indicates that monochloramine CT requirements are one to many orders of magnitude greater than those required for free chlorine for achieving similar levels of inactivation of heterotrophic bacteria, *E. coli*, nitrifying bacteria, enteric viruses and *Giardia* (LeChevallier and Au, 2004; Wojcicka et al., 2007; Cromeans et al., 2010; Health Canada, 2012b, 2017, 2018a). Reported CT values also demonstrate that similar to free chlorine, monochloramine is not effective for inactivation of *Cryptosporidium* (LeChevallier and Au, 2004; Health Canada, 2017).

Given the operational benefits of secondary disinfection, operators should strive to maintain a stable disinfectant residual throughout the system. Regular monitoring of distribution system water quality (e.g., disinfectant residual, microbial indicators, turbidity, pH) and having operations and maintenance programs in place (water mains cleaning, cross-connection control, replacements and repairs) are important for ensuring drinking water is transported to the consumer with minimum loss of quality (Kirmeyer et al., 2001, 2014).

7.1.1 Disinfectant residual and microbial control

To control bacterial regrowth and biofilm formation, a strong, stable disinfectant residual is needed that is capable of reaching the ends of the distribution system. The amount of disinfectant needed to maintain water quality is dependent on the characteristics of the distribution system, species of bacteria, the type of disinfectant used, temperature, pH and the amount of biodegradable organic material present (Kirmeyer et al., 2004). When applying monochloramine as a disinfectant, utilities should be aware of their target disinfectant residual value and adjustments should be made to address monochloramine demand and decay. Full-scale and laboratory-scale studies have been conducted to examine the effectiveness of monochloramine residual concentrations in controlling biofilm growth in drinking water distribution systems. Camper et al. (2003) observed that a monochloramine residual of 0.2 mg/L did not completely control biofilm growth on coupons of epoxy, ductile iron, PVC or cement. Similarly, Pintar and Slawson (2003) noted that maintaining a low monochloramine residual of 0.2–0.6 mg/L was not sufficient to inhibit the establishment of biofilms containing nitrifying bacteria and heterotrophic bacteria on PVC coupons. Wahman and Pressman (2015) have noted that when using inorganic chloramines (monochloramine), a "detectable" total chlorine residual is not sufficient to effectively limit bacterial growth in the distribution system. In full-scale investigations conducted by Norton and LeChevallier (1997) and Volk and LeChevallier (2000), water samples from drinking water systems maintaining monochloramine residual concentrations of >1.0 mg/L maintained lower heterotrophic bacterial counts and substantially fewer coliform occurrences compared to systems with lower monochloramine levels. In laboratory experiments a

monochloramine residual of >1.0mg/L reduced viable counts by greater than 1.5 log for biofilms grown on PVC, galvanized iron, copper and polycarbonate (LeChevallier et al., 1990; Gagnon et al., 2004; Murphy et al., 2008). When biofilms were grown on iron pipe, a monochloramine residual of >2.0 mg/L was needed to reduce bacterial numbers by greater than 2 log (LeChevallier et al., 1990; Ollos et al., 1998; Gagnon et al., 2004). Monochloramine residual concentrations of >2 mg/L may similarly be required to control the development of nitrifying biofilms (see Sec. 7.1.4.2).

Monochloramine has been perceived to penetrate biofilms better because of its low reactivity with polysaccharides – the primary component of the biofilm matrix (Vue et al., 2009; Xue et al., 2014). In disinfection transport experiments using chlorine/monochloramine-sensitive microelectrodes, monochloramine was shown to penetrate biofilm faster and further than free chlorine but did not result in complete inactivation (Lee et al., 2011, Pressman et al., 2012). Work by Xue et al. (2013, 2014) suggests that monochloramine disinfection efficacy and persistence may be affected by the combination of polysaccharide EPS obstructing monochloramine reactive sites on bacterial cells, and protein EPS components reacting with monochloramine. Free chlorine on the other hand was more effective near the biofilm surface where it penetrated, but had little biofilm penetration (Lee et al., 2011). The authors noted that these findings highlight the challenges for chloraminating drinking water utilities that employ free chlorine application periods for nitrification control and help explain why nitrification is so hard to stop once it has started.

An understanding of system-specific factors that may make it difficult to achieve target residuals is important for maximizing the effectiveness of strategies for secondary disinfection.

7.1.2 Considerations when changing disinfection practices to chloramination

A change in disinfectant (oxidant), including changing secondary disinfection to chloramine can impact water quality. It is always recommended that site-specific water quality/corrosion studies be conducted to capture the complex interactions of water quality, distribution system materials and treatment chemicals used in each individual water system. Some considerations when applying chloramine treatment include nitrification, biofilm, residual loss, the formation of disinfection by-products, and the impact on corrosion of distribution system and premise plumbing materials and the degradation of elastomer materials.

7.1.3 Presence of ammonia in source water

Ammonia may be present in source water and strategies to treat it will depend on many factors, including the characteristics of the raw water supply, the source and the concentration of ammonia (including variation), the operational conditions of the specific treatment method and the utility's treatment goal. In some cases, utilities will form chloramines as a strategy to remove naturally occurring ammonia in the raw water supply while others may use breakpoint chlorination. In both cases, frequent monitoring of relevant parameters (ammonia; combined, total and free chlorine) is needed to ensure that objectives are achieved at all times. More details on ammonia removal technologies and strategies, including biological treatment, can be found in Health Canada (2013a).

7.2 Distribution system considerations

The use of chloramines as a secondary disinfectant can have impacts on the distribution system water quality including corrosion, nitrification, microbial regrowth and the growth of opportunistic pathogens.

7.2.1 Lead and copper release

Several studies have compared the impact of chlorine and chloramines on lead release. In a study where three utilities had converted from chlorine to chloramines, Dyksen et al. (2007) found that one utility had decreased lead levels; a second utility experienced an increase in lead release that was below the U.S. EPA Lead and Copper Rule (LCR) action level while the third utility experienced increases that exceeded the LCR action level. As part of an all-encompassing strategy to reduce lead exposure and provide effective corrosion control, the San Francisco Public Utilities Commission increased the pH of their low alkalinity, soft water supply (pH 8.6–9.4). As a result, San Francisco did not experience lead and copper release nor did it impact their ability to meet the LCR action levels following conversion to chloramines from chlorine (Wilczak et al., 2010).

Conversely, conversion from chlorine to chloramines as a secondary disinfectant was implicated as a cause of increased lead release in the Washington, DC water crisis in 2004 (Renner, 2004; Dyksen et al., 2007). High oxidation-reduction potential (ORP) conditions favour the formation and accumulation of lead dioxide (PbO_2) scales (Schock and Gardels, 1983; Schock et al., 1996). Since chlorine is a powerful oxidant, switching from chlorine to chloramines reduced the oxidizing potential of the distributed water and destabilized the PbO_2 scale, resulting in increased lead release (Schock and Giani, 2004; Lytle and Schock, 2005). A number of studies confirmed that stable PbO_2 deposits could be readily formed and subsequently destabilized and reduced to (soluble) Pb(II) in a short period (weeks to months) under realistic conditions of distribution system pH, ORP and alkalinity (Edwards and Dudi, 2004; Lytle and Schock, 2005; Switzer et al., 2006; Valentine and Lin, 2009). Valentine and Lin (2009) suggested that for chloraminating systems, this type of lead release could be managed through higher pH (>8), carbonate levels >50mg/L, minimizing the monochloramine dose and using a lower chlorine to ammonia molar ratio (Cl:N) of 0.7 – 1. However, the authors noted that this lower ratio could enhance nitrification when adequate residual is not maintained. They also noted that NOM was a more significant agent for reducing lead oxide compared to monochloramine. In pipe loop experiments (water with <5 mg/L $CaCO_3$ and pH 7.3, zinc orthophosphate of 0.8 mg/L as PO_4), lead release was significantly higher (approximately 1-order of magnitude) after a 30 minute and 24 hour stagnation period for the chloraminated (1 mg/L and 5mg/L residual) pipe loops compared to chlorinated (1 mg/L) pipe loops (Woszczynski et al., 2013). Similarly, in simulated partial lead service line replacement experiments, sodium silicate treated water at pH 8, with a monochloramine residual of 3 mg/L was found to increase lead release compared to the chlorinated water (1 mg/L) (Zhou et al., 2015).

Edwards and Dudi (2004) found that high initial concentrations of lead were leached from in-line devices such as meters and shut-off valves, and decreased exponentially over the 58 day test period. The authors found that more lead was leached from brass treated with chloramines than chlorine, although this was only significant at the 85% confidence level, which the author's attributed to the small sample size. In Lin et al. (1997), in the absence of corrosion inhibitors, chloramines were found to suppress copper release and increase lead release from brass (3% lead content) compared to chlorine. The authors also examined lead and copper release from brass in the presence of zinc orthophosphate; sodium phosphate blend; long-chain phosphate blend; and a commercial sodium phosphate and found that lead and copper release were elevated in the chloraminated systems compared to the chlorinated systems.

A study assessed the leaching potential for several components tested under NSF/ANSI Standard 61 protocols with both chlorinated and chloraminated water. This study also included results from a benchmarking study undertaken to assess 28 waters (chlorinated and

chloraminated), collected from utilities across the U.S., against the NSF/ANSI Standard 61 exposures waters (pH 5 and pH 10 water [Section 8] and pH 8 water [Section 9]) with respect to the leaching of lead, copper, and zinc from brass samples (rods). Results indicated that neither chlorine nor chloramines were a dominant factor in the metal release of the brass rods (Sandvig et al., 2012). Laboratory experiments were conducted to quantify the levels of lead leached from seven commercially available low-lead brass alloys containing lead at 0.25% or less. The tests were conducted with two different waters, including an NSF International (NSF) / American National Standards Institute (ANSI) Standard 61 section 9 test water and a low-pH, low-alkalinity, chloraminated water expected to be aggressive with respect to lead leaching. The concentrations of lead leached from all low-lead alloys were below 1 µg/L under both leaching conditions for the 4-week duration of the experiment (Triantafyllidou and Edwards, 2010).

Douglas et al. (2004) determined that nitrification within the distribution system was the cause of a reduction in pH that resulted in high lead levels in an area of the city with lead service lines. Concentrations of lead at the tap (10–15 µg/L for flowing samples) were seen in the distribution system where a reduction in pH from 8.5 to a range of 7.8–8.2 was observed.

Limited information has been reported in the literature about the effect of other disinfectants on copper. In a 2007 utility survey, two of eleven participating utilities reported copper data before and after conversion from chlorine to chloramines (Dyksen et al., 2007). The two utilities both reported decreases in copper release post-chloramination. A bench-scale study by Rahman et al. (2007) examined the effect of three disinfectants (chlorine, chlorine dioxide, and chloramines) under two pH (7.2 and 8.5) and alkalinity (10 or 100 mg $CaCO_3$/L) conditions. The authors found that there was no significant difference in dissolved copper release for the disinfectant-free control compared to any of the disinfectants used in the study. Generally, the study found that the application of disinfectant lowered the copper release, with the lowest total copper release found under the pH 8.5, 10 mg $CaCO_3$/L and 1.0mg Cl_2/L conditions.

As part of a study assessing the leaching potential for brass components tested under NSF/ANSI Standard 61 protocols using chlorinated and chloraminated water, utilities throughout the U.S. were surveyed on copper and lead release issues. The survey responses indicated few problems with copper and lead release when chloramines were used for secondary disinfection. However, the authors cautioned that their observations did not specifically examine switching from chlorine to chloramines (Sandvig et al., 2012).

Boyd et al. (2008) studied the effects of changing disinfectants from free chlorine to chloramines and vice versa on leaching rates of metals and concentrations of metals from lead, brass, and copper components in the distribution system. Local tap water was used and water quality parameters (disinfectant residual, pH, alkalinity, and orthophosphate concentration) were monitored and maintained. The authors conducted pipe loop testing using new copper tubing and bronze piping (as a surrogate for standard brass) with copper-bronze, lead-bronze, and lead-copper galvanic couplings). Copper concentrations in unpassivated copper and bronze pipe loops were sensitive to free chlorine and chloramines but the effects were transient and not related to a specific disinfectant.

For a more detailed discussion on corrosion control, see Health Canada (2009).

7.2.2 Iron

There is limited information on the impacts of chloramines on iron. However, in a utility survey by Dyksen et al. (2007), three utilities that had converted from chlorine to chloramines responded with data on "red water". Generally, discoloured water complaints decreased following the switch to chloramines; however two utilities observed an initial increase in complaints for

several months before they decreased to below complaint levels observed during chlorine treatment. The implications of discoloured water events should not be ignored, as trace inorganics such as lead (Camara et al. 2013; Trueman and Gagnon, 2016; Masters and Edwards, 2015) as well as arsenic, chromium, uranium, and vanadium (Friedman et al., 2010) have been associated with iron scale release. For a more detailed discussion on corrosion control, see Health Canada (2009).

7.2.3 Elastomeric materials

The effect of chloramines on gasket material is a common concern. In a study by Seidel et al. (2005), 16% of utilities reported that they experienced gasket deterioration with the use of chloramines. Rockaway et al. (2007a) conducted a series of accelerated degradation experiments at 23, 45, and 75°C and 1, 30, 60 mg/L of chlorine and chloramines for six different elastomer materials: natural rubber, neoprene rubber, ethylene propylene diene monomer-peroxide–cured (EPDM-P), ethylene propylene diene monomer-sulphur–cured (EPDM-S), styrene butadiene rubber (SBR) and nitrile rubber. Generally, elastomers were more susceptible to degradation in the presence of chloramines compared to chlorine. Elastomers exposed to chloramine exhibited greater loss of hardness, tensile strength, and increased welling. The authors evaluated the overall performance of the materials and their sensitivity to degradation and rated the EPDM-P and EPDM-S as the least sensitive, the natural rubber, SBR and nitrile rubber as sensitive, and the neoprene rubber as acutely sensitive. Nagisetty et al. (2014) determined that degrading elastomers can release organic materials that are the result of leaching of additives from the elastomer itself or by-products of the reaction of chloramines and the elastomer. Using accelerated degradation processes at 40 and 30 mg/L chloramines found that a total of eighteen different organic compounds were released from natural rubber, SBR, and EPDM-S after 3 and 30 days. Bonds (2004) compared the degradation of fluorocarbons (FKM), SBR, EPDM, nitriles, and neoprenes as mechanical joint and push-on joints exposed to chloramines solution (110 mg/L) over 364 days. The author reported that with the exception of FKM, all the materials showed significant signs of deterioration when exposed in the sheet (large surface area) configuration but that the same extent of degradation was not observed when the surface area was small (as in the fitted gasket formation). Rockaway et al. (2007a, 2007b) stressed that the selection of elastomer material is an engineering decision as it required assessment of the suitability of each material for the intended environment as well as other considerations for the consequences of critical failure. The possibility of release of other compounds and degradation by-products should also be considered.

7.2.4 Nitrification

Nitrification, the microbiological process whereby ammonia is sequentially oxidized to nitrite and nitrate by ammonia-oxidizing bacteria and nitrite-oxidizing bacteria, respectively, is a significant concern for utilities using chloramines for secondary disinfection. Free ammonia can be present as a result of treatment (e.g., improper dosing or incomplete reactions) or release during chloramine demand and decay (Cunliffe, 1991; U.S. EPA, 2002).

Water quality problems caused by nitrification include the formation of nitrite and nitrate, loss of disinfectant residual, bacterial regrowth and biofilm formation, disinfection by-product formation, and decreases in pH and alkalinity which can lead to corrosion issues including the release of lead and copper (U.S. EPA, 2002; Cohen and Friedman, 2006; Zhang et al., 2009, 2010). Growth of nitrifying bacteria leads to a loss in disinfectant residual and increased biofilm production, which further escalates the chlorine demand, ammonia release and bacterial regrowth

(Kirmeyer et al., 1995, Pintar and Slawson, 2003; Scott et al. 2015). Cometabolism of monochloramine by ammonia oxidizing bacteria and reactions between chloramines and nitrite are also significant mechanisms for the loss of chloramine residual (Health Canada, 2013b; Wang et al., 2014, Wahman et al., 2016).

Factors favouring nitrification include warm water temperatures, long detention times, and the presence of high levels of organic matter in the distribution system (Kirmeyer et al., 2004; AWWA, 2006a). Nitrification episodes have typically been reported during the summer months when water temperatures range from 20°C to 25°C (Pintar et al., 2000). Utilities should consider increasing the frequency of sampling during warmer months for this reason (AWWA, 2103). Full-scale distribution systems may also be impacted by nitrifying bacteria during typical North American winter conditions, in addition to summer and fall seasons (Pintar et al., 2000).

In general, for the prevention of nitrification it is recommended that utilities maintain a minimum monochloramine concentration of 2 mg/L leaving the treatment plant and preferably greater than >1.5 mg/L at all monitoring points in the distribution system (U.S. EPA, 1999; Skadsen and Cohen, 2006; Norton and LeChevallier, 1997). Once it has started, nitrification cannot be easily stopped, even by applying high chloramine doses. Nitrifying bacteria have been detected in drinking water distribution systems in the presence of chloramine residuals exceeding 5 mg/L (Cunliffe, 1991; Baribeau, 2006). Nitrifying biofilms may harbour viable bacteria even after complete penetration with monochloramine at elevated concentrations (Pressman et al, 2012; Wolfe et al., 1990).

Utilities should be aware of the chemistry of their water and system materials before considering conversion from chloramines to free chlorine and vice versa (Wilczak, 2006; Hill and Arweiler, 2006). When establishing monitoring programs for nitrification in the distribution system, the most useful parameters are: total chlorine, free ammonia, nitrite, temperature and pH (Smith, 2006). Heterotrophic plate counts or adenosine triphosphate measurements as indicators of biological growth or biostability are also considered valuable (Smith, 2006; LeChevallier et al., 2015; Health Canada, 2018b).

Detailed information on the causes of nitrification and its monitoring, prevention and mitigation are available elsewhere (AWWA, 2006a). It is important to note that even the stringent control of excess free ammonia and the maintenance of a proper Cl_2:NH_3 ratio may not always be effective in preventing nitrification. This is due to the fact that chloramine in the distribution system will start to decay based on water quality conditions and water age, releasing free ammonia into the water (Cohen and Friedman, 2006).

7.2.5 Residual loss

Chloramines auto decompose through a series of reactions (Jafvert and Valentine, 1992). However, decomposition of chloramines can also be impacted by interactions with pipe materials and NOM and result in loss of residual.

Vikesland and Valentine (2000) demonstrated a direct reaction between Fe(II) and the monochloramine molecule, ultimately forming ammonia. Iron oxides play an autocatalytic role in the oxidation of Fe(II) by monochloramine (Vikesland and Valentine, 2002). In bench-scale experiments, Westbrook and DiGiano (2009) compared the rates of chloramine loss at two pipe surfaces (cement lined ductile iron and tuberculated, unlined cast iron pipe). Chloramine decay occurred faster (from 3.8 to < 1 mg/L in 2 h) for the unlined cast iron compared to the cement lined ductile iron (3.7 mg/L to 1.5 mg/L in 2 h).

Duirk et al. (2005) described two reaction pathways between chloramines and NOM: one fast reaction and a slow reaction where chloramines were hypothesised to hydrolyse to HOCl. The

slow reaction was reported to account for the majority of the chloramine loss in this mechanism. Work by Zhou et al. (2013) reported that the mixing ratio of chloramines impacted their decay rate in the presence of NOM: a higher chloramines decay rate observed for chloramines mixed in a ratio of 3:1 compared to 4:1. Wilczak et al. (2003b) suggested that the nature and characteristics of NOM are important factors in determining how reactive chloramine is with NOM. Additionally, the authors observed that bacterial cell fragments shed from full-scale biologically active GAC filters exerted a significant chloramine demand.

Carbonate has been observed to accelerate monochloramine decay by acting as a general acid catalyst (Vikesland et al., 2001). Nitrite was shown to exert a significant long-term monochloramine demand (Vikesland et al., 2001). Vikesland et al. (2001) demonstrated that although bromide affects chloramine loss, at low concentrations of bromide (<0.1 mg/L), bromide did not have a significant role. Wahman and Speitel (2012) explored the important role of HOCl in nitrite oxidation and found that it peaked in the pH range of 7.5-8.5. A 5:1 Cl_2:NH_3 ratio was also associated with increased nitrite oxidation (compared to a 3:1 Cl_2:NH_3 ratio). Increased oxidation of nitrite by HOCl was also associated with lower nitrite concentration (0.5 mg N/L compared to 2 mg/L of N) and decreased monochloramine concentrations (1 mg Cl_2/L compared to 4 mg Cl_2/L).

Factors such as mixing ratios, pH, and temperature have also been shown to play an important role in chloramine decay rates. In experiments by Zhou et al. (2013), chloramines decay rate was to shown to increase over time (72h). At pH > 7, the decay rate was higher for chloramines mixed at a ratio of 3:1 compared to 4:1. However, at pH < 7, that ratio did not play an obvious role. Chloramines loss was greater at low pH. Generally, chloramines loss increased with increasing temperature, and the decay rate was higher for chloramines mixed in a ratio of 3:1 compared to 4:1. Research conducted by the Philadelphia Water Department similarly showed monochloramine decay was slow at lower water temperatures (38% decay at 7°C) and increased at higher temperatures (84% decay at 30°C) (Kirmeyer et al. 2004).

7.2.6 Rechlorination and temporary breakpoint chlorination

As part of a comprehensive distribution management plan, both rechlorination and temporal breakpoint chlorination could be considered as potential tools. Maintaining sufficient disinfectant residual is important and recombining the (released) free ammonia in the distribution system by booster chlorination can be used in order to maintain the ratio near 5:1 throughout the system (Wilczak, 2006). Free ammonia residual needs to be measured before chemical addition. If sufficient free ammonia is still present, only chlorine needs to be added.

Temporal disinfectant switch to chlorine as a method for controlling nitrification is common practice (Vikesland et al., 2006.) Depending on whether nitrification is localized or widespread, the practice may range from a short-term targeted breakpoint of an isolated area of the distribution system, to a longer system-wide chlorine burnout (Skadsen and Cohen, 2006; Hill and Arweiller, 2006). Periodic free chlorination has not been demonstrated to be effective for long term nitrification control (Vikesland et al., 2006). In a full-scale study, the process of switching from chloramines to chlorine and back to chloramines created a breakpoint chlorination reaction, which resulted in a low chlorine residual "transitional front" in the distribution system. Although the HPC temporarily decreased, THMs also increased upon switching back to chloramines. While conducting breakpoint chlorination experiments in distribution systems, Rosenfeldt et al. (2009) observed that incorporating systematic flushing was important to achieving chlorine residual and decreasing chloroform production.

7.2.7 *Opportunistic pathogens*

The microbiological ecology of distribution systems and piped plumbing supplies can be influenced by factors such as the disinfection strategy, operational and water quality parameters, system materials and the age of the system (Baron et al., 2014; Ji et al., 2015). Chloramine and free chlorine have different capabilities for disinfection and therefore have different influences on the microbial composition of biofilms in the distribution system (Hwang et al., 2012; Ji et al., 2015). Hwang et al. (2012) reported that certain bacterial groups showed higher relative abundance during chloramination or chlorination, and that overall, shifts in microbial communities were more pronounced with chloramination. Other researchers have similarly shown evidence of monochloramine treatment leading to more distinct changes in the proportions of specific groups within bacterial communities in the bulk water and biofilms than free chlorine (Norton et al., 2004; Williams et al., 2005; Chiao et al., 2014; Mi et al., 2015).

Distribution system and premise plumbing biofilms can serve as reservoirs for opportunistic premise plumbing pathogens (OPPPs) such as *Legionella pneumophila*, non-tuberculous mycobacteria (e.g., *M. avium, M. intracellulare*), *Pseudomonas aeruginosa* and *Acinetobacter baumanii* (Fricker, 2003; Falkinham, 2015). In developed countries, *Legionella* and non-tuberculous mycobacteria are becoming increasingly recognized as important causes of waterborne disease for vulnerable sections of the population (Wang et al., 2012, Beer et al., 2015 Falkinham, 2015).

It has been proposed that the use of chloramines in the distribution system may contribute to environmental conditions that are less favourable for *Legionella* and more favourable for non-tuberculous mycobacteria (Gomez-Alvarez et al., 2016). A few studies have reported a lower prevalence of *Legionella* colonization in building plumbing systems using monochloramine for residual disinfection compared to systems using free chlorine (Flannery et al., 2006; Moore et al., 2006; Mancini et al., 2015). On the other hand, several studies have provide evidence of members of the genus *Mycobacterium* being selected for in chloraminated drinking water distribution systems (Norton et al., 2004; Williams et al., 2005; Gomez-Alverez et al., 2012; Revetta et al., 2013; Baron et al., 2014; Chiao et al., 2014; Gomez-Smith et al., 2015). Mycobacteria were also the dominant bacteria in biofilms in water mains from a full-scale chloraminated distribution system in a study conducted by Gomez-Smith et al. (2015).

The free-living amoeba *Naegleria fowleri* has also received an increased profile as a drinking water pathogen of emerging concern in the United States as a result of recent infections linked to municipal drinking water supplies in Arizona and Louisiana (Bartrand et al., 2014). *N. fowleri* causes Primary Amebic Meningoencephalitis (PAM), an extremely rare, but commonly fatal disease that is transmitted via inhalation of the amoeba into the nasal cavity. PAM cases to date have been predominantly associated with recreational water exposures at warm freshwater locations (Yoder et al., 2012; Bartrand et al., 2014). Two cases in Louisiana represent the first time disinfected tap water has been implicated in *N. fowleri* infection (Yoder et al., 2012). A review of the current knowledge on the occurrence, survival, pathogenicity, and disinfection of *N. fowleri* has been published (Bartrand et al. 2014). When developing a strategy for the control of *N. fowleri*, maintaining a minimum monochloramine residual of 0.5 mg/L throughout the distribution system has been recommended for systems using chloramines (Robinson and Christy, 1984; Trolio et al., 2008; NHMRC, 2011).

A well-maintained distribution system is an important component in minimizing microbiological growth in distributed water in premise plumbing systems. Utilities also need to be aware that changes in the microbiological diversity of drinking water systems can occur with changes to disinfection strategies. An understanding of the effects different disinfectants may

have on drinking water system ecology is necessary to maximize the effectiveness of disinfection strategies and minimize unintended consequences such as the potential enrichment of specific microbial groups (Williams et al., 2005; Baron et al., 2014).

7.3 Residential scale

Generally, it is not necessary to use drinking water treatment devices with municipally treated water. The use of residential-scale treatment devices on municipally treated water is based primarily on individual choice. Although private residential drinking water treatment devices may be an option for reducing concentrations of chloramines in drinking water if the consumer finds the taste objectionable, removal of the disinfectant is not recommended. Treatment devices for removal of chloramines for aesthetic concerns are covered under NSF/ANSI Standard 42 which establishes minimum requirements for materials, design and construction, and performance of drinking water treatment systems that are designed to reduce specific aesthetic-related (taste and odour) contaminants (NSF/ANSI, 2016). Systems certified under NSF/ANSI Standard 42 must be able to reduce an influent concentration of 3.0 ± 0.3 mg/L monochloramine to less than or equal to 0.5 mg/L monochloramine (NSF/ANSI, 2016).

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2016):

- CSA Group (www.csagroup.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- UL LLC (www.ul.com);
- Bureau de normalisation du Québec (www.bnq.qc.ca);
- International Association of Plumbing & Mechanical Officials (www.iapmo.org); and
- Truesdail Laboratories Inc. (www.truesdail.com)

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

7.4 Opportunities for research

There are several areas where further research would help regulators and practitioners in the application of chloramine treatment. For example, Wahman and Pressman (2015) suggest that the use of the indophenol method described in Harp et al. (2001) shows promise, as interference from organic chloramines does not affect the assessment of total and free chlorine. The method, although not approved by the U.S. EPA for use in direct measurement of monochloramine, could be a useful field test to evaluate contribution of organic chloramines to the total chlorine residual and avoid overestimating the disinfectant residual. Evidence from the application of the indophenol method (monochloramine) in field studies, particularly in the Canadian context, would be helpful in understanding its usefulness as a monitoring and operational tool.

Formation potential and effective reduction of newly regulated or unregulated disinfection by-products also merit further research. For example, both Krasner et al. (2015) and Uzen et al. (2016) expressed the need for further research to understand some of the conditions (which are likely site-specific) that affect NDMA pre-cursor removal.

Further exploration of seasonal breakpoint chlorination to determine its value as a practice for a utility is warranted given the paucity of Canadian literature on the subject. New and affordable molecular methods allow for the rapid and detailed characterization of drinking water microbiomes. A greater understanding of how disinfection strategies affect microbiological community dynamics in distribution systems and premise plumbing, specifically the effects on the ecology of OPPPs in biofilms, would be beneficial.

8.0 Kinetics and metabolism

No information relating to dermal or inhalation exposure to either mono-, di- or trichloramine was located in the literature. The only available kinetics studies were oral and *in vitro* studies that used monochloramine. As an oxidant, monochloramine is unlikely to undergo absorption, distribution and excretion intact (National Research Council, 1987). Rather, it will react with organic and inorganic substrates in saliva and stomach fluid to form organic chloramines and iodinated compounds (National Research Council, 1987; Scully and White, 1991). Metabolism studies demonstrated that the chloride ion and not monochloramine is absorbed into the bloodstream, distributed into the tissues and excreted in the urine (Abdel-Rahman et al., 1983).

8.1 Absorption

Based on *in vitro* time persistence studies and estimated chemical reactions in saliva and gastric juice, monochloramine is unlikely to be absorbed intact following ingestion (Scully and White, 1991; Kotiaho et al., 1992). By adding water containing monochloramine at levels found in drinking water (typically 1 to 3 ppm) to samples of human saliva, Kotiaho et al. (1992) showed that the reaction of monochloramine with saliva was concentration dependent. At a low concentration of 0.7 ppm, monochloramine remained in human saliva for up to 5 minutes while at a concentration of 1.8 ppm it persisted for up to 50 minutes. At higher concentrations (3.6 to 15 ppm) monochloramine did not completely react with saliva even after 2 hours (Kotiaho et al., 1992). These measured decay times of monochloramine in saliva and the short residence time in the mouth suggest that the majority of monochloramine in treated drinking water likely reaches the stomach unchanged.

However, in stomach fluid, depletion of monochloramine was rapid (within 30 seconds for concentrations of 0.7 to 15 ppm) so that intact monochloramine is unlikely to enter systemic circulation (Kotiaho et al., 1992). A metabolism study in male Sprague-Dawley rats (n=4) given ^{36}Cl radiolabelled monochloramine (1.1 mg/rat) orally showed $^{36}Cl^-$ appeared in the bloodstream and that chlorite and chlorate were not seen as metabolites. Chloride reached a peak plasma level of 10.3 µg/L 8-hours post-dosing (Abdel-Rahman et al., 1983). The absorption rate constant was 0.278 h^{-1} and the absorption half-life was 2.5 h for the labelled chloride.

8.2 Distribution

Abdel-Rahman et al. (1983) examined the distribution of the ^{36}Cl portion of radiolabelled monochloramine given orally to male rats (1.1 mg/rat) and found plasma contained the highest

amount (3.15 µg ^{36}Cl/g of tissue), followed by whole blood (2.66 µg/g), skin (2.13 µg/g), testes (2.09 µg/g) packed cells (1.90 µg/g), bone marrow (1.82 µg/g), kidney (1.62 µg/g), lung (1.58 µg/g), stomach (1.53 µg/g), thyroid (1.36 µg/g), thymus (1.36 µg/g), duodenum (1.20 µg/g), spleen (1.11 µg/g), carcass (0.77 µg/g), liver (0.74 µg/g), ileum (0.59 µg/g) and fat (0.18 µg/g).

8.3 Metabolism

Ingested monochloramine is quickly broken down in the stomach (Kotiaho et al., 1992). The reaction products formed are influenced by the concentration of monochloramine, the pH and composition of stomach fluid, and diet (Scully and White, 1991). The pH of the stomach ranges from 1 to 8 (Scully and White, 1991). At a pH near 1, the protonated form of monochloramine is more prevalent and more likely to transfer its chlorine to amino acids present in the gastric juice thereby producing N-chlorinated amino acids (Scully and White, 1991). Monochloramine may also generate iodinated organic compounds in gastric juice and saliva in the presence of nutrients such as tyrosine, 4-aminobenzoic acid, arachidonic acid, and folic acid (Bercz and Bawa, 1986). Formation of dichloramine, trichloramine or molecular chlorine did not occur in gastric juice *in vitro* (Kotiaho et al., 1992). The presence of food would likely increase reaction rates of organics with monochloramine resulting in a shorter half-life for monochloramine in saliva or stomach fluid (Scully and White, 1991). A metabolism study by Abdel-Rahman et al. (1983) that focused on chloride, chlorite and chlorate as metabolites found only chloride present in the bloodstream of rats following oral dosing with ^{36}Cl radiolabelled monochloramine (1.1 mg/rat).

The results obtained by Kotiaho et al. (1992), Abdel-Rahman et al. (1983) and Scully and White (1991) suggest that any observed toxicity associated with the ingestion of monochloramine is likely due to the formation of reaction products in the stomach rather than absorption of intact inorganic chloramines.

8.4 Excretion

Abdel-Rahman et al. (1983) showed that monochloramine is partly excreted in the urine as chloride. Excretion data for male Sprague-Dawley rats (n=4) given ^{36}Cl radiolabelled monochloramine (1.1 mg/rat) showed only 0.40 % and 0.08% of the administered dose was excreted in the urine and faeces in the first 24 h post-treatment, respectively. After 120 hours, the values were 25.15% in urine and 1.98% in faeces. No ^{36}Cl was detected in expired air at any time point (Abdel-Rahman et al., 1983).

9.0 Health effects

The following discussion on health effects will focus primarily on studies conducted via the oral route since it is the most relevant route of exposure for chloramines. Most available studies are for monochloramine, the predominant species in drinking water. Dichloramine and trichloramine are infrequently detected in drinking water, with each having only one oral study available from the literature. Minimal to no effects were seen in both humans and animals following ingestion of monochloramine, with the most significant effect (decreased body weight gain) attributed to a reduction in water intake caused by decreased palatability from high levels of monochloramine.

9.1 Effects in humans

Despite more than 90 years' history of using monochloramine as a drinking water disinfectant (U.S. EPA, 2009; Vermont Department of Health, 2012), little data exist concerning its health effects via drinking water. Only a few clinical and case-control studies and surveys are available from the literature. Results from these studies did not show any adverse health effects although limitations of the studies (e.g., weak exposure assessment, chloramination used as control, sample bias) do not allow for definitive conclusions to be drawn.

In contrast, numerous studies have been published regarding the toxicity of chloramines via inhalation. These studies are related to accidental intoxication from chloramine gas (monochloramine and dichloramine) due to improper handling of cleaning agents (Reisz and Gammon, 1986; Tanen et al., 1999; Cohle et al., 2001) or occupational/recreational exposure to trichloramine from use in food industry facilities or from swimming pools, scenarios that are not relevant to drinking water exposure. Although several papers have reported negative health effects (decreased haptoglobin, decreased haemoglobin, formation of Heinz bodies, haemolytic anaemia, methaemoglobinaemia) in haemodialysis patients when tap water containing chloramines was used for dialysis (Eaton et al., 1973; Kjellstrand et al., 1974; Klein, 1986; Fluck et al., 1999; Weinstein et al., 2000; Junglee et al., 2010), these changes were not observed in healthy volunteers deliberately ingesting chloraminated drinking water (Lubbers et al., 1982 and 1984).

9.1.1 Acute toxicity

Only two short-term studies were located regarding the human health effects following ingestion of drinking water containing monochloramine. These did not show any adverse effects at doses of up to 24 mg/L.

In phase I of a double-blind acute rising-dose tolerance study, no effects in liver, thyroid function, kidney function, haematology or overall health were observed in male volunteers consuming distilled water containing up to 24 mg/L of monochloramine (Lubbers et al., 1982). Males (10/group, aged 21 – 35 yrs. old) with normal methaemoglobin levels, thyroid function and glutathione levels, were given two 500 ml portions of either organic-free demineralized deionized water alone or containing monochloramine to drink, with a 4 hour interval between portions. Treatment days occurred every three days for a total of 5 treatment days over a period of 13 days. Doses of monochloramine were increased over the course of the treatments, beginning with 0.01 mg/L on Treatment Day 1 and increasing to 24 mg/L by the end of treatment. A battery of tests, including blood and urine biochemistry (e.g., cholesterol, triglycerides, triiodothyronine (T3)), haematology (blood cell counts, haemoglobin, haptoglobin and methaemoglobin levels), cell morphology, and a physical examination found no difference between pre-treatment and post-treatment values (Lubbers et al., 1982).

In a randomized, controlled parallel trial study by Wones et al. (1993), thyroid and lipid effects were generally absent except for a slight increase in apolipoprotein B levels at 15 ppm/day of monochloramine. Three groups of healthy men (16/group) were given distilled water and were fed a diet high in fat and cholesterol for the first 4 weeks of the study to establish a baseline. For the 4-week treatment period, all subjects continued on the study diet and were given 1.5 L/day of water containing monochloramine at 0 ppm (control), 2 ppm or 15 ppm. Blood levels were taken at the end of each 4-week period to assess lipid (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, apolipoprotein A_1, A_2 and B) and thyroid (thyroid stimulating hormone (TSH), T3, thyroxine (T4)) metabolism. No changes were observed in thyroid function in either treatment group. No change in lipid function was seen except for a slight, statistically significant increase in apolipoprotein B (a component of LDL cholesterol) observed at 15 ppm (15 mg/L). The significance of increased apolipoprotein B independent of changes in LDL cholesterol is unknown. Study limitations included relatively brief baseline and treatment periods, and previous consumption of chlorinated drinking water by most subjects.

9.1.2 Subchronic and chronic toxicity and carcinogenicity

Except for a slight increase (although within normal range) in T3 seen at 5 mg/L per day (Lubbers et al., 1984), the available long-term studies did not find any association between chloramination and health effects including dermal symptoms, upper respiratory effects and bladder cancer (Zierler et al., 1986 and 1988; McGeehin et al., 1993; Weintraub et al., 2006; CDC, 2008; Vermont Public Health, 2012). Most long-term chloramine studies compared the effects of different disinfection treatment methods (e.g., chlorination vs chloramination) on specific health outcomes (e.g., bladder cancer) or used chloramination exposure as the control group. Other shortcomings of these studies included: lack of exposure characterization, previous or concurrent exposure to chlorine, and recall bias, making the results unsuitable for risk assessment (Zierler et al., 1986, 1988; McGeehin et al., 1993; Weintraub et al., 2006; CDC, 2008; Vermont Public Health, 2012).

In a continuation of an earlier study (described in Sec. 9.1.1), two groups of healthy male volunteers (n=10/group; 21 – 35 yrs. old) were given unlimited organic-free demineralized deionized water to drink and asked to refrain from drinking tap water. One group also consumed 500 ml of water containing 5 ppm of monochloramine daily for 12 weeks followed by an eight-week recovery period (Lubbers et al., 1984). The same battery of tests as the previous study (Lubbers et al., 1982) was conducted. The only statistically significant effect was an increase in T3 uptake which changed over time when compared to the control group; however, this change remained within the normal T3 range and was clinically irrelevant.

No direct link between reported health effects and chloramination could be established in two surveys conducted in the United States following the switch from chlorine to chloramination as a secondary disinfectant by local public utilities (Weintraub et al., 2006; CDC, 2008).

After the local water utility switched from chlorine to chloramine as its secondary disinfectant, the San Fransico Health Department received a small number of complaints of dermatitis (Weintraub et al., 2006). These complaints prompted a questionnaire-based study. Despite widespread publicity, only 17 respondents completed the questionnaire from a total population of 2.4 million in the service area. Of these, 11 had histories of allergies while 8 had histories of skin issues (e.g., hives, shingles, and eczema). Of the 14 that sought medical treatment, no diagnoses were recalled by respondents. Since the complaints were heterogeneous (no consistency between individual complaints), and respondents had underlying or pre-existing conditions that plausibly explained the reported symptoms, the effects were likely unrelated to

chloramination according to the authors. Study shortcomings included the use of a convenience sample, small sample size, no dermatological exam, and not validating the questionnaire. Media coverage linking health complaints to chloramination may have influenced symptom reporting (Weintraub et al., 2006).

Similarly, Vermont's Champlain Water District and the Public Health Service of the Centers for Disease Control and Prevention (CDC) conducted a joint investigation into health complaints (n=74) such as upper respiratory tract symptoms, watery eyes/nose, scratchy throat, gastrointestinal ailments, and skin rashes/itching following the water district's change to chloramine as a secondary disinfectant (CDC, 2008). The switch to monochloramine was widely publicized and a mass media campaign against the use of chloramination was undertaken by People Concerned about Chloramine (PCAP) prior to the switch. Both home visits and telephone interviews (46/50 subjects met the inclusion criteria) were conducted with persons expressing health concerns. Twenty-five (54%) respondents had at least one pre-existing health condition (allergies/asthma, skin issues, diabetes, autoimmune disorders, cardiac history, respiratory, arthritis, cancer). Eight of the 32 who sought medical help received a diagnosis (5 cases of psoriasis/eczema and one each of fluid in lungs, writer's rash and surface eye irritation). Only 23 of the 34 participants who changed their water use habits to treat their symptoms showed improvement. Chloramine concentrations of 1.8 to 2.3 mg/L were reported at the distribution entry point. Consumer exposure was not measured but was expected to be lower than in the distribution system. Symptoms may have been biased by self-reporting, the media campaign and the presence of PCAC members at home visits. No clear link could be drawn between treatment and symptoms (CDC, 2008).

A follow-up survey of 173 health care providers, including family practice and primary care physicians and specialists, was conducted by the Department of Health in Vermont to assess prevalence of health problems related to monochloramine use. Of the 81 surveys returned, no patients were reported to have an illness directly related to monochloramine use while only 2 patients were considered to have an underlying disease that was exacerbated by chloraminated water use. Eleven providers reported they were unsure if patient complaints were related to the water while 59 providers reported the water did not cause patient complaints. It was concluded that it is possible that some people may be sensitive to monochloramine in the water (Vermont Department of Health, 2012).

No association was seen between chloraminated drinking water and bladder cancer when compared to chlorinated drinking water in three studies (Zierler et al., 1986, 1988; McGeehin et al., 1993).

McGeehin et al. (1993) investigated the possible association between bladder cancer and drinking water disinfection methods using a population-based, case-control study in Colorado. Cases (327 subjects with bladder cancer) and controls (261 subjects with other cancers, except colorectal and lung) were identified through the Colorado Central Cancer Registry and were limited to living, white subjects, aged 21 to 84 yrs. Residential and water source histories and information on potential confounders were obtained through telephone interviews. Residences were linked to water utilities information (e.g., water source, disinfection type) and used to create exposure profiles. Logistic regression was used to adjust for cigarette smoking, consumption of tap water and coffee, and medical history. The mean person-years of exposure to chloraminated surface water was lower ($p=0.02$) for cases (mean 14.8 years) than for controls (mean 18.8 years). The risk of bladder cancer decreased with increasing duration of exposure to chloraminated surface water ($p<0.01$) with a risk estimate of 0.7 (95 % confidence interval or CI 0.4–1.1) for subjects who consumed chloraminated water for 21 to 40 years while those who consumed

chloraminated water for more than 40 years had an odds ratio of 0.6 (95 % CI 0.4–1.0). The decreased risk seen likely corresponded to the decrease in years of exposure to chlorinated water and not to any protective effect of chloramination since there is no biological evidence that suggests chloramination inhibits neoplastic transformation of bladder epithelium. Some potential shortcomings of study included: changes over time by some water utilities in their disinfection methods, assumption that water parameters and individual consumption patterns were constant over time, gaps in historical data on water treatment and individual exposure profiles, and the potential for recall bias.

Using Department of Public Health death records, Zierler et al. (1986) examined mortality patterns between Massachusetts residents (≥45 years of age) consuming chlorine-treated and chloramine-treated drinking water. Subjects were assigned to either group based on residence at time of death. No correlation was seen between cancer mortality and consumption of chloraminated water but the chloramine group did have a slight excess of deaths from pneumonia and influenza (standardized mortality ratio [SMR] of 118; CI 116–120 for chloraminated water vs SMR of 98; CI 95–100 for chlorinated water). Bladder cancer deaths were moderately associated with chlorinated-treated (SMR of 105; CI 99–111) but not chloraminated-treated (SMR 91; CI 88–98) drinking water. The results should be considered preliminary and qualitative since the study had a number of shortcomings (e.g., exposure history based on residence at time of death, error in assigning disease status, failure to assess previous residence histories, length of exposure and water quality) and may have been influenced by unidentified or uncontrolled confounding factors. The authors also suggested that deaths from pneumonia may have been a secondary cause of death, with cancer or some other underlying illness likely the primary cause.

In a follow-up case-control study that considered exposure duration, Zierler et al. (1988) again found no correlation between bladder cancer mortality and consumption of chloraminated surface water. The study looked at data on 614 individuals who died of primary bladder cancer who had been exposed to surface water treated by chlorination or chloramination for either a lifetime or 50% of residence. The control group (1074 individuals) consisted of five disease groups: cardiovascular disease, cerebrovascular disease, lung cancer, chronic obstructive pulmonary disease, and lymphatic cancer. Potential confounders (e.g., age, sex, pack-years of smoking, occupation, socioeconomic status) were provided through proxy interviews and were controlled by a multiple logistic regression model. The frequency of bladder cancer mortality increased among lifetime residents of communities receiving chlorinated drinking water compared to residents of communities receiving chloraminated drinking water. However, the U.S. EPA (1994b) pointed out that it is impossible to find control subjects who have not been exposed to chlorine or chloramines, and indicated that the relationship between chloraminated water consumption and bladder cancer incidence cannot be defined based on the results of these studies.

9.1.3 Developmental and reproductive toxicity

In the only developmental study available, chloramination was less likely to cause adverse pregnancy outcomes when compared to chlorination. Aschengrau et al. (1993) conducted a case-control study comparing adverse pregnancy outcomes (congenital anomalies, stillbirths, neonatal deaths) with a variety of community drinking water quality parameters (source, treatment, routine chemistry). Residential address at the time of pregnancy outcome or during the first trimester was matched to routine water quality analyses conducted by the Massachusetts Department of Environmental Protection and used to characterize exposure. After adjusting for potential confounding factors (e.g., maternal race, age, previous birth with congenital anomaly, medical

insurance coverage type, alcohol consumption and water source), chlorinated surface water for drinking was associated with an increase in both stillbirths (adjusted OR=2.6; 95% CI 0.9–7.5) and major malformations (adjusted OR=1.5; 95% CI 0.7–2.1) when compared to chloraminated drinking water. A number of study shortcomings such as the lack of a non-treated control group, no consideration of other maternal health issues, the rough estimates of individual exposure, no water consumption data, no measurement of chloramine levels, make the results difficult to interpret (Aschengrau et al., 1993).

9.2 Effects on experimental animals

The main effects seen in studies with monochloramine were decreased body weight gain, decreased organ weights and alterations of blood parameters. However, paired water studies indicate that these effects are likely caused by decreased water consumption and not the toxicity of monochloramine (Daniel et al., 1990, 1991; Poon et al., 1997).

No dermal studies were located in the literature for any of the chloramines. The majority of available oral studies in animals were for monochloramine with only one subchronic oral study available for both di- and trichloramine. No inhalation studies were found for either mono- or dichloramine. Two acute inhalation studies were available for trichloramine (Barbee et al., 1983; Gagnaire et al., 1994).

9.2.1 Acute toxicity

Acute oral exposure to monochloramine caused stomach irritation at high doses (Kato et al., 1997; Nishiwaki et al., 1997; Umeda et al., 1999) while its effects on blood parameters (e.g., glutathione - GSH) were transient (Abdel-Rahman et al., 1984). Inhalation of high doses of trichloramine resulted in severe respiratory irritation (Barbee et al., 1983; Gagnaire et al 1994).

9.2.1.1 Oral

No significant effects on blood parameters were observed in a limited number of acute oral studies using monochloramine although stomach effects were seen in high dose studies.

Monochloramine given orally to male rats (5/dose) at high concentrations (20, 60 and/or 120 mM, corresponding to approximately 1,000, 3,100 and 6,200 mg/L) was shown to irritate the gastric mucosa and impair the ulcerogenic/repair process in the stomach, with doses of $\geq$ 60 mM (corresponding to 11.25 mg/kg bw, calculated) inducing severe mucosal lesions (Kato et al., 1997; Nishiwaki et al., 1997; Umeda et al., 1999).

In another study examining several blood parameters, male Sprague-Dawley rats (4/dose) were gavaged with a single dose of monochloramine in deionized water (0, 10, 20 or 40 mg/L) (Abdel-Rahman et al., 1984). Osmotic fragility was unaffected, whereas increases in blood GSH, an antioxidant, were noted at 20 and 40 mg/L 15 minutes after dosing and continued for up to 60 minutes, but returned to normal after 2 hours.

9.2.1.2 Inhalation

Barbee et al (1983) reported an inhalation LC_{50} (1 hour) of 112 ppm (550 mg/m^3) in rats exposed to trichloramine. Pulmonary edema, and clear fluid in the lung and trachea were seen in the animals that died following exposure. No mortality was seen at the lowest concentration of 58 ppm. At the highest concentration of 157 ppm, rats displayed effects such as eye irritation, excessive lacrimation, salivation, gasping and inactivity, as well as convulsions and nasal discharge.

In another inhalation study to evaluate upper airway irritation from airborne chemicals, male OF_1 mice (n~8/concentration) were exposed oronasally to 0.19-5.0 ppm trichloramine for 60 minutes (Gagnaire et al., 1994). The RD_{50}, an exposure concentration producing a 50% respiratory rate decrease and an indication or respiratory irritation, was calculated at 2.5 ppm. Once exposure was discontinued, recovery was fairly rapid except for the highest dose, where mice had a slower recovery.

9.2.2 Short-term exposure

9.2.2.1 Monochloramine: Decreased body weights and blood effects

Daniel et al. (1990) exposed Crl:CD BR Sprague-Dawley rats (10/sex/dose) to 0, 25, 50, 100 and 200 mg/L monochloramine in drinking water (equivalent to 0, 1.8, 3.4, 5.8, 9.0 mg/kg bw per day for males and 0, 2.6, 4.3, 7.7, 12.1 mg/kg bw per day for females) for 90 days. A significant dose-related reduction in daily water consumption was seen in both sexes at all doses. In addition, a significant reduction in body weight gain (males at ≥50 mg/L, and females at 200 mg/L) and in final body weight (both sexes at the highest dose) were noted. Changes in some haematological parameters and in absolute and relative organ weights were also noted in the absence of histopathological effects. Clinical chemistry results showed a dose-dependent decrease in the level of calcium at all doses in treated males, whereas an increase was seen in females at the highest dose only. The haematological and clinical chemistry changes were either not dose dependent, not biologically significant or within the normal range for rats of that age and strain. A NOAEL of 100 mg/L (equivalent to 7.7 mg/kg bw per day for females and 5.8 mg/kg bw per day for males) was proposed in the study based on final body weight. The authors suggested conducting a matched watering and feeding study (where controls are given reduced water to match the treated group) to help distinguish between systemic toxic effects and effects on weight gain due to taste aversion.

A decrease in body weight gain (≥50 mg/L in males and ≥100 mg/L in females), final body weight (at ≥100 mg/L both sexes), water consumption (≥12.5 mg/L for females; ≥100 mg/L for males) and food consumption (females only at 100 ppm and above) were also observed in B6C3F1 mice exposed to monochloramine at 0, 12.5, 25, 50, 100 and 200 mg/L (equivalent to 0, 2.5, 5, 8.6, 11.1, 15.6 mg/kg bw per day for males and 0, 2.8, 5.3, 9.2, 12.9, 15.8 mg/kg bw per day for females) in their drinking water for 90 days (Daniel et al., 1991). Changes in relative and/or absolute organ weights at ≥ 100 ppm were seen in the absence of compound-related gross or microscopic lesions. A dose-dependent increase in white blood cells was seen in female mice at 25 mg/L and above; similarly, increases were seen in male but were not dose-dependent. In addition, a significant decrease in the percent of neutrophils was seen at the top 2 doses in both male and female mice, and an increase in lymphocytes were seen in males only at the top 2 doses. Other haematological and clinical chemistry changes were also noted at 12.5 mg/L and above but were inconsistent and not dose-dependent. A NOAEL of 50 mg/L (8.6 mg/kg bw per day for males and 9.2 mg/kg bw per day for females) based on decreased organ weights, decreased weight gain and decreased consumption of food and water, is reported in the study. The authors indicated that the observed effects could be a consequence of the decreased water consumption associated with taste aversion (Daniel et al., 1991).

The impact of taste aversion and reduced water intake on body and organ weights was assessed by Poon et al. (1997) using male Sprague-Dawley rats (10/dose) exposed to 0 or 200 ppm of monochloramine (equivalent to 0 or 21.6 mg/kg bw per day as calculated by the study authors) for 13 weeks. A paired-water control, with restricted water intake, and a control group,

given bicarbonate buffered water ad libitum, were used. Over the course of the study, the monochloramine group consistently drank less water ($p<0.05$) than the control given water ad libitum. Both the monochloramine group and the paired-water control group showed similar reduced body weight gain, final body weights and food consumption. Changes in organ weights, and minor changes in biochemistry, haematology, immunological and histopathology, were also seen in the treated group as well as in the paired-water controls. The authors concluded that these changes were related to the reduced water and food consumption seen in these two groups and not as a result of monochloramine toxicity.

Body weight loss (50 ppm and above) and decreased water consumption (25 ppm and above) were observed in male A/J mice (12/dose) administered monochloramine in drinking water (0, 2.5, 25, 50, 100 or 200 ppm) for 30 days (Moore et al., 1980). No evidence of haemolysis or other blood effects was reported.

In contrast, adult African green monkeys (5 males and 7 females) exposed to monochloramine in drinking water up to 100 mg/L per day (10 mg/kg bw per day) using a rising dose protocol[2] did not show adverse effects on body weight nor on thyroid function (serum thyroxine (T4) concentrations), haematology, haematological oxidative functions, or serum chemistry (Bercz et al., 1982). Three other chemicals (chlorine dioxide, sodium chlorite and sodium chlorate) were also tested on the same monkeys with a 9 week rest period before a new chemical was introduced. No separate control group was used; however, the monkeys served as their own control.

Similarly, no signs of overt toxicity, decreased body weight gain or haematological changes were observed in rats exposed to monochloramine in drinking water (up to 100 mg/L) for 45 days in a study sponsored by the U.S. EPA's Health Effects Research Laboratory (Bull, 1980). However, a decrease in the amount of methaemoglobin in blood was noted at the highest dose, contrary to the authors' expectations of an increase based on observations in patients dialyzed with chloraminated tap water (Eaton et al., 1973; Kjellstrand et al., 1974; Klein, 1986; Fluck et al., 1999; Junglee et al., 2010).

Body weights were significantly decreased starting at 3 months and above at the highest dose in male Sprague-Dawley rats (4/dose) exposed to monochloramine in drinking water at 0, 1, 10 or 100 mg/L for up to 12 months (Abdel-Rahman et al., 1984). Blood parameters were also investigated; however, the observed changes (increased blood osmotic fragility and decreased blood GSH) were not consistent among the treatment groups and were not dose- or time-dependent. Other parameters (decreased red blood cell count and haematocrit) were seen at mid-time points but not at 10 months. Haemoglobin and mean corpuscular haemoglobin concentrations were reduced at 100 mg/L after 10 months which, according to the authors, was an indication of erythrocyte damage. No data on water consumption was provided in this study, however the authors noted significant decreases in body weights at 100 mg/L, which may have had effects on blood parameters, as seen in previous studies above.

9.2.2.2 Monochloramine: Immunotoxic effects

Immunotoxic effects of monochloramine were investigated by Exon et al. (1987). Male Sprague-Dawley rats (12/dose) were exposed to monochloramine concentrations in drinking water (0, 9, 19 or 38 ppm) from weaning (3 weeks old) for 9 weeks. A reduction in relative and absolute spleen weight at the highest dose, and an increased production of prostaglandin E2 by

[2] The study also looked at other drinking water chemicals.

adherent resident peritoneal cells were observed at the 2 highest doses. Other effects observed were a decrease (inverse dose-dependent) in serum antibody synthesis at the 2 lowest doses (9 and 19 ppm). A review by U.S. EPA (1994a) indicated that the biological importance of these immunotoxic effects from monochloramine was not clear as there was no correlation among the various immunological endpoints studied. They also noted deficiencies in some of the methodologies used (e.g., ELISA test to analyze antibodies). No other remarkable findings were noted with respect to body weights, or in the battery of other immuno-assays used (Exon et al., 1987).

No immunotoxic effects[3] related to monochloramine exposure were observed when female B6C3F1 mice (8/dose) were exposed to monochloramine in drinking water at 0, 2, 10, 20, 100 and 200 ppm (0, 0.4, 2, 4, 20 and 40 mg/kg bw per day) for 28 days (NTP, 2000; Guo et al., 2011).

In a 13-week drinking water study, a small, statistically significant increase in Concanavalin A-mediated lymphocyte transformation activity (a measure of cell agglutination) was observed in male Sprague-Dawley rats (10/group) given administered 200 ppm (21.6 mg/kg bw/day) monochloramine in drinking water compared to paired-water controls (Poon et al., 1997). A second control group was given bicarbonate buffered water ad libitum throughout the study. Both the monochloramine group and the paired-water control group showed similar reduced body weight gain which the authors concluded was related to the reduced water and food consumption seen in these two groups. The authors also concluded that monochloramine was not likely to be a significant immunotoxicant given that there were no effects observed on the relative thymus weight and no treatment-related histopathological changes in the thymus and spleen.

9.2.2.3 Dichloramine and trichloramine

Only one subchronic study assessed the oral toxicity of di-and trichloramine in rats. Biochemical and mild to minimal histological effects were seen at doses of 0.2 ppm and above in females and males in the absence of clinical signs or weight gain changes.

Sprague-Dawley rats (10/sex/dose) were exposed to dichloramine (0, 0.2, 2, 20 and 200 ppm; calculated as 0.019, 0.19, 1.9 and 18 mg/kg bw per day for males and 0.025, 0.26, 2.5 and 24 mg/kg bw per day for females) or trichloramine (0, 0.2, 2, 10 and 90 ppm; calculated as 0.020, 0.23, 1.1, and 9.6 mg/kg bw per day for males and 0.028, 0.29, 1.3 and 13 mg/kg bw per day for females) in drinking water for 13 weeks (Nakai et al., 2000). Dichloramine produced minimal histological effects (epithelial hyperplasia) in the gastric cardia at ≥2 ppm (≥0.19 mg/kg bw per day) in males, and at ≥20 ppm (≥2.5 mg/kg bw per day) in females. Minimal to mild effects were seen in the kidney and thyroid without any clear dose-response and in the absence of changes in relative organ weight or clinical manifestations. Other relatively mild effects, considered adaptive, were also seen in the liver. Trichloramine exposure produced minimal to mild histological effects in the thyroid, at 2 ppm and above in both males (≥0.23 mg/kg bw per day) and females (≥0.29 mg/kg bw per day). Minimal to mild changes (considered adaptive by the authors) in the liver of males were noted at ≥0.2 ppm (≥0.02 mg/kg bw per day), whereas at 90 ppm (13 mg/kg bw per day), females showed an increase in hepatic enzyme activity. At the highest dose, minimal histopathological changes in the kidney were also seen in males and increased relative kidney weight in both males and females. Although histological changes in the kidney were noted in females at all doses, no dose response in incidence or severity was observed.

[3] Immunotox endpoints included: Natural Killer Cell Activity assay; IgM antibody titers; hemolytic plaque assay; red blood cell counts; white blood cell counts and differentials; and organ weights (including thymus and spleen).

It must be noted that water consumption was decreased in both studies and that the minimal effects reported did not have clinical manifestations over the dose range examined.

9.2.3 Long-term exposure and carcinogenicity

The National Toxicological Program (NTP, 1992; Dunnick and Melnick, 1993), exposed F344/N rats and B6C3F1 mice (n=70/sex/species/group) to monochloramine in drinking water[4] (0, 50, 100 and 200 ppm) for 2 years. The calculated weighted mean equivalent doses[5] were 0, 2.6, 4.8 and 8.7 mg/kg bw per day in male rats; 0, 2.7, 5.2, and 9.5 mg/kg bw per day in female rats; 0, 7.4, 14.0, and 23.8 mg/kg bw per day in male mice; and 0, 7.6, 14.2 and 24.2 mg/kg bw per day in female mice. Interim sacrifices (10/sex/species/dose) were conducted at weeks 14 and 66. Both rats and mice showed a dose-related decrease in water consumption throughout most of the study which was attributed to palatability.

In treated F344/N rats, feed consumption was similar to that of the controls. However, mean body weights in the high dose rat group (both sexes) were decreased (5-10%) compared to the low- and mid-dosed rats. Changes in absolute and relative liver, brain and/or kidney weight were also observed but were considered by the authors to be related to the lower body weights and were not biologically significant. In female F344/N rats, there was a marginal statistically significant increase in the incidence of mononuclear cell leukaemia (MNCL) at the top 2 doses, but this increase was not dose-dependent since the response at these 2 doses were very similar: [8/50 (16%), 11/50 (22%), 15/50 (30%), and 16/50 (32%) for control, low-, mid- and high-dose groups, respectively]. In addition, this marginal increase was within the range (although in the upper range) reported for historical controls (16-33%) and no reduced latency of MNCL in treated female rats was noted. According to NTP (1992), the evidence was weak in support of an association between MNCL in female rats and the consumption of chloraminated water. No increase in MNCL was observed in male rats. No other clinical findings or haematological effects, or effects on survival or gross microscopic lesions were attributable to the consumption of chloraminated water. A NOAEL was set at 8.7 mg/kg bw per day (200 ppm) based on the absence of biologically significant adverse effects in male rats exposed at the highest concentration tested. Although lower body weights were observed at this level of exposure, they were likely caused by the unpalatability of the drinking water.

In mice (both sexes), there were also dose-related decreases in mean body weights during most of the study. Feed consumption was similar in treated male mice compared to controls and only slightly lower in high-dose females compared to controls. Changes in absolute and relative organ weight (kidney, liver and brain) were also observed in the high dose mice and were also considered to be related to the lower body weights. No other clinical findings, effects on survival rates or gross microscopic lesions were attributable to the consumption of chloraminated water.

At the time of the study, the NTP (1992) concluded that under conditions of the bioassay, there was equivocal evidence of carcinogenicity in female F344/N rats based on MNCL but no evidence of carcinogenicity in either male F344/N rats or B6C3F1 mice of either sex. Beginning in 2006, NTP discontinued the use of F344 rats in carcinogenicity studies (King-Herbert and Thayer, 2006; Maronpot et al., 2016) because of the high and variable background incidence of

[4] drinking water was buffered, charcoal-filtered and deionized

[5] Sample calculation taken from NTP 1992 appendix L (tables L3, L4, L7 and L8) dose per day: [(13weeks /total number of weeks) X mean value for week 1-13)] + [(39 weeks/total number of weeks) * mean value for week 14-52] + [(49 weeks /total number of weeks) X mean value for weeks 53-101)] = calculated weighted mean equivalent doses

MNCL in F344 rats, the species- and strain-specificity of MNCL and its questionable significance to humans, especially when rates fall within normal historical control values (King-Herbert and Thayer, 2006; Maronpot et al., 2016).

In a rat liver foci assay, chloramine failed to induce an increase in γ-glutamyl-transpeptidase foci (GGT foci; an indicator of carcinogenicity) in male Sprague-Dawley rats given 14.75 mg/kg of chloramine in drinking water (Herren-Freund and Pereira, 1986). Based on this study monochloramine did not show any potential for tumor initiation in this study. Negative results were also seen using concentrated drinking water samples disinfected with monochloramine in another liver foci assay in rats (Miller et al., 1986).

9.2.4 Genotoxicity

The literature on the genotoxicity of chloramines is limited to four *in vitro* studies and two *in vivo* studies; these studies investigated the genetic toxicology of monochloramine only. Monochloramine was not genotoxic in *in vivo* studies or in a modified Ames test but was weakly mutagenic in *Bacillus substili* assay.

9.2.4.1 In vitro findings

In *in vitro* studies, monochloramine was shown to be weakly mutagenic in *Bacillus subtilis* (Shih and Lederberg, 1976a) but not mutagenic in *Salmonella typhimurium* TA100 in a modified Ames test without metabolic activation (Thomas et al., 1987).

Monochloramine induced single-strand breaks in *Bacillus subtilis* (Shih and Lederberg, 1976b), double-strand plasmid DNA breakage (Shibata et al., 1999), DNA fragmentation and DNA double-strand breaks as well as chromatin condensation in rabbit gastric mucosal cells and human gastric cancer cells (Suzuki et al., 1997, 1998).

9.2.4.2 In vivo findings

Monochloramine did not induce chromosomal damage *in vivo* in either bone marrow or sperm of orally dosed mice.

No increases in micronucleated polychromatic erythrocytes or in chromosomal aberrations were seen in the bone marrow of Swiss CD-1 mice (5/sex/dose) gavaged with 1 ml of 0, 50, 100 or 200 mg/L of monochloramine per day for 5 days and then sacrificed (Meier et al., 1985). In the same study, single, gavage doses of monochloramine (0, 50, 100 or 200 mg/L) in Swiss CD-1 mice (4/sex/dose) also did not cause any chromosomal aberrations.

Abdel-Rahman et al. (1984) investigated DNA synthesis in various organs (via incorporation of [3H] thymidine into the nuclei), by administering methyl thymidine intraperitoneally to rats treated with 0, 1, 10 and 100 mg/L monochloramine for 3 months. Increased DNA synthesis as indicated by increased [^{3}H] thymidine uptake into the testes cell nuclei was noted at 100 mg/L after the 3-month treatment, whereas increased uptake into the kidney and spleen cell nuclei were noted at the two lower doses (1 and 10 mg/L) only. Monochloramine did not increase the number of sperm-head abnormalities in male B6C3F1 mice (10/group) gavaged with 1ml of 0, 50, 100 or 200 mg/L of monochloramine per day for 5 days and then sacrificed (Meier et al., 1985).

9.2.5 Reproductive and developmental toxicity

No development or reproductive effects were seen in two limited oral rat studies using monochloramine in drinking water. No studies were located for di- and trichloramine.

Adult male (12/dose) and female Long-Evans rats (24/dose) were gavaged with monochloramine in deionized water at doses of 0, 2.5, 5 and 10 mg/kg bw per day for 66 days (males) and 76 days (females) before and during mating. Dosing continued throughout gestation and up to day 21 of lactation for females (Carlton et al., 1986). No changes in body weight gain, haematology, fertility, reproductive histopathology or sperm parameters (including motility, morphology and count) were seen in adults. Lactation, litter viability, litter size, mean pup weight and day of eye opening were not affected up to postnatal day (PND) 21. Several female pups were retained until PND 28-40 for observation and showed no effect on average days of vaginal patency. Statistical analysis of the data is not provided in the study.

No significant external or soft tissue anomalies, or resorption were seen in foetuses, when female Sprague-Dawley rats (6/dose) were exposed to monochloramine in drinking water (0, 1, 10 or 100 mg/L) for 2 ½ months prior to mating and up to gestation day 20 (Abdel-Rahman et al., 1982). Information on statistical analyses, maternal weight, drinking water intake, and monochloramine intake were not provided in the study. The study also used a small number of animals per dose and reported foetal effects based on individual pups rather than by litter or maternal unit.

10.0 Classification and assessment

The International Agency for Research on Cancer (IARC, 2004) has classified monochloramine as "not classifiable as to its carcinogenicity to humans" (Group 3) based on inadequate evidence in humans and in experimental animals. Similarly, the U.S. EPA (1994a) classified monochloramine as not classifiable to human carcinogenicity (Group D), based on inadequate evidence of cancer in both humans and animals. The NTP (1992) study concluded that there was equivocal (marginal) evidence of carcinogenic activity in female rats based on an increase in the incidence of mononuclear cell leukaemia (MNCL) and that there was no evidence of carcinogenic activity of chloraminated water in male rats, male mice, or female mice. Although an increased incidence of MNCL in female rats was observed, there was no evidence of a dose–response relationship and no evidence of a temporal relationship between increasing dose and incidence of tumours. In addition, it was noted that MNCL has a high spontaneous rate of occurrence in female F344 rats and that the levels reported in the NTP (1992) study were within the historical control range reported for historical controls (U.S. EPA, 1994a). The use of F344 rats by NTP has since been discontinued in carcinogenicity studies because of the high and variable background incidence of MNCL in F344 rats, the species- and strain-specificity of MNCL and its questionable significance to humans, especially when rates fall within normal historical control values (King-Herbert and Thayer, 2006; Maronpot et al., 2016).

The databases for di- and trichloramine were weak with only two subchronic oral or drinking water studies available. Although additional studies are available for trichloramine via inhalation, these pertain to occupational and swimming pool exposures which occurred at different conditions than those found in drinking water systems. It is unlikely that trichloramine would be produced during regular residential use of chloraminated drinking water (e.g., during showering or bathing scenarios).

The database for monochloramine is better characterized and consists of studies conducted orally, with several studies dosing in drinking water. In drinking water, monochloramine is the predominant chloramine present while dichloramine and trichloramine are infrequently detected.

A decrease in animal body weight gain was observed in a number of subchronic and chronic studies conducted with monochloramine with rats and mice. These effects occurred at doses of 50 to 200 ppm (2.6 to 9.5 mg/kg bw per day for rats; 7.4 to 24.2 mg/kg bw per day for

mice). Several authors have suggested that this response is likely linked to decreased water consumption by rodents (Daniel et al., 1990, 1991; NTP, 1992) most likely due to aversion to the taste of high levels of chloramine in drinking water and thus not considered biologically significant. This opinion is also shared by the U.S. EPA (1994b) and the WHO (2011). Poon et al. (1997) demonstrated this effect by adding a paired-water control to their study and also found changes in body weights, organ weights, and minor changes in biochemistry, haematology, immunological and histopathology in the treated group as well as in the paired-water controls. The authors concluded that these changes were related to the reduced water and food consumption seen and not as a result of monochloramine toxicity.

Some possible immunologic effects have been reported, although the biological significance of these effects is unclear. No treatment-related developmental or reproductive effects have been observed in rats exposed to monochloramine in drinking water in limited studies. It should also be noted that monochloramine rapidly breaks down in the stomach (see Sec. 9.2.3) forming other potentially toxic compounds (e.g., disinfection by-products) depending on the stomach contents and pH.

In humans, results from available studies and surveys did not indicate any adverse health effects associated with exposure to monochloramine in drinking water. Because there were limitations with these studies (e.g., weak exposure assessment, chloramination used as control, sample bias), no definitive conclusions could be drawn. There have been no published reports of dermal or ocular irritation in humans following bathing or showering with chloraminated tap water. In addition, no information is available on any potential systemic toxicity that can be caused by exposure to chloramine via the dermal route.

A toxic endpoint from exposure to monochloramine (or di- or trichloramine) has not been identified due to the lack of toxicity observed in rodent or human studies. Hence, it was deemed not necessary to establish a Health Based Value for chloramine in drinking water.

10.1 Aesthetic considerations

At 3 mg/L, only a slight intensity was detected overall by the panel. Lubbers and Bianchine (1984) also found a wide variability in individual perception of taste. Although a dose of 24 mg/L was slightly (6/10) to very (2/10) unpleasant to volunteer test subjects (n=10) to most test subjects, one subject could not detect a taste and another did not find it objectionable. According to White (1992), concentrations of 3 and even 5 mg/L of monochloramine in drinking water are unlikely to cause taste and odour complaints. Odour is more closely related to the ratio of dichloramine to monochloramine than to their absolute concentrations. Problems with taste and odour may result when the concentration of dichloramine exceeds 20% of the monochloramine concentration (Mallevialle and Suffet, 1987).

10.2 International considerations

Several organizations have set guidelines or regulations pertaining to the concentration of chloramines in drinking water, all based on the same chronic 2-year study (NTP, 1992), which indicated a NOAEL of 200 ppm, the highest dose of the study. None of the agencies applied an additional uncertainty factor for possible carcinogenicity, as the carcinogenic effects reported in the study were equivocal and the tumour incidences were within the range observed in historical controls.

The U.S. EPA (1998) has established a maximum residual disinfectant level (MRDL) and a maximum residual disinfectant level goal (MRDLG) for chloramine, both set at 4.0 mg/L (4000 µg/L) and measured as combined total chlorine (as Cl_2). The U.S. EPA (1998) considers MRDLs

to be enforceable standards, analogous to MCLs, which recognize the benefits of adding a disinfectant to water on a continuous basis and to maintain a residual to control for pathogens in the distribution system. The MRDL and MRDLG are the same because there are no limitations imposed by the analytical methods or treatment technology.

The World Health Organization (2004, 2011) established a drinking water guideline of 3 mg/L (or 3000 µg/L) based on the same NTP (1992) study. WHO (2011) noted that there was insufficient data to establish a guideline for the other 2 forms of inorganic chloramines, di-and trichloramine. The Australian drinking water guideline for chloramine is also set at 3.0 mg/L (NHMRC, 2011), based on the same NTP (1992) study.

11.0 Rationale

The protection of public health by maintaining the microbiological safety of the drinking water supply during distribution is the primary concern when using monochloramine for secondary disinfection. Health risks from chloramines or from any of its disinfection by-products are much lower than the risks from consuming water that has not been adequately disinfected. Minimal to no effects were seen in both humans and animals following ingestion of monochloramine, with the most significant effect being decreased body weight gain in animal studies. However this effect is attributed to a reduction in water consumption caused by taste aversion of drinking water with high levels of monochloramine. The information on dichloramine and trichloramine is insufficient to establish any link with unwanted health effects in animals or in humans. These forms are also not frequently detected in drinking water.

Health-based values have been established for chloramines in other countries or by international organizations. WHO and Australia have established guideline values for chloramines of 3 mg/L in drinking water, whereas the U.S. EPA has set a maximum residual disinfectant level goal of 4 mg/L for chloramines. These health-based values have all been derived from the same NTP (1992) study, using the highest dose administered. These standards or guidelines are considered to be conservative since there were no documented health effects in that study, or any other available studies. A true NOAEL was not identified in the NTP study due to aesthetic considerations limiting the highest doses tested in rodents. Based on the lack of toxicity observed in rodent studies, the Federal-Provincial-Territorial Committee on Drinking Water has deemed that there is no need to establish a guideline for chloramines in drinking water. The Committee has also determined that an aesthetic objective is not necessary, since levels commonly found in drinking water are within an acceptable range for taste and odour, and protection of consumers from microbial health risks is paramount.

Where chloramines are used as drinking water disinfectant, it is recommended that their concentration be determined on a system-specific basis to ensure effectiveness of disinfection and maintenance of an appropriate residual, while minimizing by-product formation and aesthetic concerns.

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Appendix A: List of acronyms

ANSI	American National Standards Institute
APHA	American Public Health Association
bw	body weight
CDC	Center for Disease Control (United States)
CI	confidence interval
Cl_2:NH_3	chlorine:ammonia weight ratio
CT	concentration × time
DBPs	disinfection by-products
DPD	N,N-diethyl-p-phenylenediamine
EPDM-P	ethylene propylene diene monomer-peroxide – cured
EPDM-S	ethylene propylene diene monomer-sulphur – cured
FKM	fluorocarbons
GGT	γ-glutamyl-transpeptidase
GSH	glutathione
HAAs	haloacetic acids
HDL	high-density lipoprotein
HOCl	hypochlorous acid
HPC	heterotrophic plate count
IARC	International Agency for Research on Cancer
I-DBPs	iodinated disinfection by-products
LCR	Lead and Copper Rule (United States)
LD_{50}	median lethal dose
LDL	low-density lipoprotein
MAC	maximum acceptable concentration
MCL	maximum contaminant level (United States)
MNCL	mononuclear cell leukemia
MRDL	maximum residual disinfectant level (United States)
MRDLG	maximum residual disinfectant level goal (United States)
NA	not available
NDMA	N-nitrosodimethylamine
NOAEL	no-observed-adverse-effect-level
NOM	natural organic matter
NSF	NSF International
NTP	National Toxicology Program (United States)
OPPPs	opportunistic premise plumbing pathogens
OR	odds ratio
ORP	oxidation-reduction potential
SCC	Standards Council of Canada
SMR	standardized mortality ratio
T3	triiodothyronine
T4	thyroxine
THMs	trihalomethanes
TSH	thyroid stimulating hormone
UV	ultraviolet
WHO	World Health Organization

Appendix B: Provincial and territorial anticipated impacts

Please note that this information is not available in both official languages because the source of the information is not subject to the Official Languages Act.

Prince Edward Island

Newfoundland and Labrador

Nova Scotia

New Brunswick

Quebec

Ontario

Manitoba

Saskatchewan

Alberta

British Columbia

Yukon

Northwest Territories

Nunavut

4 Parameters - Chemical

4-B NOM

Reference/Action:

- Oral presentation on the draft guidance document on natural organic matter (NOM) in drinking water
- Status: The work on the NOM document was initiated in March 2014. The document was drafted and went through an external peer-review process which ended in February 2017. Comments from peer-reviewers were addressed and the document was revised accordingly. The document was sent to CDW members in the summer of 2017 for their comments and input about their preference between a guidance and a guideline document. All comments from CDW members were considered and the document was revised. The document is presented to CDW members for approval for a 2-month public consultation period.
- To be sent prior to meeting: Draft guidance document for natural organic matter in drinking water
- For CDW discussion/approval

Notes:

4 Parameters - Chemical

4-C HAAs – Screening values for BCA & BDCA

Reference/Action:

- Oral presentation on the screening values prepared for BCA and BDCA, which are two brominated HAAs.
- Status: At the Fall 2016 CDW meeting, members requested drinking water screening values for BCA and BDCA, two HAAs that are not part of the existing guideline technical document. Draft screening values were prepared and underwent an external peer-review process. The comments from peer-reviewers were all considered and the documents revised accordingly. The screening values are shared with CDW members for information only.
- To be sent prior to meeting: Drinking water screening values documents for BCA and BDCA
- For information only

Notes:

4 Parameters - Chemical

4-D PFNA – Screening value

Reference/Action:

- Oral presentation on the drinking water screening value for PFNA in drinking water
- Status: At the Spring 2017 CDW meeting, members were interested in the new science about PFNA. Based on this request, the Secretariat gathered some information and developed a drinking water screening value on PFNA.
- For information only

Notes:

4 Parameters - Chemical

4-E Boron

Reference/Action:

- Verbal update on the status of the guideline development for boron in drinking water.
- For information only

Notes:

4 Parameters - Chemical

4-F Cadmium

Reference/Action:

- Oral presentation on the draft guideline technical document on cadmium in drinking water
- Status: The work on the cadmium document was initiated in June 2017. The document is being drafted and will go through internal and external peer-review processes in winter 2017-2018. The document is expected to be presented to CDW members at the spring 2018 meeting for approval for a 2-month public consultation period.
- For information only

Notes:

4 Parameters - Chemical

4-G Barium

Reference/Action:

- Oral presentation on the draft guideline technical document for barium in drinking water
- Status: The work on the barium document was initiated in January 2016. The draft document was drafted and went through peer-review during the summer of 2017. Comments from peer-reviewers were addressed and the draft document was revised accordingly. The document is presented to CDW members for approval for a 2-month public consultation period.
- Attached: Draft guideline technical document for barium in drinking water.
- For CDW discussion/approval.

Notes:

Barium in Drinking Water

Document for Public Consultation

Prepared by the Federal-Provincial-Territorial Committee on Drinking Water

Consultation period ends
XXXXX, 2018

Barium in Drinking Water
Document for Public Consultation

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October 2017

Barium in Drinking Water

Purpose of consultation

The Federal-Provincial-Territorial Committee on Drinking Water (CDW) has assessed the available information on barium with the intent of updating the current drinking water guideline and guideline technical document on barium in drinking water. The purpose of this consultation is to solicit comments on the proposed guideline, on the approach used for its development and on the potential economic costs of implementing it, as well as to determine the availability of additional exposure data.

The existing guideline on barium, last updated in 1990, established a maximum acceptable concentration (MAC) of 1.0 mg/L (1000 µg/L) based on the absence of adverse effects on blood pressure in humans. This new document provides updated scientific data and information related to the health effects of barium, and now focuses on kidney effects in male mice. It outlines analytical methods and treatment technologies available at the municipal and residential scales. It proposes a new MAC of 2.0 mg/L (2000 µg/L) for barium in drinking water.

The CDW has requested that this document be made available to the public and open for comment. Comments are appreciated, with accompanying rationale, where required. Comments can be sent to the CDW Secretariat via email at water_eau@hc-sc.gc.ca. If this is not feasible, comments may be sent by mail to the CDW Secretariat, Water and Air Quality Bureau, Health Canada, 3rd Floor, 269 Laurier Avenue West, A.L. 4903D, Ottawa, Ontario K1A 0K9. All comments must be received before March 29, 2017.

Comments received as part of this consultation will be shared with the appropriate CDW member, along with the name and affiliation of their author. Authors who do not want their name and affiliation shared with their CDW member should provide a statement to this effect along with their comments.

It should be noted that this guideline technical document on barium in drinking water will be revised following evaluation of comments received, and a drinking water guideline will be established, if required. This document should be considered as a draft for comment only.

Barium

Part I. Overview and Application

1.0 Proposed guideline

A maximum acceptable concentration (MAC) of 2.0 mg/L (2000 µg/L) is proposed for total barium in drinking water.

2.0 Executive summary

Barium occurs in various compounds in the environment either naturally or from human activities. While the main use of barium is as drilling fluid additive in oil and gas exploration, it is also used as a contrast agent in X-ray diagnostic tests, and in a wide array of products including plastics, rubbers, paint, glass, carpets, ceramics, sealants, furniture, fertilizers and pesticides. Naturally occurring barium can be found in most types of rocks and can enter surface and groundwater by leaching and eroding from sedimentary rocks. A total of over 20 radioactive isotopes have been identified in the environment for barium, with various degrees of stability and radioactivity. However, the focus of this document is limited to barium's chemical properties.

This guideline technical document reviews and assesses all identified health risks associated with barium in drinking water. It assesses new studies and approaches and takes into consideration the availability of appropriate treatment technology. Based on this review, the proposed guideline for barium in drinking water is a maximum acceptable concentration of 2.0 mg/L.

During its fall 2017 meeting, the Federal-Provincial-Territorial Committee on Drinking Water reviewed the guideline technical document for barium and gave approval for this document to undergo public consultations.

2.1 Health effects

The International Agency for Research on Cancer has not classified barium as to its carcinogenicity. The U.S. Environmental Protection Agency concluded that barium is not likely to be carcinogenic to humans from exposure through ingestion; other international agencies agree that there is no evidence showing that exposure to barium through ingestion could cause cancer.

Studies have found links between the ingestion of barium and unwanted effects on blood pressure in animals and humans. However, adverse effects on the kidneys have shown the strongest association with chronic oral exposure to barium. In humans, effects have been observed on the kidneys following exposure to high levels of barium in poisoning events; in animals, kidney effects are considered the most sensitive health effect associated with long term ingestion of barium, especially in mice, the most sensitive species. Consequently, the proposed MAC of 2.0 mg/L has been established to be protective of the general population, based on studies of kidney effects in mice.

2.2 Exposure

Canadians are primarily exposed to barium through food and drinking water, with food being the main source of exposure. Concentrations of barium in food items in Canada vary widely depending on the food item and soil conditions. Barium levels can vary greatly in Canadian

drinking water, depending on geological formations and anthropogenic activities surrounding the source water. Intake of barium from drinking water is not expected through either skin contact or inhalation.

2.3 Analysis and treatment

There are several analytical methods available for the analysis of total barium in drinking water at levels well below the proposed MAC. Total barium includes both the dissolved and particulate forms of barium in a water sample. Therefore, if the two forms are measured separately, the two concentrations must be added before comparison with the MAC.

Although conventional coagulation treatment is not effective for barium removal, there are several effective methods for the removal of barium from municipal drinking water supplies. Effective technologies for reducing barium in drinking water include lime softening, ion exchange softening, as well as high pressure membrane separation processes such as reverse osmosis and nanofiltration. Other control strategies include switching to a new source, blending and interconnecting with another water system.

At the residential level, there are certified residential treatment devices for the removal of barium from drinking water. Drinking water treatment technologies able to effectively remove barium include ion exchange and reverse osmosis. It is important to note that reverse osmosis systems should be installed only at the point of use, as the treated water may be corrosive to internal plumbing components.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

For drinking water supplies that occasionally experience short-term exceedances of barium above the guideline value, it is suggested that a plan be developed and implemented to address these situations. For more significant, long-term exceedances that cannot be addressed through treatment, it is suggested that alternative sources of drinking water be considered.

3.1 Monitoring

3.1.1 Source characterization

Source water should be characterised to determine if barium is present. If the barium concentration is approaching the proposed MAC and/or the concentration is known or expected to be changing with time (e.g., anthropogenic activities are introduced), monitoring of the source water should be conducted annually. Authorities may consider reduced monitoring when there is sufficient data demonstrating that barium is present at concentrations equal or below 2.0 mg/L in the source water and/or appropriate treatment is in place.

Utilities practicing control options for addressing barium concentration in source water should assess water quality of new sources to ensure that it does not interfere with the existing treatment processes, impact the distribution system, and/or cause other water quality issues.

3.1.2 Operational monitoring

Utilities that treat their water for the removal of barium need to conduct frequent monitoring of the treated water in order to make necessary process adjustments and to ensure that treatment processes are effectively removing barium and other co-contaminants below their respective MACs.

Utilities using lime softening for barium removal should conduct operational monitoring of pH. Utilities using ion exchange water softening (i.e. a strong-acid cation [SAC] exchange resin in sodium form) for hardness and barium removal in their source water should monitor for hardness breakthrough in each ion exchange vessel to identify the timing for resin regeneration and achieve an effective barium removal. An operational consideration when using SAC resins in hydrogen form includes chromatographic peaking. Since barium and calcium are the most preferred cations by these ion exchange resins, chromatographic peaking may be observed for ions such as sodium and magnesium in the product water. Hydrogen form of SAC and weak-acid cation (WAC) exchange resins must be followed by a carbon dioxide stripping process and a pH or alkalinity adjustment step of the product water to reduce corrosivity. Utilities using SAC exchange resins in sodium form should be aware that this process may introduce undesirable quantities of sodium in the treated water.

Reverse osmosis (RO), ion exchange and electrodialysis/electrodialysis reversal (ED/EDR) are often operated with a bypass blending of a portion of the influent flow with the treated water to obtain the desired water quality. It is important to monitor blended treated water to determine final barium concentrations when this control option is used.

3.1.3 Compliance monitoring

When treatment is in place for barium reduction (including control options), it is recommended that compliance monitoring be conducted annualy, at minimum, to confirm the proposed MAC is not exceeded. Samples should be collected after treatment prior to distribution (typically at the entry point to the distribution system). Paired samples of source and treated water should be taken to confirm the efficacy of the treatment or control option.

3.1.4 Distribution system

Like other inorganics, barium has potential for the accumulation and intermittent release in distribution systems. Consequently, monitoring should also be conducted throughout the distribution system when barium is or was historically present in the source water. Since the stability of metals accumulated in distribution system piping scales is unpredictable, it is difficult to establish a monitoring program for barium in distribution systems. The number and location for monitoring of barium in the distribution system should take into consideration the site-specific accumulation and release risk factors. Factors that influence barium accumulation (i.e., manganese deposits, iron corrosion products and phosphate precipitates) and remobilization such as changes to water chemistry and physical/hydraulic disturbances in the distribution system could be used as indictors of when and where to monitor for barium releases. When water quality changes or physical disruptions occur in the system, the release of barium and other contaminants may be indicated by the presence of discoloured water or increased turbidity resulting from the release of deposits or scales present on the pipe wall. When this occurs, monitoring for barium and other contaminants should be conducted when the system is back to normal operation. However, the absence of discoloured water should not be interpreted as the absence of metal release. Monitoring for barium should be done in conjunction with other metals that can co-occur in the distribution system (e.g., iron, manganese, arsenic, lead).

Homeowners with private wells are encouraged to have their water tested for barium to ensure that the concentration in their water supply is below the MAC. Homeowners with private wells using residential treatment devices should conduct routine testing on both the water entering the treatment device and the treated water to verify that the treatment device is effective. Homeowners using ion-exchange softeners should be aware that the treatment unit may introduce undesirable quantities of sodium in the treated water.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Barium (Ba; CAS Registry No. 7440-39-3) is a soft, silvery white element. It is a divalent cation and belongs to the Group IIA (alkaline-earth metal) of the periodic table of elements. It has a specific gravity of 3.6 at 25°C, a melting point of 727°C and a boiling point of 1897°C (CRC, 2017). Barium is widely distributed across the earth's crust (0.04%) with an average concentration of 10–425 mg/kg, and ranks 16t^{h} in abundance amongst non-gaseous elements (Taylor, 1964; Schroeder et al., 1972). Coal can contain barium in concentrations up to 3000 mg/kg (WHO, 2001; ATSDR, 2007). Naturally occurring barium is a combination of seven stable isotopes. However, more than 20 isotopes have been identified, most of them being highly radioactive and with half-lives ranging from several milliseconds to several minutes (WHO, 1990; Boffito, 1991; U.S. EPA, 2005). Only non-radiological forms of barium will be assessed in this document.

Barium does not occur in its elemental form in nature; it occurs as a divalent cation associated with other elements and is mostly found in igneous, sedimentary and metamorphic rocks (Boffito, 1991). Common barium compounds include barium sulphate (barite), barium carbonate (witherite), barium chloride, barium hydroxide, barium oxide, and barium sulphide. Barium reacts with water to form barium hydroxide. Water soluble barium compounds include salts of acetate, hydroxide, silicate, chlorate, nitrate, thiocyanate, cyanide, oxide and halides (excluding fluoride); salts of arsenate, carbonate, citrate, fluoride, oxalate, and tartrate are only slightly soluble in water but soluble in acids. Barium chromate and phosphate are insoluble in water, but soluble in acids whereas barium sulphate is insoluble in water and only slightly soluble in acids. All barium salts, excluding sulphate, show increasing solubility with decreasing pH (WHO, 1990). Table 1 provides the physicochemical properties of common barium compounds.

Table 1: Physicochemical properties of barium compounds (adapted from CCME, 2013)

Substance	Chemical formula	Physical description	Molecular weight (g/mol)	Vapour pressure (mm Hg)[a]	Solubility (g/100 g water)
Barium	Ba	Silvery yellow metal (cubic)	137	6.65×10^{-4} at 630°C	Reacts with water
Barium carbonate	$BaCO_3$	White orthorhombic crystals	197.34	Essentially zero	0.0014 at 20°C
Barium chloride	$BaCl_2$	White orthorhombic crystals; hygroscopic	208.3	Essentially zero	37.0 at 25°C
Barium sulphate	$BaSO_4$	White orthorhombic crystals	233.39	No data	0.00031 at 20°C
Barium hydroxide	$Ba(OH)_2$	White powder	171.34	0 at 15°C	4.91 at 25°C
Barium oxide	BaO	White, yellowish powder; cubic and hexagonal	153.33	Essentially zero	1.5 at 20°C
Barium sulphide	BaS	Colourless cubic crystals or gray powder	169.39	No data	8.94 at 25°C

[a] Data from ATSDR (2007)

The main use of barium (as barite) is as a drilling fluid additive to increase fluid density (hydrostatic pressure) in applications such as oil and gas exploration, representing 85% of the global use. Barite is also used as a contrast agent to improve the visibility of certain organs in X-ray diagnostic tests; in the chemical sector it is used in plastic and rubber products, paint, glass, carpets, ceramics, sealants, furniture, cement vessels, superconducting films, and nuclear reactors (Dumont, 2007; CCME, 2013). Barium nitrate is used in the manufacturing of pyrotechnics. Barium chloride is used in the production of sodium hydroxide, aluminum alloys, pigments and textiles, and in the treatment of boiler water (Dibello et al., 2003). Barium is also used in some pesticide applications such as barium metaborate (used as a microbiocide/microbiostat in paints, paper/paper products, industrial adhesives and coatings) and barium carbonate is used as a rodenticide (U.S. EPA, 1993; ATSDR, 2007).

Barite and witherite are two commercial barium compounds widespread throughout Canada with more than 150 deposits identified and four main orebodies (Giant Mascot and Mineral King in BC; Buchans in NL; and Walton in NS) (CCME, 2013). Small deposits of witherite have been found in Thunder Bay (Dumont, 2007). In 2007, Canadian production of barite and witherite was estimated to be 7,196 tonnes while 68,971 tonnes were used in Canada (Dumont, 2007).

4.1 Environmental fate

Barium is naturally present in metamorphic, igneous and sedimentary rocks at a wide range of concentrations, however, anthropogenic activities, such as the dispersal of barium-rich fertilizers, and insecticides, drilling mud, and shale gas development, can also increase its concentration. Sulphates and carbonates precipitate barium in the soil, and metal oxides and hydroxides also favour its adsorption onto soil particles. The mobility of barium in soil is generally low given it adsorbs easily to clay minerals and organic matter; it tends to form insoluble salts and not soluble humic complexes. Under acidic, anaerobic and high chloride/low sulphate conditions, as well as conditions of reduced reduction-oxidation potential, barium mobility is increased, favouring its migration to groundwater (Kravchenko et al., 2014).

The release of barium into the air can result from electric power generation, heating plants, gasoline combustion, metal smelters, kiln operations in cement plants, as well as mining and refuse incineration (CCME, 2013). Point sources of barium include effluents and cuttings from oil drilling sites, since barite is often used as a main constituent in drilling mud suspensions (Breuer et al., 2004). Barium in the air is associated with particulate matter and mainly occurs in insoluble forms (e.g., sulphate) (Kravchenko et al., 2014).

Naturally occurring barium can be found in most types of rock including igneous, metamorphic and sedimentary. Leaching and eroding of barium from sedimentary rocks can be a substantial source of barium in surface and groundwater with barium concentrations in water determined by dissolved ion concentrations (mainly sulphate and carbonate) and by adsorption of barium ions onto suspended particulate matter, clay, metal oxides, and hydroxides (Taylor, 1964; WHO, 2001; Colbert and McManus, 2005; CCME, 2013). The formation of barium sulphate leads to its precipitation (CCME, 2013). As pH decreases, the sulfur species present in water will be reduced to lower oxidation states, increasing the water solubility of barium compounds, with barium sulphate ($BaSO_4$) and carbonate ($BaCO_3$) being more dependent on pH than barium chloride (ATSDR, 2007; Kravchenko et al., 2014). The presence of chloride and other anions such as nitrate (NO_3) and carbonate (CO_3^{2-}) generally increases the solubility of barium sulphate, and when present in water with a pH less than 9.3, 98 % of barium will be found as the free divalent cation (Ba^{2+}) while less than 2% will be present as other chemical species including

$BaB(OH)^{4+}$, $BaCl^{+}$, $BaCO_3$, $BaNO^{3+}$ and $BaOH^{+}$ (Venugopal and Luckey, 1978; ATSDR, 2007; Tudorache et al., 2010; CCME, 2013). In water with a pH greater than 9.3, the dominant species of barium is $BaCO_3$, limiting its solubility (ATSDR, 2007). Substantial quantities of barium can be released due to ion exchange reactions or oxide dissolution surrounding deep submarine springs (Charette and Sholkovitz, 2006; Moore, 2010). Barium and barium sulfide (BaS) may be solubilized from barite during anaerobic respiration by sulphate-reducing bacteria (Baldi et al., 1996).

5.0 Exposure

Food and drinking water represent the main sources of exposure to barium for the general population; however, the available data indicates that contribution from these sources can be highly variable. In drinking water, barium content can vary greatly depending on geological formations and anthropogenic activities surrounding the source water. Exposure from air, consumer products or soil is expected to be negligible. Allocating 20% source contribution to drinking water is deemed appropriate given that the available exposure data reported below suggests that food represents the main source of exposure to barium with drinking water representing a significant, but lesser, source of exposure.

5.1 Water

In Prince Edward Island, 14,236 samples from private drilled wells and municipal wells using the same aquifer were analysed for barium over a 7 year period (June 2010 to February 2017) (PEI Department of Communities, Land and Environment, 2017). Of 14,236 samples, 1006 were equal to or less than the detection limit of either 10 or 2 µg/L depending on when the samples were taken; the mean concentration of barium was 290 µg/L, the median was 17 µg/L and the maximum level detected was 5452 µg/L.

In Newfoundland and Labrador, barium levels in 483 public drinking water systems were reported from 2012 through 2016 using a detection limit of 1 µg/L (Newfoundland and Labrador Department of Environment and Conservation, 2017). For raw surface water, 169 out of 762 samples were below the detection limit and 25 out of 101 samples were below the detection limit for raw groundwater. Raw surface water had a mean of 20 µg/L, a median of 10 µg/L and a maximum of 130 µg/L; raw groundwater had a mean and median of 90 µg/L, and a maximum of 560 µg/L. In treated surface water, 2590 out of 3259 samples were below the detection limit; the mean was 20 µg/L, the median was 10 µg/L and the maximum level detected was 140 µg/L. In treated groundwater, 567 out of 1683 samples were below the detection limit; the mean was 90 µg/L, the median was 60 µg/L and the maximum level detected was 700 µg/L.

In New Brunswick, barium in drinking water was measured in 231 Crown (groundwater wells only) and 476 municipal water supply systems (ground and surface water) between 2007 to 2017 using a detection limit of 10 µg/L (New Brunswick Department of Health, 2017). In the Crown systems, 364 out of 1544 samples were below the detection limit. In treated groundwater, the mean was 111 µg/L, the median was 54 µg/L and the maximum was 1300 µg/L. In raw groundwater, the mean was 52 µg/L, the median was 53 µg/L and the maximum was 301 µg/L. In municipal systems, 590 out of 4203 samples were below the detection limit. In the municipal water distribution system, the mean was 70 µg/L, the median was 25 µg/L and the maximum was 3330 µg/L. In municipal raw water, the mean was 120 µg/L, the median was 65 µg/L and the maximum was 986 µg/L. In municipal surface water sources, the mean was 28 µg/L, the median was 15 µg/L and the maximum was 746 µg/L; for groundwater sources, the mean was 126 µg/L, the median was 76 µg/L and the maximum was 986 µg/L.

In Quebec, 11,889 samples of treated drinking water were taken from 3178 distribution systems between 2013 and 2016 (Ministère du Développement durable, de l'Environnement et de la Lutte contre les changements climatiques, 2017). There were 3843 samples below the detection limit of 0.2–50 µg/L (32%), the mean was 69 µg/L, the median was 20 µg/L and the maximum was 11,000 µg/L. As part of a long-term groundwater survey, more than 1,719 barium analyses were conducted between 1971 and 2014 in various regions of Quebec; these barium data are from various research projects with varying analytical methodologies. From a total of 1490 observation wells, individual wells and drinking water facilities, the mean barium level was 153 µ/L and the maximum concentration was 10600 µg/L.

The Ambient Groundwater Geochemistry project characterizes the chemical state of groundwater for southern Ontario (area of 96 000 km^2), with about 2300 samples taken between 2007 and 2014 (Hamilton, 2015). There were 40 out of 2255 samples below the detection limit of 0.1 µg/L (1.8%); the mean was 128 µg/L, the median was 64.5 µg/L and the maximum was 4940 µg/L.

In Manitoba, from 2009 to 2017, 1478 raw and 1722 treated water samples were analyzed for total barium using a detection limit of 0.3 µg/L (Manitoba, 2017). For raw water, the mean was 70 µg/L, the media was 30 µg/L and the maximum was 2473 µg/L; for treated water (which includes distribution system data), the mean was 50 µg/L, the median was 20 µg/L and the maximum was 2170 µg/L. Manitoba surface waters are monitored through a series of monitoring programs such as the Long-term Water Quality Monitoring Program, Lake Winnipeg Monitoring Program and the Coordinated Aquatic Monitoring (CAMP) Program. Between 2006 and 2017, the mean and median total barium concentrations in surface waters were 52 µg/L and 43 µg/L, respectively, with a maximum value of 1720 µg/L; only one sample out of 6777 samples was below the detection limit of 0.2 µg/L. In northern Manitoba lakes and rivers, an average concentration of less than 10 µg/L (range of 4.6 to 8.7 µg/L; n=5) has been reported (CCME, 2013).

In Saskatchewan, total drinking water barium levels were reported for 2007–2017 using a detection limit of 0.1–0.5 µg/L (Saskatchewan Department of Environment and Resource Management, 2017). Groundwater (raw) (n=1243) had a mean of 51 µg/L, a median of 14 µg/L and a maximum of 1210 µg/L. Surface water (raw) (n=451) had a mean of 51 µg/L, a median of 46 µg/L and a maximum of 920 µg/L. Treated water (n=223) had a mean of 78.3 µg/L, a median of 64 µg/L and a maximum of 1440 µg/L.

An average concentration of 91 µg/L was reported for 5 river basins in Alberta (range of 7 to 389 µg/L; n=748) (CCME, 2013)

In British Columbia, barium is not included in the typical drinking water testing; however, Interior Health Authority has reported 11 elevated barium results ranging from 1500 to 106,000 µg/L in 6 treated drinking water sites (British Columbia Ministry of Health, 2016).

In Yukon, levels of barium in drinking water were reported for samples taken from 2009 to 2017 (Yukon Environmental Health Services, 2017). Overall, the mean was 59 µg/L, the median was 27 µg/L and the maximum was 819 µg/L (29 out of 315 samples were below the detection limit of 0.1–25 µg/L). For raw water, the mean was 95 µg/L, the median was 80 µg/L. For groundwater, the mean was 50 µg/L, the median was 25 µg/L. The mean was 57 µg/L in treated water (n = 30) and 26 µg/L in surface water (n = 5).

As part of the National Survey on Disinfection By-Products and Selected Emerging Contaminants, Health Canada collected drinking water at three points throughout the distribution systems from 65 sites across Canada both during the 2009 and 2010 summer and winter months (limit of detection = 5 µg/L) (Health Canada, 2016). In raw surface water samples (n=89), barium had a mean concentration of 27 µg/L, a median of 19 µg/L and a maximum of 120 µg/L. In

treated surface water (n=70), barium had a mean concentration of 24 µg/L, a median of 16 µg/L and a maximum of 120 µg/L. In raw well water samples (n=35), barium had a mean concentration of 103 µg/L, a median of 52 µg/L and a maximum of 500 µg/L. In treated well water (n=27), barium had a mean concentration of 105 µg/L, a median of 80 µg/L and a maximum of 510 µg/L.

Environment Canada collected freshwater quality data from over 200 federal and federal-provincial sampling sites at various locations and sampling frequencies throughout Canada's aquatic ecosystems between 2000 and 2016 (ECCC, 2017). For total barium, all 18,985 samples were above the detection limit of 0.02–1 µg/L, the mean was 40.1 µg/L, the median was 25.3 µg/L and the maximum was 1900 µg/L.

The Canadian Total Diet Study (TDS) is a Health Canada initiative that measures the concentrations of different chemicals in foods and uses these data to estimate dietary exposures for different age-sex groups of the Canadian population (Health Canada, 2012b). In this study barium concentrations were measured in tap water in 9 cities between 2000 and 2012. In Montreal, the mean was 15–247 µg/L, in St-John's <3.6–57 µg/L, in Vancouver <11–62 µg/L, in Winnipeg 1.2–14 µg/L, in Toronto <1–14 µg/L, in Halifax 5.9–73 µg/L, in Ottawa 13–42 µg/L, Quebec city 21–61 µg/L, and Calgary 31–46 µg/L.

From the Canadian Provincial/Territorial monitoring data reported above as well as data from the National Survey on Disinfection By-Products and Selected Emerging Contaminants, an average of approximately 88 µg/L can be derived using the means for treated drinking; using an adult body weight of 70 kg and a drinking water consumption rate of 1.5 L/day (Health Canada, 1994), an estimated intake of 2 µg/kg bw per day (rounded) for barium from drinking water can be calculated for adults of the general Canadian population.

5.2 Food

Diet is estimated to be the primary route of barium exposure for the general Canadian population. The average dietary exposures to barium in Canada have been assessed through the Canadian TDS (Health Canada, 2012a). Based on the TDS data collected between 1993 and 2010 from nine Canadian cities (Montreal, Ottawa, St. John's, Vancouver, Winnipeg, Toronto, Whitehorse, Calgary, and Halifax), the average dietary exposures to barium expressed on a body weight basis were estimated to be between 12.4–27.7 µg/kg bw per day for those aged 0 to 6 months old, 16.6–26.6 µg/kg bw per day for 7 months to 4 years old, 14.5–19.9 µg/kg bw per day for 5 to 11 years old, 9–12.4 µg/kg bw per day for 12 to 19 years old, and 5.1–10.1 µg/kg bw per day for 20 years old and above.

Based on the TDS data between 1993 and 2012, average barium concentrations in common food items varied between the different years and cities in Canada. Sources of dietary exposure include food commodities such as grain-based products, fruits, vegetables, nuts, and herbs and spices (Health Canada, 2012b). Average barium concentrations from the TDS ranged from 19 to 5,403 µg/kg in grain-based products, 15 to 3,169 µg/kg in fruits, 3 to 4,023 µg/kg in vegetables, 1,755 to 5,033 µg/kg in nuts, and 20,750 to 38,172 µg/kg in herbs and spices. Average barium concentrations in infant milk and soy formulas had concentrations from 16 to 216 µg/L. The Canadian Council of Ministers of the Environment (CCME) estimated the average barium concentrations in human breast milk to be 3.61 µg/L based on an average of barium concentrations from 6 international studies (Canadian, Austrian, Italian, and Emirati) (CCME, 2013). Environment and Climate Change Canada (2016) reported average and 95th percentile intakes of 0.21 µg/kg bw/day and 0.24 µg/kg bw/day, respectively, for infants based on measured concentrations in breast milk from 2001 Canadian mothers between 2008 and 2011 as part of the core Maternal-Infant Research on Environmental Chemicals (MIREC) study.

5.3 Air

In air, barium is associated with dust and suspended particulates. Barium occurs mainly as the sulphate or carbonate form and possibly as other insoluble forms (WHO, 1990; ATSDR, 2007). Data from the National Air Pollution Surveillance Program suggest that much of the barium in ambient air is bound to the coarse fraction of particulate matter (2.5 to 10 µm) (CCME, 2013). The Canadian National Air Pollution Surveillance Program collects data on more than 300 ambient air pollutants across Canada (Environment Canada, 2013). For fine particulates ($PM_{2.5}$), the mean was 7 ng/m^3, the median 4 ng/m^3, and the maximum was 58 ng/m^3 (n=157). For coarse particulates (PM_{10}), the mean was 9 ng/m^3, the median 6 ng/m^3, and the maximum was 50 ng/m^3 (n=1735). A mean of 2.7 ng/m^3 was reported for background concentration in indoor air in Canada based on two small monitoring studies (two Canadian homes in Alberta and one American retirement facility; SD=4.2, n=40 samples) (CCME, 2013). In a Science Approach Document (SciAD) by ECCC (2016), barium levels in 1025 household dust samples were reported as 277 µg/g (median; 528 µg/g, 95th percentile); barium levels for outdoor and indoor air associated with $PM_{2.5}$ were reported as 0.94 ng/m^3 (median; range 0.04 – 18.89 ng/m^3; n=910) and 1.06 ng/m^3 (median; 95th percentile 4.71 ng/m^3), respectively (Environment Canada, 2011; Rasmussen et al., 2016).

5.4 Consumer products

Barite is licensed in different oral natural health products in Canada and as a radiological contrast media for opacification of the gastrointestinal tract; however, the compound is insoluble and absorption is considered minimal (Health Canada, 2017). Skin products, cosmetics and tattoo inks can also contain barium (CCME, 2013; New Zealand Ministry of Health, 2013); however, daily intakes from these products were not estimated, as there are no available data on the proportion of the general population using these items and absorption through the skin is considered negligible based on the physicochemical properties of the element.

5.5 Soil

Soil concentrations of barium vary widely depending on geological formations and anthropogenic inputs ranging from 15 to 3000 mg/kg (up to 37,000 mg/kg near barite deposits). The Geological Survey of Canada reported a mean concentration in Canadian soil of 140 mg/kg (SD=120, n=7397) (CCME, 2013). Moreover, a mean concentration of barium in indoor dust was estimated at 305.3 mg/kg (SD = 311.3; n = 165) based on the Ottawa residential study of Rasmussen et al. (2001).

5.6 Biomonitoring data

The most common biological matrix used as an indicator of barium exposure in biomonitoring studies is urine. In the U.S., the National Health and Nutrition Examination Survey (NHANES) III (1988-1994) as well as seven consecutive cycles of the Centers for Disease Control (CDC)-NHANES (up to 2012) provide data on urinary barium concentrations (normalized to creatinine concentrations) based on a representative sample of the U.S. population of all ages (n = 2502 during the 2011-2012 cycle) (Paschal et al., 1998; CDC, 2015). Generally, urinary barium concentrations have remained relatively stable over the years with children (6–11 years) having significantly higher urinary barium levels (median 2.18 µg/g creatinine (95% CI = 1.70–2.61) than adolescents (12–19 years; median 1.42 µg/g creatinine (95% CI = 1.24–1.78) and adults (≥20 years; median 1.31 µg/g creatinine (95% CI = 1.20–1.43). In the 2011-2012 cycle, females had a significantly higher median urinary barium concentration than males, at 1.51 versus 1.17 mg/g creatinine, respectively; however, this difference was not found to be statistically

significant at the 95th percentile level. Similarly, a Germany study by Heitland and Koster (2006) reported mean urinary barium levels of 1.2 µg/g creatinine for 72 children (2–17 years) and 1.3 µg/g creatinine for 87 adults (18–65 years) and a French study by Goullé et al. (2005) reported a median of 0.89 mg/L (corrected for creatinine enzymatic determination) in the urine of 100 healthy adults.

5.7 Multi-route exposure through drinking water

Barium can be absorbed via the inhalation route; however, exposure to barium vapours while showering or bathing is not expected to occur since barium is not volatile (vapour pressure close to null). Dermal absorption of barium during showering and bathing is considered negligible since the skin permeability constant is 1×10^{-3} cm/hr (U.S. EPA, 2004) indicating that the dermal route of exposure would contribute less than 10% of the drinking water consumption level (Krishnan and Carrier, 2008). Hence, the inhalation and dermal routes during showering and bathing are unlikely to contribute significantly to the total exposure.

6.0 Analytical methods

The U.S. Environmental Protection Agency (EPA) currently has three approved analytical methods (Method 200.5 revision 4.2, Method 200.7. revision 4.4, and Method 200.8 revision 5.4) for the analysis of total barium in drinking water. The U.S. EPA also approved several methods (SM 3111D, SM 3113B, and SM 3120B) developed by a voluntary consensus standard organization (U.S. EPA, 2016).

The method detection limit (MDL) for each of the approved methods are provided in Table 2. MDLs are dependent on the sample matrix, instrumentation, and selected operating conditions and will vary between individual laboratories.

Table 2: Approved analytical methods for the analysis of barium in drinking water

Method (Reference)	Methodology	MDL (µg/L)	Interferences/Comments
EPA 200.5 Rev. 4.2 (U.S. EPA, 2003)	Axially viewed inductively coupled atomic emission spectrometry (AVICP-AES)	0.05	Subject to spectral, physical, chemical and memory interferences. Matrix interferences: Ca, Mg and Na >125 mg/L and Si >250 mg/L
EPA 200.7 Rev. 4.4 and SM 3120B (U.S. EPA, 1994a; APHA et al., 1992, 1995, 1998, 2005, 2012)	Inductively coupled plasma-atomic emission spectrometry (ICP-AES)	1.0	Subject to spectral, physical, chemical and memory interferences. Matrix interferences: TDS>0.2% (w/v) for EPA 200.7 and TDS>1500 mg/L for SM 3120B
EPA 200.8 Rev. 5.4 (U.S. EPA, 1994b)	Inductively coupled plasma-mass spectrometry (ICP-MS)	0.04[a] – 0.8[b]	Subject to isobaric elemental and polyatomic ion interferences, and physical. Matrix interferences: TDS>0.2% (w/v)
SM 3111D (APHA et al., 1992, 1995, 2005, 2012)	Flame atomic absorption spectrometry	30.0	Subject to several interferences; primarily chemical interference (lack of adsorption by atoms). To prevent barium ionization Na^+, K^+ and Li^+ cations are added in excess.
SM 3113B (APHA et al., 1992,	Electrothermal atomic absorption spectrometry	2.0	Subject to molecular absorption, chemical and matrix interferences.

1995, 2005, 2012)			

[a]MDL in scanning mode; [b]MDL in selective ion monitoring mode

The current U.S. EPA practical quantitation limit (PQL) for barium is 0.15 mg/L and based on the capability of laboratories to measure the concentrations of barium within reasonable limits of precision and accuracy. In the second-six year review of existing National Primary Drinking Water Regulations, the performance evaluation and proficiency testing data suggested that the current PQL could be lower; however this reduction might be small due to the lower passing rate of the laboratories at the lowest spike concentration. No new or revised methods have been approved that may be expected to improve analytical performance in the vicinity of the current PQL for the detection of barium in water (U.S. EPA, 2009).

6.1 Sample preservation and preparation

Generally, operational considerations for analysis of barium in drinking water (i.e., sample preservation, storage, etc.) can be found in the references listed in Table 2 above. Accurate quantification of dissolved, particulate (suspended) and total barium in samples is dependent on the proper sample preservation and preparation steps. SM 3030B provides guidance on filtration and preservation procedures for the determination of dissolved or particulate metals (APHA et al., 2012). To determine dissolved barium concentrations, samples should be filtered (0.45 µm pore diameter) at the time of collection using preconditioned plastic filtering devices under either vacuum or pressure. The filtrate should be acidified to pH < 2 with concentrated nitric acid. To determine particulate barium, the filter should be retained and the particulate material on it digested in the laboratory using appropriate methods (APHA et al., 2012).

Currently, EPA methods 200.7 and 200.8 and SM 3111D, SM 3113B, SM 3120B do not require hot acid digestion for total recoverable metals unless turbidity of the sample is greater than 1 nephelometric turbidity unit (NTU). Digestion for EPA methods is performed by transferring an aliquot of the sample into a solution of nitric acid and hydrochloric acid followed by gentle heating to a temperature of approximately 85° C (i.e., hot digestion) (U.S. EPA, 1994a, 1994b). Microwave assisted digestion (SM 3030 K) is recommended for analysis of total recoverable metals using SM methods that are based on ICP-MS. Although these methods do not require hot acid digestion unless turbidity is greater than 1 NTU, research conducted on other metals such as lead and chromium has indicated that this does not accurately quantify the total metal concentration in a sample. As such, the current protocol may underestimate total barium in drinking water when particulate barium is present. For example, analytical requirements under UCMR3 include solubilizing the acid preserved sample by gentle heating using nitric acid, regardless of the sample turbidity or the method used (U.S. EPA, 2012a).

7.0 Treatment technology and distribution system considerations

7.1 Barium in water

In aqueous environments, barium typically exists in divalent form as free barium cation (Ba^{2+}). Under certain conditions, barium may form mineral precipitates involving sulphate, carbonate or chromate (Friedman et al., 2010). In the presence of sulphate (SO_4^{2-}) concentration ≥2 mg/L and pH levels below 9.3, insoluble barite ($BaSO_4$) may precipitate and become the dominant barium species. Most water sources contain sufficient SO_4^{2-} concentration to precipitate $BaSO_4$, thus maintaining barium concentrations at low levels. In the presence of carbonate (CO_3^{2-}) ions and at a pH greater than 9.3, whiterite ($BaCO_3$) exhibits fast precipitation kinetics and becomes the dominant species, limiting barium solubility (Rai et al., 1984; Snyder et al., 1986;

McComish and Ong, 1988; ATSDR, 2007; Menzie et al., 2008;). Barium ions form weak complexes with Cl^-, OH^- and NO_3^- and the solubilities of these complexes are less dependent on pH than that of barite or whiterite (Menzie et al., 2008; Tang and Johannesson, 2010; Kravchenko et al., 2014).

Barium is not readily oxidized or reduced (Menzie et al., 2008; Groschen et al., 2009). Kravchenko et al. (2014) indicated that changes in the oxidation state do not directly affect barium solubility in natural water. However, the redox potential may impact the species of sulfur. For example, if the SO_4^{2-} oxidation state is reduced to a lower oxidation state (e.g., H_2S), the depleted SO_4^{2-} concentration will result in an increase of barium solubility.

Due to the cationic nature of soluble barium species, barium may be associated with various solid matrices such as metal oxides, clay and organic matter. A study found that barium may displace other sorbed alkaline earth metals from manganese dioxide (MnO_2), silicon dioxide (SiO_2) and titanium dioxide (TiO_2). However, these alkaline metals may displace barium from aluminium oxide (Al_2O_3) (Rai et al., 1984). Similarly to most cationic trace metals, the sorption properties of barium are enhanced at higher pH (Friedman et al., 2010).

7.2 Municipal scale treatment

Limited data exist on the removal of naturally occurring barium in drinking water. The U.S. EPA (1998) lists lime softening, ion exchange, reverse osmosis (RO) and electrodialysis/electrodialysis reversal (ED/EDR) as the most effective treatment processes for the removal of barium in drinking water.

Conventional coagulation/filtration techniques showed low barium removal from drinking water (up to 30%). Two-stage coagulation processes may achieve a greater barium removal (approximately 80% removal) than conventional coagulation; however they are not common practice in Canada (Sorg and Logsdon, 1980; Lovins et al., 1999).

Early pilot- and full-scale lime softening studies reported up to 95% of barium removal in drinking water at a pH range from 10.0 to 10.5. Dissolved barium is precipitated as barium carbonate, a mechanism that occurs for calcium removal during treatment of hard water (Sorg and Logsdon, 1980).

One of the most effective technologies for reducing barium concentration in drinking water is based on ion exchange softening. Limited full-scale data and a number of comprehensive bench scale studies indicated that SAC and WAC exchange resins remove from 95% to 97% of barium to achieve treated water concentration below 1.0 mg/L (Kojola et al., 1978; Snoeyink et al., 1984,1987a, 1987b; Myers et al., 1985; Snyder et al., 1986).

High pressure membrane separation processes such as RO and nanofiltration (NF) are proven technologies for hardness removal from drinking water and are, therefore, expected to be very efficient for barium removal. ED/EDR is less commonly reported, however, it is also effective for the reduction of barium in drinking water. Electrodialysis is typically applied for desalination of seawater and brackish water with a low turbidity (Sorg and Logsdon, 1980; Krause and Stover, 1982).

The selection and effectiveness of each treatment strategy are driven by several factors, including source water chemistry, the concentration of barium, pre-existing treatment processes, operational conditions of a specific treatment method, the utility's treatment goals, and residual handling concerns and costs. Careful selection of the appropriate technology for a specific application is important, as the performance of each treatment technology is impacted by the specific chemical quality of the water being treated.

Where applicable, the appropriate authorities should be consulted to ensure that the disposal of liquid and solid waste residuals from the treatment of drinking water meet applicable regulations.

7.2.1 Control options

Typical control options for reducing excess barium levels in drinking water include switching to a new source, blending, and interconnecting with and/or purchasing water from another water system (Willey, 1987; U.S. EPA, 2012b). Attention must be given to the water quality of a new source prior to making any changes (i.e., switching, blending, and interconnecting) to an existing supply. Characterization of the water quality must be carried out to ensure that changes in water quality resulting from control options are assessed and that potential impacts to the existing treatment processes and distribution system are determined. For example, if the new water source is more aggressive, it may cause leaching of lead or copper in the distribution system. Any change in water quality should not result in other compliance issues. The disinfectant type (chlorine or chloramine) should be the same type when blending two different water sources, to avoid water quality and disinfection issues.

Switching to another source may involve drilling a new well in an aquifer containing low barium levels, sealing off water producing zones containing high barium levels, or finding an uncontaminated surface water source. Switching to another source may also be limited by the availability of new sources, existing water rights, and/or costs for transporting the new source water to the treatment plant.

Blending involves diluting the barium concentrations of a contaminated source with another source containing low or no barium. To minimize piping required to carry the sources to a common mixing point, it would be ideal for the sources to be close to each other. Blending usually occurs in a storage tank or a common header with resulting barium concentrations below the MAC. Corrosion issues should be considered when blending different water qualities.

When interconnecting with another water system, the recipient system must consider a number of factors including whether there is a nearby water supply that meets the barium MAC, whether this other system is willing to interconnect or consolidate and whether the interconnecting system can handle increased demand resulting from additional customers. Costs are an additional consideration in the decision-making process for interconnection.

7.2.2 Conventional coagulation

Conventional coagulation with alum and iron salts provides low levels of barium removal (Krause and Stover, 1982). In a jar-test study, conventional coagulation has been shown to achieve an approximately 30% removal of total barium, reducing concentrations to approximately 5.0 mg/L from 7.0 to 8.5 mg/L in groundwater with either alum or ferric sulphate doses as high as 120.0 mg/L and a pH range from 7.5 to 8.0 (Sorg and Logsdon, 1980). The test indicated that the formation of $BaSO_4$ was a very slow process and conventional coagulation was not effective mechanism for barium removal. Due to the high solubility of barium hydroxide [$Ba(OH)_2$] and barium chloride ($BaCl_2$) the formation of these complexes were reported also ineffective factors in removing of barium by a conventional coagulation treatment (Sorg and Logsdon, 1980).

A two-stage coagulation process may achieve a more efficient removal of barium, however is not recommended since the second step is costly and requires additional space to store treated water between two coagulation steps. In a bench-scale two-stage coagulation study, up to 80% of barium was removed, reducing an approximately 8.0 mg/L barium in the feed water to less than 1.6 mg/L. The process used 100.0 mg/L of either alum or ferric sulphate and allowed for

1 hour of sedimentation, followed by a second stage using 20.0 mg/L doses of coagulant and another 1 hour of sedimentation (Sorg and Logsdon, 1980).

7.2.3 Chemical precipitation

Chemical precipitation process is commonly used in water treatment utilities to remove hardness and heavy metals such as iron and manganese as well as barium, radium, cadmium, arsenic, lead, strontium and uranium. Chemical precipitation can also be used as a pre-treatment or intermediate treatment in membrane systems to reduce the potential for scaling/fouling of membranes by mineral salts.

Lime softening is the most common application of chemical precipitation. During lime softening, dissolved barium is precipitated as $BaCO_3$, the same mechanism that occurs for calcium removal from hard water. Jar-tests, pilot- and limited full- scales data indicated that barium was effectively removed from water and that the efficiency was pH dependent. Jar-tests reported that a barium concentration in the range from 7.0 to 8.0 mg/L in groundwater was effectively reduced by lime softening. The removal was pH dependent and increased from 65% at pH 8.7 to a peak of 98% at pH 10.5 and then declined to 55% at pH greater than 11.6. Barium and hardness removal curves follow the same trend except in a pH range from 10.6 to 11.4 when the hardness removal curve developed a sharp increase due to the magnesium removal. At a pH greater than 11.0, barium can become more soluble as barium hydroxide and therefore becomes more challenging to remove. Pilot- and full-scales treatment data have confirmed these trends with respect to the dependence of barium removal on pH. At a pilot-scale tests, raw water barium concentrations of 12.6 mg/L, 10.1 mg/L and 10.4 mg/L, were reduced to 2.0 mg/L, 0.7 mg/L and 1.6 mg/L in the filtered water at pH levels of 9.2, 10.5 and 11.6, respectively. The hardness reductions achieved were: from 214 mg/L to 109 mg/L, from 216 mg/L to 86 mg/L and from 209 mg/L to 42 mg/L, respectively. Grab samples from two full-scale lime softening plants operating at pH levels of 10.5 and 10.3, showed 88.0% and 95.3% barium removal, respectively. The source waters had average influent barium concentrations of 7.5 mg/L and 17.4 mg/L and average hardness of 272 mg/L and 246 mg/L as $CaCO_3$, respectively (Sorg and Logsdon, 1980).

Although not a conventional softening method, Parks and Edwards, (2006) found that precipitative softening using sodium carbonate (Na_2CO_3) only was highly effective for barium removal. The primary objective of their study, which sampled 370 raw waters (2/3 groundwater, 1/3 surface water), was to survey the range of removals of inorganic contaminants by precipitative softening using Na_2CO_3. They reported that raising the pH of water samples to 10.3 using a fixed dose of Na_2CO_3, an approximately 100% removal of barium from 145 raw water samples containing barium in the range of 10 to 884 µg/L was achieved. Their findings suggest that further research should be done on softening using Na_2CO_3 when requiring removal of only barium, rather than total hardness.

Since $BaSO_4$ is relatively insoluble in water under alkaline conditions, it may precipitate when a sulphate-containing compound, such as gypsum ($CaSO_4$), is used as a precipitating chemical and sodium hydroxide is used for a pH adjustment (Krause and Stover, 1982). Krause and Stover, (1982) reported on the effectiveness of a pilot-scale system using chemical precipitation followed by direct filtration. The system demonstrated that with an addition of 100 mg/L of $CaSO_4$ and 352 mg/L NaOH and that a barium concentration of approximately 6.0 mg/L was reduced to 0.5 mg/L in the treated water at a pH 11.0 (91.0% removal). The removal occurred at a filter hydraulic loading rate of 1.5 gpm/ft^2 (2.4 mm/s) with a filter head-loss of 27 in (69 cm) after an 8-hour run (end of the run). The precipitation process removed $BaSO_4$ along with calcium hardness in drinking water. Other chemicals such as alum, calcium hydroxide and ferric sulphate used for precipitation of barium were less effective. Since the sodium concentration in the

finished water increases, due to pH adjustment with sodium hydroxide, the authors indicated that modification of the chemicals used for pH adjustment would be required. Although the authors tested the precipitation of $BaSO_4$ at a pH of 11, such a high pH is likely not necessary based on the several kinetic studies of $BaSO_4$ (Aoun et al., 1996; van Leeuwen et al., 1996; Kugler et al., 2015). In addition, the high chemical doses used would affect the cost and sludge production. Bench, pilot, and full-scale research are needed on the precipitation of $BaSO_4$ from drinking water supplies.

7.2.4 Ion exchange

The most common application of ion exchange in drinking water treatment is water softening. Extensive research has been conducted on the applicability of SAC and WAC exchange resins for the removal of scale-forming calcium (Ca^{2+}) and magnesium (Mg^{2+}) cations and, to lesser extent, on other alkaline earth metals including Ba^{2+} and radium (Ra^{2+}) in drinking water (Sorg and Logsdon, 1980; Krause and Stover, 1982; Snoeyink et al., 1984, 1987a, 1987b; Myers et al., 1985; Snyder et al., 1986; Clifford, 1999; Elder and Budd, 2011). These types of ion exchange resins come in different forms. SAC exchange resins in sodium (Na^+), hydrogen (H^+) and calcium (Ca^{2+}) forms as well WAC in (H^+) form can be used for barium removal in drinking water.

Clifford et al. (2011) compared separation factors of a number of cations on SAC resins and produced an ion selectivity sequence (order of preference for exchange) for ten divalent cations. The sequence describes the selectivity order in which cations are preferred by SAC resins and suggests that Ba^{2+} cations are preferentially removed compared to Ca^{2+} and Mg^{2+} during water softening. The WAC resins exhibit the same selectivity sequence as SAC resins except that the H^+ ion is the most preferred cation (Clifford et al., 2011).

7.2.4.1 SAC resins in sodium and hydrogen forms

The SAC resins in sodium (Na^+) or hydrogen (H^+) forms exchange the Na^+ or H^+ cations for Ca^{2+}, Mg^{2+} and other cations such as Ba^{2+} in the water, either as carbonate hardness or noncarbonate hardness, in a pH range from 2 to 11. The pH and alkalinity of the treated water from the SAC (Na^+) remained approximately unchanged throughout the production run. However, the SAC (H^+) resin is rarely used in water softening because it produces acidic and corrosive water (Clifford, 1999) requiring acid-resistant materials, CO_2 stripping and pH adjustment of the product water (Snoeyink et al., 1984, 1987a, 1987b; Myers et al., 1985; Snyder et al., 1986).

Barium showed similar breakthrough curves for both SAC (Na^+) and SAC (H^+) resins, hardness showed similar trends as well (Snyder et al., 1986; Snoeyink et al., 1987a). One of the major operational considerations when using ion exchange treatment, especially with SAC (H^+) resins includes chromatographic peaking, whereby the less preferred ions (i.e., Na^+ and Mg^{2+}) are displaced by more preferred ions (Ba^{2+} and Ca^{2+}) causing the effluent of Na^+ and Mg^+ concentrations to be greater than influent concentration (Snoeyink et al., 1987a; Clifford, 1999). For conventional SAC (Na^+) softening, chromatographic peaking is not a major operational consideration if the treatment run is terminated at hardness breakthrough.

With resins such as SAC (Na^+) that have a strong affinity for barium, it may be difficult to remove barium from the exhausted resin. Barium accumulates on resin with repetitive exhaustion-regeneration cycles and higher doses of regenerant are required to regain the resin's capacity. The regeneration curve of the SAC (H^+) resin conducted with hydrochloric acid (HCl) follows the same trend as the regeneration curve of SAC (Na^+) conducted with sodium chloride (NaCl) regenerant. Although, barium can be precipitated in the spent NaCl brine before disposal, the authors stated that this brine cannot be reused due to the depletion of Na^+ ions (Snoeyink et al.,

1984; 1987a, 1987b; Myers et al., 1985). However, recent research has demonstrated that a spent brine can be reused (after barium removal) by adding NaCl to maintain the Na^+ concentration of the brine (Clifford et al., 2011).

An early study reported that two full-scale ion exchange softening plants were capable of achieving a barium concentration of 1.0 mg/L in treated water (Sorg and Logsdon, 1980). Plant 1 had two ion exchange beds operating in a parallel mode which treated groundwater barium concentrations of 10.0 mg/L (hardness 218 mg/L as $CaCO_3$). Plant 2 had three parallel resin beds which treated groundwater with barium concentration of 19.0 mg/L (hardness 230 mg/L as $CaCO_3$). Samples were collected from raw and treated water through one treatment cycle for one ion exchange bed from each treatment plant. The plant 1 treatment run was terminated before either hardness or barium achieved breakthrough. The plant 2 run was terminated beyond both hardness and barium breakthrough. The tested ion exchange beds reduced the barium concentrations to 1.0 mg/L for 153 BVs (7.14×10^5 L) and 100 BVs (7.87×10^5 L) for plants 1 and 2, respectively. Plant 1 achieved barium removal in the range from 94% to 99% and hardness removal from 95% to 99%. However, plant 2 reduced hardness and barium concentration to 142 mg/L and 5.8 mg/L, respectively, when the process was terminated. Both treatment plants practiced blending of a portion of the raw water with the treated water to increase the hardness and to stabilize the distributed water. Since the blended waters had barium concentrations in the range of 1.5 mg/L to 4.5 mg/L for both treatment plants, the authors concluded that the blending was not a feasible practice at these two locations because the high influent barium concentrations at both locations would increase barium levels above the treatment goal of 1.0 mg/L even if only a small portion of the raw water was blended with the treated water (Sorg and Logsdon, 1980).

In comprehensive laboratory studies, a SAC (Na^+) resin with an exchange capacity of 1.8 meq/mL (4.8 meq/g resin) was tested in repetitive exhaustion-regeneration cycles for barium, radium and hardness reduction in drinking water (Snoeyink et al., 1984; 1987a). The virgin resin was capable of reducing an influent barium concentration of 20.0 mg/L to 1.0 mg/L for approximately 1,200 BVs. The results indicated that the magnesium concentration in the treated water reached a peak concentration of approximately two times the influent concentration at approximately 600 BVs and subsequently reached the influent concentration after approximately 1200 BVs. The calcium effluent concentration was also greater than the influent concentration at the end of the same process conducted with the virgin resin. Each exhaustion run had been terminated at hardness breakthrough of 40.0 mg as $CaCO_3$/L and a regenerant dose of 1.8 meq NaCl/mL resin [6.5 lb NaCl/ft^3 resin (3 kg NaCl/m^3 resin)], was used in the regeneration cycle. During several repetitive exhaustion-regeneration cycles, the regenerated resin was capable of treating approximately 225 BVs of water before both barium and hardness achieved breakthrough (together) at 1.0 mg/L and 40.0 mg as $CaCO_3$/L, respectively. A regenerant dose of 2.7 meq NaCl/mL resin [9.75 lb NaCl/ft^3 resin (4 kg NaCl/m^3 resin)] was capable of increasing the number of the BVs processed per exhaustion cycle to 260 – 270 BVs. However, an increase of the regenerant dose from 1.8 meq NaCl/mL resin to 2.7 meq NaCl/mL decreased the regeneration efficiency from 60% to 46 %. The early breakthrough of barium indicated that it was accumulating on the resin. The virgin resin concentration was increased from 0.15 meq Ba^{2+}/mL to a constant value of 0.38 meq Ba^{2+}/mL after several regeneration cycles with a regenerant dose of 1.8 meq NaCl/mL resin. At steady-state (i.e., when the barium uptake by the resin was equal to the barium removed by regeneration), the regenerant dose of 1.8 meq NaCl/mL removed only 20% of the accumulated barium from the resin. Despite the barium accumulation, the number of the bed volumes to hardness breakthrough remained constant. The study found that the barium concentration was effectively reduced to below 1.0 mg/L as long as SAC (Na^+) resin was not exhausted for hardness ions (Snoeyink et al., 1984; 1987a). These results have been confirmed by

full-scale SAC (Na^+) columns used to remove hardness and barium in groundwater (Snoeyink et al., 1987a). One of the SAC (Na^+) columns was run beyond the hardness breakthrough and achieved water hardness and barium concentrations of 153 mg as $CaCO_3$/L and 6.4 mg/L, respectively. Another column, treating source water from another well at the same site, however, operating the exhaustion run to hardness breakthrough, was capable of reducing hardness and barium concentrations to 7.0 mg as $CaCO_3$/L and 0.3 mg/L, respectively.

Snoeyink et al. (1987a) concluded that for a raw water quality similar to the water used in laboratory study above, two parallel SAC (Na^+) columns operating in a staggered regeneration mode with a regenerant dose of 1.8 meq NaCl/mL resin could effectively reduce barium concentration below 1.0 mg/L in a blended treated water, if the exhaustion cycles were terminated at the hardness breakthrough. An important advantage of operating several columns in parallel with staggered regeneration is that product water quality is less variable compared with single-column operation. This can be a major consideration when the contaminant leakage and/or chromatographic peaking are high during a portion of the exhaustion run (Clifford et al., 2011).

It should be noted that using SAC (Na^+) resins may result in undesirable quantities of sodium in the treated water. Therefore, SAC ($Ca^{2+}$and H^+) and WAC (H^+) resins are alternative that can be used for the production of sodium-free treated water. However, proper corrosion control in the finished water should be practiced.

7.2.4.2 SAC resin in calcium form

Several studies reported that SAC (Ca^{2+}) resin was capable of effectively reducing barium and (radium Ra^{2+}) concentrations in drinking water (Myers et al., 1985; Snoeyink et al., 1987b; Clifford, 1999; Atassi et al., 2007). However, until approximately 100 to 200 BVs of SAC (Ca^{2+}) exhaustion, calcium ions are exchanged for all the cations in the feed water resulting in finished water that is very high in hardness and after that point the total hardness decreases to the influent level. An exhausted SAC (Ca^{2+}) resin requires calcium chloride ($CaCl_2$) brine to be regenerated and the spent brine may be reused after precipitating and removing barium. Proper doses of calcium sulphate ($CaSO_4$) are needed to precipitate barium as $BaSO_4$ in the spent brine and to prevent fouling of the resin during the following regeneration cycle. If the brine also contains Ra^{2+}, it will coprecipitate on the $BaSO_4$ and will also be removed (Myers et al., 1985).

A pilot-scale SAC (Ca^{2+}) system was tested in several repetitive exhaustion-regeneration cycles. The regenerated resin was capable of reducing an influent barium concentration of 12.0 mg/L to 1.0 mg/L for run lengths of approximately 1,300 BVs during the third loaded (exhaustion) run. The regeneration has been conducted with a regenerant dose of 6.0 eq $CaCl_2$/L resin (compared with only 1.8 eq NaCl/L resin [Snoeyink et. al., 1987]) and the spent $CaCl_2$ brine was reclaimed and reused. The exhausted SAC (Ca^{2+}) resin required less frequency of regeneration compared to the SAC (Na^+) resin (Atassi et al., 2007).

In laboratory tests, a virgin SAC (Ca^{2+}) resin was capable of reducing barium concentration of up to 23.0 mg/L to below 1.0 mg/L in the treated water for a run length of approximately 1,200 BVs, at a loading rate of 5.4 gpm/ft^2 (13.2 m/h) and an empty bed contact time (EBCT) of 2.5 minutes (Myers et al., 1985). The hardness, alkalinity and pH of the water were nearly unchanged throughout the treatment runs. The exhausted SAC (Ca^{2+}) resin was effectively regenerated (92–100 % removal of barium from the column) with a regenerant dose of 6 eq 0.85 M $CaCl_2$/L. Both regenerant concentration and regenerant dose affected the barium concentration in the treated water in the following exhaustion runs. When the regenerant doses were increased from 4.0, to 6.0 and to 8.0 eq $CaCl_2$/L resins, barium concentration of 1.0 mg/L was achieved for run lengths of 500, 900 and 1,100 BVs, respectively. The study reported that a mole ratio of 1.1:1 ($CaSO_4$: barium) reduced barium concentration in the spent brine and the

brine was successfully reused (Myers et al., 1985). Snoeyink et al. (1987b) indicated that the use of SAC (Ca^{2+}) resin in parallel with SAC (Na^{+}) may produce treated water with desire level of hardness in addition to barium removal. However, to prevent the increase of sodium concentration in the treated water, SAC (Ca^{2+}) can be use in parallel with SAC (H^{+}) and WAC (H^{+}), followed by carbon dioxide stripping.

7.2.4.3 WAC resin in hydrogen form

The WAC (H^{+}) resins have a weak-acid functional groups and only exchange ions in the neutral to alkaline pH range. The ion exchange process results in partial softening and produces treated water with a low alkalinity and low total dissolved solids levels. WAC (H^{+}) resins also require acid-resistant material, CO_2 stripping and pH adjustment of the product water (Snoeyink et al., 1984, 1987a, 1987b; Myers et al., 1985; Snyder et al., 1986). Although WAC (H+) resins can be regenerated by weak acids that are only slightly stronger than the resin functional group, strong acids such as HCl are usually applied. However, sulphuric acid (H_2SO_4) should not be used due to the precipitating of $BaSO_4$ on the resin and destroying its capacity. Since barium is easily removed from the exhausted WAC (H^{+}) resin with approximately 5 to 10 % excess regenerant, it does not accumulate on the resin. The regeneration of WAC (H^{+}) resin produced less spent regenerant per unit volume of treated water than the regeneration of SAC column (Snyder et al., 1986; Clifford, 1999; Elder and Budd, 2011). WAC (H^{+}) systems can be complex to operate and maintain, and may have increased costs related to chemicals and materials used (Snoeyink et al., 1984, 1987a, 1987b; Clifford, 1999; Clifford et al., 2011).

In laboratory tests, WAC (H^{+}) resin was found to effectively to remove barium (22.0 mg/L), radium and hardness without increasing the sodium concentration in the treated water . A virgin WAC (H^{+}) resin (capacity of 11.5 meq/g resin) showed an approximately identical selectivity for barium and calcium ions, as both contaminants breakthrough at approximately 800 BVs; while magnesium ions breakthrough earlier at 650 BVs. The virgin WAC (H^{+}) resin showed a lower capacity for barium but greater capacities for hardness and alkalinity than virgin SAC (H^{+}) resin under similar operating conditions. Through several repetitive exhaustion-regeneration cycles, WAC (H^{+}) resin was capable of producing treated water with barium concentration below 1.0 mg/L (22.0 mg/L influent) for run lengths 600–650 BVs. A regenerant dose of 8.5 meq HCl/g resin (i.e. only 75% of the stoichiometric amount) was capable of achieving 93–95% regeneration efficiency and greater than 99% removal of divalent ions from the resin. However, the resin regenerated with a dose of 7.6 meq HCl/g resin (i.e., 66% of the stoichiometric amount), produced higher barium concentration ranging from 0.5 to 1.3 mg/L in the treated water as a result of incomplete removal of barium from the resin during the regeneration cycles (Snyder et al., 1986).

A common practice in water softening is a bypass blending, which involves diverting of a portion of the influent flow around the treatment vessel and blending the diverted water with the treated water. Blending of finished water with raw water may stabilize finished water, and decrease the cost of treatment by reducing the volume of water treated, which results in less frequent regeneration and therefore a savings in chemical and brine disposal costs (Clifford, 1999). However, the barium concentration in the bypass water needs to be considered to ensure that the finished water concentration is not above the MAC.

7.2.5 Membrane technology

Effective membrane technologies for barium removal in drinking water include RO, NF, as well as ED/EDR (U.S. EPA, 1998; Odell, 2010). The primary difference between RO and NF is the size of dissolved contaminants that can be removed. RO membranes effectively reduce total

dissolved solid (TDS) and monovalent ions while NF membranes are mainly used for hardness (Ca^{2+}, Mg^{2+}) and organics (e.g., DBP precursors) removal. ED/EDR is most typically used for TDS reduction and inorganic ion removal (U.S. EPA, 2012b).

RO treatment systems typically require prefiltration for particle removal and often include other pre-treatment steps, such as the addition of anti-scaling agents, dechlorination and/or softening. Pretreatment is required to preserve membrane life because the presence of chlorine residuals, particulates, and scale-forming ions ([i.e., Ca^{2+}, Ba^{2+}, iron (Fe), and silica (Si)] in the feed water can adversely affect the performance of RO processes.

Post-treatment for RO permeate (i.e. finished water) typically includes pH adjustment, addition of corrosion inhibitors and disinfection. RO concentrate disposal must also be considered in the design and operation of RO plants. Systems that integrate two or more membrane processes or combine a membrane process with other treatment processes (i.e. integrated membrane system [IMS]) are implemented to improve overall process water recovery and reduce waste stream concentrations (Ning et al., 2006; Gabelich et al., 2007).

Pilot-scale testing evaluated the effectiveness of five different RO membranes for the reduction of inorganic contaminants and were tested according to the manufacturer's specifications. Selected membranes demonstrated a high rejection rate in the range of 98% to >99% for barium, under variety of operating conditions. The reported influent concentrations ranged from 1.1 mg/L to 3.7 mg/L (Huxstep and Sorg, 1988).

Performance of an IMS was tested for the removal of barium from May 1998 to January 1999 at a 56.6 MGD water treatment plant located in East St. Louis, Illinois (Lovins et al., 1999). The IMS was supplied with surface water pre-treated by conventional coagulation/sedimentation/ filtration processes (CSF). Raw water had a low barium concentration (average of 0.11 mg/L) and the CSF pre-treatment achieved an average barium concentration of 0.07 mg/L. The IMS unit consisted of three spiral wound, crossflow nanofiltration (NF) membranes with maximum pressure of 400 psi (27 bars): a composite thin-film membrane with a cut-off rating of 100–200 Da and 85 m^2 of filtration area (CSF-NF1); a composite thin-film membrane with cut-off rating of 150–300 Da and 97 m^2 of filtration area (CSF-NF2); and a cellulose acetate membrane with cut-off rating of 300 Da and 123 m^2 of filtration area (CSF-NF3). Inorganic permeate water quality varied by membrane type and produced water with average barium concentrations of 0.002, 0.026, and 0.021 mg/L, respectively, corresponding to average barium removals of 97.1, 62.9 and 70.0% respectively. Since CSF-NF1 also rejected hardness and alkalinity to below detection levels (not provided) it required corrosion control measures to stabilize treated water. In contrast, the CSF-NF2 and the CSF-NF3 membranes allowed more alkalinity and hardness to pass into the permeate, which produced more stable and less corrosive product water. The CSF-NF3 membrane was more resistant to fouling than both CSF-NF1 and CSF-NF2 membranes; while CSF-NF1 and CSF-NF2 were more sensitive to the operating conditions (e.g., flux and recovery) and feed water chemistry (e.g., pH) (Lovins, 1999).

7.2.5.1 Improving recovery of reverse osmosis

Inorganic scale formation (e.g. silica, barium sulphate and calcium carbonate) remains a serious impediment to achieve a high RO recovery. Scaling resulting from the precipitation of salts within the membrane module leads to permeate flux decline and shortening of the membrane life. As water passes through the RO membrane, rejected Ba^{2+} ions accumulate near the membrane surface and its concentration may increase to the point where precipitation of barium salts occurs (Boerlage et al., 2000; Gabelich et al., 2007). Barium sulphate can be problematic for any drinking water treatment methods that concentrate barium (Boerlage et al., 2000; Ning et al., 2006; Gabelich et al., 2007; WQA, 2014). For example, membrane scaling by barium sulphate

can reduce membrane recovery, cause flux decline and potentially severe membrane damage (Boerlage et al., 2000; Ning et al., 2006).

Lime softening, followed by filtration and pH adjustment, is an effective pre-treatment to improve the performance of RO for enhanced removal of mineral salt scaling from water sources. Intermediate concentrate chemical stabilization (ICCS) strategies apply conventional or pellet softening to a primary (first pass) RO concentrate to remove scale-forming compounds such as barium, followed by secondary RO treatment to improve the overall system recovery (He et al., 2011). An implementation of conventional lime softening-based ICCS technology of a primary RO concentrate, followed by secondary RO system, was capable of improving the overall system recovery from 85% to 92.5–95.5% (He et al., 2011). Using a lime dose of 1,220 mg/L, the ICCS reduced an average barium concentration of 0.34 mg/L in the RO concentrate to an average of 0.05 mg/L (86% reduction) at pH 10.5. At this pH level silica, strontium and calcium concentrations were also reduced to 76, 84 and 77%, respectively. The authors found that a pelletized-based ICCS technique removed less barium, silica, strontium and calcium from the primary RO concentrate, when compared to conventional lime softening-based ICCS (He et al., 2011).

Ning et al. (2006) reported the results of a bench-scale and pilot-scale study at a large inland desalination plant in El Paso, Texas. Precipitative softening by magnesium hydroxide powder [$Mg(OH)_2$] and conventional lime softening using calcium hydroxide powder [$Ca(OH)_2$] were assessed for the removal of silica and barium from RO concentrate which was subsequently treated by secondary RO to demonstrate improved RO recovery. Treatment with $Mg(OH)_2$ powder reduced a barium concentration from 0.9 mg/L to 0.34 mg/L in the concentrate (64% reduction) within one hour of processing time at a pH range of 7.8 to 9.1, but did not provide sufficient silica reduction (only 16% reduction). Conventional lime softening conducted with $(CaOH)_2$ reduced a barium concentration from 0.9 mg/L to 0.43 mg/L (50%) and silica from 143 mg/L to 48 mg/L (66 %) at pH 10.3 to 10.6 after one hour. Excess lime softening at pH 12.0, improved the settleability of the sludge due to the coagulative effect of $Mg(OH)_2$ precipitates. However, an influent barium concentration of 0.9 mg/L was reduced by only 30% and 67% after 1 and 3 hours, respectively. The silica concentration of 155 mg/L was reduced by 96% and 98% after 1 and 3 hours, respectively. It was concluded that concentrate from primary (i.e., first-pass) RO membranes would be most effectively treated by conventional lime softening at a pH of 11.5 for 1 to 3 hours. In the pilot-scale study, the authors found that the performance of the primary RO had a recovery ranging from 85% to 90% which was limited by the presence of silica and precipitated barium sulphate. Treatment of the primary RO concentrate by lime softening followed by secondary RO, sufficiently reduced membrane fouling through reduction of silica and barium concentrations and also resulted in an increase overall recovery of the system to approximately 97%.

Similarly, both Rahardianto et al. (2007) and Gabelich et al. (2007) demonstrated that two-stage desalination RO, supplemented with precipitative softening treatment of primary RO concentrate, was an effective approach to remove mineral salt scaling including barium sulphate as well as improving process recovery in the range from 95% to 98%. Gabelich et al. (2007) suggested that barium removal during precipitative softening was enhanced by inclusion into or onto calcium carbonate crystalline lattice during precipitation.

7.2.6 Emerging technologies

7.2.6.1 Adsorptive media

Araissi et al. (2016) trialed an adsorptive zeolite 4A media for barium removal in batch experiments using feed water with barium concentration from 0.3 mmol (41.1 mg/L) to 25 mmol (3432 mg/L) at pH 8.2 to 11.0. The samples were stirred for 14 hours in contact with 0.15 g of the media. The maximum observed adsorption capacity was 2.25 mmol Ba^{2+}/g. The authors indicated that the mechanism of barium removal was considered as an ion exchange process. The batch experiments were also trialed with a binary system of barium and strontium and the authors found that strontium was preferentially removed by zeolite over barium. They also indicated that zeolite may provide an effective ion exchange material for the removal of barium in water. Sato et al. (2011) reported on the use of zeolite 4A media filters for the removal of radioactive contaminants including barium from drinking waters associated with the the severe incident of Fukushima Daiichi Nuclear Power Station. The authors found that synthetic zeolite 4A efficiently removed cesium, strontium and barium but gave no details regarding the capacity of the filters or the operating conditions.

7.2.7 Distribution system consideration

The accumulation of trace inorganic contaminants (TICs) in the drinking water distribution system is a complex function of numerous factors including contaminant concentration in treated water, pH and redox conditions in the distribution system and pipe material. Iron oxyhydroxides and hydrous manganese oxides are significant sinks for TICs accumulation because of their adsorptive affinity for them. Water quality changes or physical disruptions in the distribution system can remobilize contaminants into the bulk water. Indicators of potential release of TICs in the distribution system include the presence of discoloured water or increased turbidity.

Barium has been repeatedly detected in samples from both distribution system piping scales and solids mobilized during hydrant flushing (Schock et al., 2008; Freidman et al., 2010; Peng et al., 2012; Lytle et al., 2014). Barium deposition in the distribution system occurs primarily due to the surface adsorption and/or co-precipitation reactions involving soluble barium species (Ba^{2+}), which are enhanced at elevated pH (Friedman et al., 2010). Barium accumulation is strongly influenced by the co-occurrence of manganese deposits, phosphate precipitates and/or phosphate surface groups and to lesser extent the concentration of barium in the water (McComish and Ong, 1988; Sugiyama et al., 1992; Charette and Sholkovitz, 2006; Schock et al., 2008; Friedman et al., 2010; Peng et al., 2012). Barium may also enter the distribution system water through leaching from cement-based materials and linings under aggressive water chemistry and/or hydraulic conditions. Leaching of barium from cement-mortar linings can result in the precipitation of $BaCO_3$ and $BaSO_4$ in the distribution system (Friedman et al., 2010). Guo et al. (1998) conducted laboratory tests to determine the extent of leaching from ductile iron pipes lined *in situ* with Portland cement (type I) mortar. The pipes were lined, cured and subsequently disinfected in accordance with ANSI/AWWA Standards. The tests were performed using tap water from a New Jersey water distribution system. Under static conditions barium concentration was increased gradually by up to 18% of its respective U.S. EPA's drinking water standard of 2.0 mg/L during the first 14 days of water stagnation. The cement used to line the test pipes contained lower amount of metals than most commercially available cements.

Barium impurities may be present in various treatment chemicals such as alum, calcium hydroxide, calcium hypochlorite and polyaluminium chloride that are used in drinking water treatment (NHMRC, 2011). NSF/ANSI Standards 60 and 61 sets a maximum concentration for barium that can be present in materials and treatment chemicals that are in contact with drinking water. This maximum concentration is known as the single product allowable concentration

(SPAC). The current SPACs for barium under NSF/ANSI Standards 60 and 61 are 0.2 mg/L (NSF/ANSI, 2015; 2016d).

Lead-pipe scale samples collected from 91 pipe specimens of lead and lead-lined services lines from 26 different water distribution systems in the U.S. had an average barium concentration of 199.0 mg/kg scale (range of 1.0 mg/kg to 2850 mg/kg scale). Barium was detected in concentrations greater than the reporting level of 5.0 mg/kg in 87 of the 91 samples (95%) (Schock et al., 2008).

Barium was the most concentrated inorganic contaminant detected in scale samples and sediments collected from the distribution systems of 20 U.S. drinking water utilities supplied by groundwater, surface water and blended water sources (Friedman et al., 2010; Peng et al., 2012). Distributed water had barium concentrations ranging from 0.002 to 0.6 mg/L, pH 7.1 to 8.5 and alkalinity of 48 to 289 mg/L as $CaCO_3$. Friedman et al., (2010) reported that the median barium concentration of all scale deposits and sediments samples was 94 µg/g. Specifically, median barium concentrations in scale deposits and hydrant-flush solids were 88 µg/g and 104 µg/g, respectively. Five of the deposit samples with barium concentrations ranging from 460 µg/g to 2,400 µg/g also had high manganese (372 to 46,700 µg/g) and phosphorous concentrations (2,000 to 12,300 µg/g). Zasoski and Burau, (1988) indicated that manganese dioxide (MnO_2) has been extremely effective for adsorption of cationic species similar to barium. Similarly, Peng et al., (2012) observed a notable correlation between barium and manganese concentration in scale deposits. This correlation supported the data from previous studies (Murray, 1975 and Sugiyama et al., 1992) that showed that manganese oxides formed in corrosion products interact with barium more strongly than iron oxides.

Barium concentrations in 22 hydrant flush solids and 2 pipe specimen samples from 12 different water utility distribution systems ranged from 60.8 µg/g to 9,276 µg/g (Lytle et al., 2014). All waters had a pH range from 7.0 to 8.0, alkalinity from 251 to 476 mg/L as $CaCO_3$, and were sourced from groundwater.

Friedman et al. (2010) reported an estimated barium mass of 76.0 lb accumulated on a 100 mile pipe length (based on a 12 inch diameter pipe). The authors noted that theoretically 16% to 26% of the scale deposit would need to be released to exceed the U.S. EPA's drinking water standard for barium of 2.0 mg/L.

7.3 Residential scale

In cases where barium removal is desired at the household level, for example when a household obtains its drinking water from a private well, a residential drinking water treatment device may be an option for reducing barium concentrations in drinking water.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2015):

- CSA Group (www.csagroup.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- UL LLC (www.ul.com);

- Bureau de normalisation du Québec (www.bnq.qc.ca);
- International Association of Plumbing & Mechanical Officials (www.iapmo.org); and
- Truesdail Laboratories Inc. (www.truesdail.com).

An up-to-date list of accredited certification organizations can be obtained from the SCC (2015).

Water treatment technologies able to be certified to NSF Standards for reduction of barium include cation exchange, reverse osmosis and distillation. Applicable NSF/ANSI standards are: 44 – Residential cation exchange water softeners (NSF/ANSI, 2016a); 58 – Reverse osmosis drinking water treatment systems (NSF/ANSI, 2016b) and 62 – Drinking water distillation systems (NSF/ANSI, 2016c).

For drinking water treatment devices to be certified to NSF/ANSI Standards 44, 58 and 62 for the reduction of barium concentration, the devices must be capable of reducing an average influent (challenge) concentration of 10.0 mg/L to a maximum final concentration of 2.0 mg/L or less. In addition, treatment devices certified to standards 44 and 62 can be certified either specifically for barium reduction as noted above or for the removal of hardness and total dissolved solids (TDS), respectively, which are used as a surrogate for barium in these standards. If water softeners (cation exchange systems using 100% sulfonated polystyrene di-vinyl benzene resin), certified to NSF/ANSI Standard 44 and reduced hardness concentration to below 1.0 gpg (17.1 mg/L) from an influent hardness of 20 gpg (342 mg/L) will be able effectively to reduce barium in drinking water. Treatment devices certified to NSF/ANSI Standard 62 using TDS as a surrogate must achieve a minimum TDS reduction of 99% from an influent concentration of 1,000 mg/L.

RO systems are intended for POU installation, as larger quantities of influent (incoming) water are needed to obtain the required volume of treated water, which is generally not practical for residential-scale point-of-entry systems. RO systems should only be installed at point-of-use (POU) as the water they have treated may be corrosive to internal plumbing components. A consumer may need to pre-treat the influent water to reduce fouling and extend the service life of the membrane. Distillation systems are also intended for POU installation only. The distillation process is effective for the reduction of inorganic contaminants, but requires an electrical energy input.

Selection of the most effective treatment system for a household will depend on a variety of factors including the concentration of barium and other parameters such as hardness, alkalinity and pH of the source water. Before a treatment device is installed, the water should be tested to determine general water chemistry and verify the presence and concentration of barium. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Treatment devices lose their removal capacity through usage and time and need to be maintained and/or replaced. Consumers should verify the expected longevity of the components in their treatment device according to the manufacturer's recommendations and service it when required.

Various household water softeners were randomly sampled to examine barium removal efficiency. The influent barium concentrations ranged from 0.5 mg/L to 6.4 mg/L and influent hardness varied from 205 mg/L to 248 mg/L as $CaCO_3$. All tested water softeners reduced barium concentration to below 1.0 mg/L and hardness in the range 2 mg/L to 35 mg/L as $CaCO_3$ (Snoeyink et al., 1987a).

Homeowners with private wells using ion exchange softeners in sodium form should be aware that the treatment unit may introduce undesirable quantities of sodium in the treated water.

8.0 Kinetics and metabolism

8.1 Absorption

Barium absorption from the diet in humans was reported to vary widely, generally ranging from 1% to 60% (LeRoy et al., 1966; Schroeder et al., 1972; Legget, 1992; Kravchenko et al., 2014). Factors influencing absorption include age, chemical species/solubility, fasting status, vitamin D status, and the presence of other ions in the diet (Legget, 1992). Despite the variability and uncertainty of the results, Legget (1992) proposed an absorption of 20% for water soluble forms of barium by the gastrointestinal tract which at the time of the review aligned with the value applied by the International Commission on Radiological Protection (ICRP, 1980). Peak blood level was reported to occur 2 hours after ingestion of barium chloride, with a serum half-life of 3 hours (Downs et al., 1995).

A wide range of oral absorption values have also been reported in laboratory animals (from 1 to 95%), with more water soluble forms having higher absorption (Venugopal and Luckey 1978; Kravchenko et al., 2014). In rats, 85% of $BaCl_2$ was absorbed at 14–18 days of age, 63% at 22 days of age, and 6% at 6 weeks old and older (Taylor et al., 1962). Fasting adult rats for 18 hours pre-exposure increased absorption by a factor of 3. Rats receiving 10 mg /L of barium as barium sulfate by intubation exhibited peak barium blood levels 15 minutes after dosing with 50% remaining in the blood 4 hours post exposure (McCauley and Washington, 1983). The maximum blood concentration was higher with barium sulfate compared with barium chloride and barium carbonate. In dogs, oral absorption of barium chloride was reported to range from 1–7% to 50% (Cuddihy and Griffith, 1972).

Legget (1992) reported several unpublished studies with oral absorption rates ranging from 1 to 50%. In rats administered barium chloride via gavage, younger rats (14–22 days) absorbed barium more efficiently than older animals (6 to 70 weeks) (i.e., 63–84% in young animals versus 7–8% in older rats) (Taylor et al., 1962). In this same study, fasting was also found to increase absorption from 7–8% to 20%. Absorption after the first 7 hours following administration was not investigated. The International Commission on Radiological Protection (ICRP, 1993) and the World Health Organization (WHO, 1990) also reported that children may absorb barium to a greater extent than adults; the ICRP (1993) has estimated oral absorption of soluble barium to be 60% in infants, 30% in 1–15 years old and 20% in adults.

The solubility of barium compounds under environmental conditions does not necessarily influence their absorption in the body. Absorption efficiencies of different barium compounds were compared by McCauley and Washington (1983). Single gavage doses of ^{131}Ba-labeled barium sulfate and barium chloride (amounting to 10 mg of barium) were found to be absorbed at similar rates as indicated by blood and tissue levels in rats (McCauley and Washington, 1983); the authors suggested that the similar absorption efficiencies may be attributed to the solubilisation of the low dose of barium sulfate by hydrochloric acid in the stomach. Barium carbonate in a vehicle containing sodium bicarbonate was poorly absorbed most likely owing to the buffering capacity of sodium bicarbonate which may have impaired the hydrochloric acid-mediated conversion to barium chloride. These results suggest that soluble barium compounds or compounds generating barium ions in the acidic environment of the stomach have similar absorption efficiencies.

8.2 Distribution

Barium mainly deposits in bone and connective tissues, with bones containing approximately 66–90% of the total body burden (Schroeder et al., 1972; Venugopal and Luckey 1978; Tardiff et al., 1980); barium can also accumulate in teeth as shown in a study by Miller et

al. (1985) whereby the ratio of barium-to-calcium in the teeth of the children from a community with high levels of barium in drinking water (10 mg/L) was five times higher than among children from another community with barium levels of 0.2 mg/L, despite similar ethnic and socioeconomic statuses. Barium also distributes widely into different tissues, with lungs, fat, muscle, skin, connective and soft tissues found to contain 0.1–0.5 mg of barium in adult humans in the United States (Schroeder et al., 1972).

No differences in distribution were found between sexes of rats exposed to 10–250 mg/L of barium as barium chloride for 4–13 weeks (Tardiff et al., 1980). Barium is also known to cross the placental barrier (Venugopal and Luckey, 1978; McCauley and Washington, 1983). The highest concentrations of barium in rats intubated with 10 mg/L of barium chloride for 24 hours were found in the heart, muscles, eye, liver, and kidney (McCauley and Washington, 1983).

8.3 Metabolism

Barium is not metabolised in the human body. As an ion it is monovalent and not subject to changes in oxidation state.

8.4 Excretion

In humans barium is excreted in faeces and urine with faeces representing the primary route of excretion; Schroeder et al. (1972) reported that for a total intake of 1.33 mg/day (1.24, 0.086, and 0.001 mg/day from food, water, and air, respectively), approximately 90% of the barium is excreted in the feces and 2% in the urine. Similar results were observed by Tipton et al. (1969) whereby two men excreted 95%–98% and 2%–5% of a daily barium intake via faeces and urine, respectively.

8.5 PBPK models

No PBPK modelling for barium was identified in the currently available literature.

9.0 Health effects

Barium is not considered to be an essential element (Venugopal and Luckey, 1978; Ferrante et al., 2014; Chellan and Sadler, 2015).

Different barium compounds have differing solubilities in water and body fluids which influences their toxicity. The Ba^{2+} ion and the soluble compounds of barium (mainly chloride, nitrate, and hydroxide) are toxic to humans and animals. Barium carbonate, although relatively insoluble in water, is soluble in the gastrointestinal tract allowing uptake into serum and tissues thereby capable of causing effects. Insoluble barium compounds, such as barium sulfate (barite), serve as inefficient sources of Ba^{2+} ion and are therefore generally nontoxic to humans; the nontoxic nature of barium sulfate has made it useful in medical applications such as a contrast media for x-ray examination the gastrointestinal tract. Barium sulfate or other insoluble barium compounds, however, can become toxic if the gastrointestinal tract is compromised (e.g. in the case of colon cancer) thereby allowing barium to enter the blood stream (ATSDR, 2007).

9.1 Effects in humans

The database on human health effects from barium exposure is limited. Health effects reported from acute exposure to high levels of barium carbonate or chloride are largely related to hypokalemia, which can lead to complications including ventricular tachycardia, hypertension and/or hypotension, muscle weakness, and paralysis. Portal of entry gastrointestinal effects such as vomiting, abdominal cramps, and watery diarrhea have also been reported shortly after

ingestion of high doses. Associations between barium in drinking water and mortality from cardiovascular disease are largely negative; however, one retrospective study reported a positive association, although a lack of controlling for confounding factors and poor exposure characterisation render the results unreliable. The impacts of barium exposure on developmental and reproductive toxicity as well as hearing loss have been investigated; however, results are inconclusive largely due to poor exposure characterisation. The carcinogenicity of barium has not been evaluated in humans.

9.1.1 Acute toxicity

Acute poisoning with barium salts can occur (levels unreported) in cases of accidental human oral ingestion and suicide attempts. In these situations barium has caused hypokalemia (low serum potassium levels), leading to neuromuscular (e.g., muscle weakness and paralysis, abnormal reflexes, tingling, dizziness) and cardiovascular effects (e.g., arrhythmias, electrocardiogram abnormalities) (McNally, 1925; Diengott et al., 1964; Lewi et al., 1964; Ogen et al., 1967; Talwar and Sharma, 1979; Deng et al., 1991; Downs et al., 1995; Koch et al., 2003; Rhyee and Heard, 2009; Payen et al., 2011; Bhoelan et al., 2014). In one case study the absorbed barium came from a carbonate salt present in flour that was solubilized as a result of the acidic stomach pH. The suicide episode involved a commercial product that contained barium sulfide.

Gastrointestinal effects (gastric pain, vomiting, diarrhea, tightness in the throat, dryness of the mouth, hemorrhage) are reported as acute effects following barium ingestion. The acute responses can progress to increased blood pressure, progressive muscular paralysis, cardiovascular and respiratory failure, and even death (Downs et al., 1995; Jourdan et al., 2001; Bhoelan et al., 2014). Hemoglobin in the urine and renal failure have also been observed (Morton, 1945; Gould et al., 1973; Wetherill et al., 1981; Phelan et al., 1984; Jha et al., 1993; Silva et al., 2003; Koch et al., 2003; Lukasik-Glebocka et al., 2014). Doses of 1 to 15 g of barium sulfide have caused death. However, in another case medical treatment following exposure to up to 133 g of barium carbonate prevented a lethal response (Downs et al., 1995).

9.1.2 Subchronic and chronic toxicity and carcinogenicity

9.1.2.1 Cardiovascular toxicity

A retrospective study found higher mortality rates ($p < 0.05$) from all cardiovascular diseases and for heart diseases retrieved from death certificates for the years 1971–1975 in communities with barium concentrations of 2 to 10 mg/L in drinking water compared to communities with < 0.2 mg/L in Illinois (25 433 adults of 4 high-barium and 46 905 adults of 7 low-barium communities) (Brenniman and Levy, 1979; Brenniman et al., 1985). The communities were matched for demographic characteristics and socioeconomic status; however, the use of water softeners, medication, smoking, diet and exercise were not adjusted for. Moreover, the rate of population change was about 70% in the communities with the highest concentrations during the decade preceding the study cases occurrence, and no information was provided on the length of time individuals lived in a community. Additionally, exposure was poorly characterized, with no information provided on tap water consumption rates. In another study that evaluated cardiovascular morbidity, no differences in blood pressure, stroke, heart or kidney diseases were observed ($p < 0.05$) between an Illinois community with a mean of 7.3 mg/L (n=1175 adults in West Dundee) and another one with mean of 0.1 mg/L (n=1203 adults in McHenry) for the years 1976–1977 (Brenniman and Levy, 1981; as summarized in Brenniman et al., 1985).

No association between barium intake from drinking water and cardiovascular markers (i.e., cholesterol, glucose, and triglyceride levels, blood pressure, heart rate, electrocardiographic endpoints) were found in 11 American male volunteers (27–61 years old) (Wones et al., 1990). Barium was administered via the drinking water at successive barium concentrations of 0 ppm for the first 2 weeks, 5 ppm for the next 4 weeks and 10 ppm, as barium chloride, for the final 4 weeks. Factors associated with cardiovascular risk, such as exercise and food intake were controlled. However, the small number of subjects, the duration of exposure, and the lack of absorption data limit an interpretation of the results of this study.

9.1.3 Developmental and reproductive toxicity

There is little information from human studies on reproductive and developmental effects from soluble barium compounds. In a small prospective epidemiological study, there were no differences (in gestational age, birth weight, and major or minor malformations; $p = 1.0$) in babies (n=32) born to mothers who inadvertently swallowed barium sulphate used in radiography procedures during the first trimester of pregnancy compared with 94 control mothers (Han et al., 2011). Moreover, there was no evidence of teratogenicity in babies (n=5) born to mothers who were inadvertently exposed to barium via enema (Han et al., 2010). Nevertheless, the low solubility and absorption rates of barium sulphate used in medical procedures confound the interpretation of these results with respect to soluble barium compounds.

A small, single-site case-control study reported that barium was among the metals that were reported to be elevated in the hair ($p = 0.003$) and urine ($p = 0.002$) of 25 children (mean age of 5 years old) with Autism Spectrum Disorder (ASD) in Saudi Arabia compared with 25 non-autistic children matched for age and sex; however, shortcomings of this study include mothers of autistic children were exposed to second-hand smoke, controls were chosen through case referrals, and no attempt was made to identify which other trace elements and heavy metals could be responsible for the associations (Blaurock-Busch et al., 2011).

9.1.4 Other effects

In a pilot cross-sectional study, Ohgami et al. (2016) reported an association between hearing loss (auditory thresholds) and concentrations of barium in hair (odds ratio (OR) = 4.75 (95% confidence interval (CI): 1.44, 17.68) at 8 kHz and OR = 15.48 (95% CI: 4.04,79.45) at 12 kHz) and toenails (OR = 3.20 (95% CI: 1.35, 7.85)) at 8 kHz and OR = 3.63 (95% CI: 1.58, 8.55) at 12 kHz) in Bangladesh (n =145 individuals of both sexes aged 12 to 55 years); however, with no associations observed with urine levels and sources of exposure not reportedly characterized, the results of this study limits any inferences that can be made with respect to barium exposure and hearing loss.

Utilizing the data from NHANES 1999–2002 to explore the association between waist circumference and body mass index with the body burdens of various toxic metals, Padilla et al. (2010) reported that urinary barium showed a direct positive association with body weight index and waist circumference ($p < 0.05$) suggesting that environmental exposure to barium (and other metals) may influence variations in weight gain or loss in humans.

9.2 Effects on experimental animals

The database on health effects in animals following barium exposure is also somewhat limited. Investigations into cardiovascular function generally did not find any significant alterations in blood pressure or electrocardiogram (ECG) readings following low-dose oral

exposure; some studies did find significant increases in blood pressure; however, the use of a low mineral diet with less than adequate levels of calcium may have influenced the study results.

The most sensitive adverse effect of barium appears to be renal toxicity. Nephropathy has been observed in rats and mice following short and long-term oral exposure to barium with steep dose-response curves observed in both species; data in mice suggest that the severity and sensitivity to renal lesions is related to the duration of exposure.

Reproductive and developmental studies are limited with results generally being negative for impacts on reproductive tissues or reproductive performance in rats and mice. Decreases in sperm number and quality as well as shortened estrous cycle and morphological alterations in the ovaries have been observed in rats; however, study weaknesses render these results inconclusive. Decreased pup birth weight and a nonsignificant decrease in litter size have been reported in the offspring of rats exposed to barium chloride in drinking water prior to mating. Finally, several studies found that oral exposure to barium did not significantly increase tumor incidence.

9.2.1 Acute toxicity

Fluid in the trachea, inflammation of the small and large intestine, decreased liver/brain ratio, increased kidney/brain ratio, darkened liver, ocular discharge, and decreased body weight were reported in rats administered 60–960 mg Ba/kg as barium chloride by gavage in water (Borzelleca et al., 1988). In this study the LD_{50} values were reported as 419 and 408 mg $BaCl_2$/kg bw in male and female Sprague-Dawley rats, respectively. Another study reported a LD_{50} of 132 mg Ba/kg bw and 220 mg Ba/kg bw for adults and weanling Charles River rats (strain not specified), respectively, gavaged with barium chloride in water (Tardiff et al., 1980). Also, ECG abnormalities, tachycardia, ventricular fibrillation, muscle paralysis, salivation, diarrhea, hypertension, respiratory paralysis, hypokalemia, and death were observed following intravenous infusion of barium chloride in Mongrel dogs (Roza and Berman, 1971).

9.2.2 Short-term exposure

9.2.2.1 Kidney effects

The U.S. NTP (1994) conducted toxicity studies in F344/N rats and B6C3F1 mice by administering barium chloride dihydrate (99% pure) in drinking water for 15 days and 13 weeks. In the 15 day studies, rats (70 days old; 5/sex/dose) were administered barium at concentrations of 0, 125, 250, 500, l,000, or 2,000 ppm (10,15, 35, 60, or 110 mg/kg bw per day for males and females), and mice (77 days old; 5/sex/dose) received 0, 40,80,173, 346, or 692 ppm (10, 30, 65, 110, or 200 mg/kg bw per day for males; 10,35,65,115, or 180 mg/kg bw per day for females). In rats, no chemical-related deaths, differences in final mean body weights, or clinical findings of toxicity were observed; no significant differences were in absolute or relative organ weights, hematology, clinical chemistry, or neurobehavioral parameters were also reported. Water consumption by male and female rats in the highest dose group was slightly less (≤16%) than controls during the second week. In mice, no chemical-related deaths, differences in mean body weights and water consumption, or clinical/histopathological evidence of toxicity was observed; in thief highest dose group, relative liver weight of males and absolute and relative liver weights of females were significantly higher than those of the controls.

In the 13 week studies, F344/N rats and B6C3F1 mice (43 days old; 10/sex/dose) were administered barium (as barium chloride in drinking water *ad libitum*) at concentrations of 0, 125, 500, 1,000, 2,000 and 4,000 mg/L (0, 10, 30, 65, 110 or 200 mg Ba/kg bw per day for male rats; and 0, 10, 35, 65, 115 or 180 mg Ba/kg bw per day for female rats; 0, 15, 55, 100, 205 or 450 mg Ba/kg bw per day for male mice; and 0, 15, 60, 110, 200 or 495 mg Ba/kg bw per day for female

mice as determined by the study authors) (NTP, 1994). In rats, water consumption by males and females in the high dose group was 30% lower than controls; chemical-related kidney lesions (3 males and 3 females) and death (3 males and 1 female) were also observed in this dose group. No changes in blood pressure were observed throughout the 13 week period in any of the dose groups. Absolute and relative kidney weights in females of the 115 or 180 mg/kg bw per day dose groups as well as in males of the 200 mg/kg bw per day dose group were significantly higher than controls and were related to chemical-induced renal lesions; a NOAEL of 65 mg/kg bw per day for increased kidney weights in female rats can be identified from this study. In mice, final mean body weights for males and females of the highest dose group were significantly lower than controls with males consuming 18% less water than controls. More severe kidney lesions were observed in mice compared to rats with multifocal to diffuse nephropathy (i.e., tubule dilatation, regeneration and atrophy), crystals and eosinophilic casts in atrophic tubules and increased mortality reported in both sexes in the highest dose group; a NOAEL of 200 mg/kg bw per day for kidney lesions in female mice can be identified from this study.

Fisher-344/N rats and B6C3F1 mice received barium chloride dihydrate (10 animals/sex/species/dose) via drinking water at concentrations of 0, 1,000, 2,000 or 4,000 mg Ba/L (equivalent to doses of 0, 65, 110 and 200 mg Ba/kg bw per day for males; and 0, 65, 115 and 180 mg Ba/kg bw per day for females as estimated by the study authors) for 13 weeks (Dietz et al., 1992). Mortality was 10–30% for rats and 60–70% for mice in the highest dose groups. Mortality in mice was attributed to treatment-related renal toxicity whereas in rats, renal lesions were less severe and was not attributed mortality in the high dose group. Toxic nephrosis and crystals in the lumen of renal tubules (postulated by authors as insoluble barium salts) were observed in more than 80% of the mice of both sexes in the highest dose group. Renal lesions were characterized by dilatation (containing eosinophilic granular casts and crystals), regeneration, and atrophy (lined with epithelial cells with stained basophilic cytoplasm) of the tubular cells in mice. There was an irregular depression of the renal capsule near the collapsed tubules. Also, an increase in fibrous tissue was observed between the tubules in the cortex and outer medulla. In rats, only a few foci of dilated tubules were observed in the outer medulla in both sexes at the highest dose. A NOAEL of 2000 mg Ba/L (110 mg Ba/kg bw per day) was identified by the authors for this study.

In a study investigating the protective effects of pomegranate peel against barium-mediated kidney damage, a single group of 6 adult Wistar rats exposed to barium chloride (67 ppm, equivalent to 10 mg/kg bw per day as reported by the study authors) for 21 days had reduced creatinine clearance (indicator of glomerular dysfunction) compared with controls (Elwej et al., 2016a). The barium group also had various hemorrhage foci and leucocytes infiltration that were evident in the Bowman's space portion of Bowman's capsule that surrounds the glomeruli.

Female Sprague-Dawley rats gavaged for 10 days with 100, 145, 209 and 300 Ba/kg bw per day in water had a decreased kidney/brain weight ratio in all dose groups except the highest; however, the authors concluded that these results were likely not barium-related due to the absence of effects in the highest dose group (Borzelleca et al., 1988).

No adverse effects were observed in young adult rats (Charles River rats; 30 animals/sex/dose) exposed to 0, 10, 50 or 250 mg Ba/L as barium chloride in drinking water (equivalent to 2–3, 6–13, 28–64 mg Ba/kg bw per day for males; and 2–3, 7–15, or 36–68 mg Ba/kg bw per day for females as reported by the study authors) for 13 weeks (Tardiff et al., 1980).

9.2.2.2 Cardiovascular effects

An increase in barbiturate-induced myocardial contractile depression was observed in young female Long-Evans hooded rats exposed for 16 months to 100 ppm barium chloride via

drinking water (Kopp et al., 1985). An increase in systolic blood pressure was measured in barium-treated rats compared to controls (n=12). Reduced myocardial contractile velocity and conduction system in the atrioventricular nodal region, as well as disturbances in energy metabolism were also observed after 16 months of exposure.

9.2.2.3 Other effects

A decrease in motor activity (mice and rats), weaker grip strength (mice), and a decrease in thermal sensitivity (mice) were also observed at the 4000 ppm dose in the NTP (1994) study as described above; forelimb grip strength of female mice receiving 4000 ppm was also lower following 90 days of exposure.

Female ICR mice (n=5) exposed to barium chloride in drinking water for 2 weeks or 2 months (equivalent to doses of 0.14 and 1.4 mg Ba/kg bw per day, as indicated by the authors) had severe hearing loss in both dose groups after 2 weeks, and severe degeneration of inner ears after 2 months (Ohgami et al., 2012) when compared with controls. Several study weaknesses limit the interpretation of these findings. These weaknesses include: the use of a strain of mouse that have been shown to suffer from progressive hearing loss (thus this study requires replication in other species); the measurement of inner ear barium levels was done at a time (11 weeks) long after hearing analysis was performed (5 weeks); no differences in bone-barium levels were observed between the treatment groups; and levels of barium in other tissues including kidney, liver and heart were undetectable which is inconsistent with what would be expected following barium exposure.

9.2.3 Long-term exposure and carcinogenicity

9.2.3.1 Kidney effects

As part of the NTP study described above (NTP, 1994), rats and mice (60/sex/dose) were also exposed to barium chloride in drinking water at concentrations of 0, 500, 1,250 and 2,500 mg/L (as barium) (0, 15, 30, 60 mg Ba/kg bw per day for male rats; 0, 15, 45, 75 mg Ba/kg bw per day for female rats; 0, 30, 75 or 160 mg Ba/kg bw per day for male mice; and 0, 40, 90 or 200 mg Ba/kg bw per day for female mice as estimated by the study authors) for 103–105 weeks. In rats, no chemically-related effects were observed at any dose. In mice, mild to severe nephropathy in males and females (i.e., tubule regeneration, of cortical and medullary epithelium, dilatation, hyaline cast formation, multifocal interstitial fibrosis, and glumerulosclerosis in some animals; and brown crystals within tubule lumens and interstitium and renal cysts in males) and increased mortality due to kidney lesions was reported in the high dose group. In the 15 month interim evaluation, urea nitrogen levels were elevated in mice of all dose groups (although not statistically significant according to the authors) indicating that some animals were beginning to experience changes in kidney function, consistent with the observed pathology, even at the lower doses. A NOAEL of 75 mg/kg bw per day can be identified for nephropathy in male mice.

Long-Evans rats exposed to 5 mg Ba/L (52/sex; as barium acetate) via drinking water had increased proteinuria in males only after lifetime exposure, whereas females showed no significant difference from controls; no kidney lesions in treated rats were noted by the authors (Schroeder and Mitchener, 1975a). A reduction in survival was observed in male Swiss mice of the Charles River CD strain (but not females) exposed to 5 mg Ba/L (as barium acetate) via drinking water; however, no kidney lesions in treated mice were noted by the authors (Shroeder and Mitchener, 1975b).

Rats administered barium chloride via drinking water at concentrations of 1 to 1,000 mg Ba/L (the authors only indicated that 10 ppm was equivalent to 1.5 mg Ba/kg bw per day) for 16

to 68 weeks exhibited structural changes to the glomeruli at the highest dose of 1000 ppm (or approximately 150 mg/kg bw per day) (McCauley et al., 1985); thus a LOAEL of 150 mg/kg bw per day can be identified from this study.

9.2.3.2 Cardiovascular effects

Perry et al. (1985, 1989) exposed female Long-Evans weanling rats (13 per dose group) to barium chloride in drinking water at concentrations of 0, 1, 10 or 100 ppm for 1 to 16 months. An increase in mean systolic blood pressure was observed in the 10 ppm group at 8–16 months. The increase in the 100 ppm dose group was observed from the first month to the end of the study. Other studies have not observed these associations following exposures as high as 150 mg/kg bw per day (1000 ppm) (McCauley et al., 1985) and 180 mg/kg bw per day (4000 ppm) (NTP 1994). Animals in the Perry et al. (1985, 1989) studies were fed a rye-based diet with calcium levels below the recommended daily requirement (NRC, 1995) which may have rendered them more sensitive to the cardiovascular effects of barium; since some evidence in humans indicates that reduced dietary calcium is a risk factor for hypertension (McCarron et al., 1984), the relevance of the results from these studies is uncertain.

9.2.3.3 Other effects

Lymphoid depletion was observed in the spleen, thymus and lymph nodes of mice and rats exposed to 2500 ppm barium chloride dihydrate for 103–105 weeks (NTP, 1994). A NOAEL of 180 mg/kg bw per day for rats and 205 mg/kg bw per day for mice can be identified from this study.

9.2.3.4 Carcinogenicity

No increase in tumour incidence was observed in Fisher-344/N rats or B6C3F1 mice exposed to concentrations up to 2,500 mg/L of barium (60–75 mg/kg bw per day in rats; 160–200 mg/kg bw per day in mice) via drinking water for 2 years (NTP, 1994). Statistically significant decreases in the trends of mononuclear cell leukemia and neoplasms as well as non-neoplastic lesions of the adrenal gland in male rats, and of the mammary gland in female rats were observed. Also, statistically significant decreases in hepatocellular adenoma were observed in male mice. Moreover, no increase in tumours was found in Long-Evans rats or Swiss mice (52 animals/species/sex) exposed to 5 ppm barium acetate in drinking water for 540 days (Schroeder and Mitchener, 1975a, 1975b), or after male SD rats were exposed to 1–100 ppm barium chloride for 68 weeks (McCauley et al., 1985).

9.2.4 Genotoxicity

In vitro studies have generally not found evidence of barium genotoxicity; while one *in vivo* study found an increase in one type of somatic mutation at a high dose.

9.2.4.1 In vitro findings

Barium chloride (10 to 10 000 µg/plate) caused no significant increase in gene mutation frequency in *Salmonella typhimurium* (TA97, TA98, TA100, TA1535, and TA1537) with and without Aroclor 1254-induced rat or hamster liver S9 fractions (Rossman et al., 1991; NTP, 1994). Moreover, no increase in gene mutation or DNA damage was found (via assay with H17 and M45 strains of *Bacillus subtilis*, DNA polymerase test from avian myoblastosis virus, and microscreen assay with *Escherichia coli* WP2) with barium nitrate and barium chloride (Nishioka, 1975; Sirover and Loeb, 1976a,b; Kanematsu et al., 1980; Rossman et al., 1991). Also, barium chloride did not induce sister chromatid exchanges, chromosomal aberrations, or cell cycle delay

in Chinese hamster ovary cells (NTP, 1994). However, barium chloride (at 250 µg/ml and above) induced an increase in gene mutations in L5178Y mouse lymphoma cells in the presence of metabolic activation (no increase in mutant colonies were observed without S9 activation) (NTP, 1994).

9.2.4.2 In vivo findings

Yesilada (2001) reported increases in small single wing spots (wing spot test is indicative of somatic mutations) in *Drosophila melanogaster* exposed to high concentrations of barium nitrate (10 mM), but not at lower concentrations (1 mM). The effect of barium on large single spots and twin spots was inconclusive at both 1 and 10 mM.

9.2.5 Reproductive and developmental toxicity

In the NTP (1994) study, as described above, significantly increased testicular ($p \leq 0.01$) and uterine ($p \leq 0.05$) weights were observed in rats of the 2500 ppm dose group (60 mg Ba/kg bw per day for males and 75 mg Ba/kg bw per day for females) following 15 months of exposure via drinking water; no significant changes in the weights of reproductive organs were observed in mice. A NOAEL of 60 mg/kg bw per day for rats and 160 mg/kg bw per day for mice can be identified from this study. The significance of these findings, however, is unknown since reproductive and developmental toxicity was not assessed in this study.

A single-generation mating trial was conducted by Dietz et al. (1992) whereby groups of male and female F-344/N rats and B6C3F1 mice (20/sex/species/group) were exposed to barium chloride dihydrate in the drinking water at 0, 1000, 2000, or 4000 ppm for the rats and 0, 500, 1000, or 2000 ppm for the mice for 60 days (males) or 30 days (females). Estimated doses (from a subchronic study by the same authors as described in Section 9.2.2) for rats were 0, 65, 110, and 200 mg/kg-day for males and 0, 65, 115, and 180 mg/kg per day for females; for mice the estimated doses were 0, 55, 100, and 205 mg/kg per day for males and 0, 60, 110, and 200 mg/kg per day for females. After the exposure period, males and females from the same exposure groups were housed together until there was evidence of mating or until the end of the mating period (8 days). Numerous reproductive parameters were assessed. For both rats and mice no changes in epididymal sperm counts, sperm motility, sperm morphology, testicular or epididymal weights, or vaginal cytology were observed. In rats, pregnancy rates were below historically normal values for the laboratory, however, they were not treatment related. No significant alterations in gestation length, pup survival, or occurrence of external abnormalities were observed. A statistically significant ($p<0.01$) decrease in live pup weight at birth was observed in the 4000 ppm group, however, after 5 days of age no significant alterations in pup body weight were observed. In mice, no alterations in maternal weight gain, average length of gestation, pup survival, or pup weights were observed. A statistically significant ($p<0.05$) decrease in average litter size occurred on days 0 and 5 in the 1000 ppm treatment group but not in the 2000 ppm treatment. No external abnormalities were observed in the offspring. A NOAEL of 115 mg/kg bw per day for rats and 200 mg/kg bw per day for mice can be identified from this study.

Decreased ovary weight and ovaries/brain weight ratio were observed in 29–37 days of age Sprague-Dawley rats (10 animals/sex/dose) exposed to 198 mg Ba/kg from barium chloride administered by gavage in water once daily for 10 days, but not at 138 mg Ba/kg (Borzelleca et al., 1988) thus a NOAEL of 138 mg Ba/kg can be identified from this study.

9.3 Mode of action

As reported in Section 9.2, chronic and subchronic drinking water studies in rats and mice indicate that the kidney is a sensitive target of barium toxicity; however, the mode of action for

barium-mediated kidney toxicity has not been fully elucidated. Available data indicates that kidney toxicity may be associated with oxidative processes. Wistar rats receiving 67 mg/L barium chloride for 21 days had an increase in kidney and liver markers of oxidative stress (tissue lipoperoxide, lipid hydroperoxides, advanced oxidation protein product, malondialdehyde, and H_2O_2 levels), a decrease in catalase, superoxide dismutase and glutathione peroxidase enzyme activities, vitamin C, and glutathione and non-protein thiol. An increase in metallothionein content was also observed (Elwej et al., 2016a, 2016b). Thus, oxidative stress could be responsible for damaged cellular macromolecules, such as proteins, cell membranes and/or disruption of the mitochondrial respiration chain (Storz et al., 2005). The oxidative stress hypothesis is supported by high levels of H_2O_2, malondialdehyde and advanced oxidation protein product. More specifically, H_2O_2 can be converted to the hydroxyl radical, which can cause rapid lipid peroxidation, and the depletion of glutathione levels increasing the susceptibility of organs to oxidative stress. Moreover, the oral administration of pomegranate peel powder (5% of diet) improved all barium-induced renal and liver damage, possibly by acting as an electron donor (anti-oxidant).

The acute cardiovascular and neuromuscular toxicity of barium reported in case studies has been attributed to its hypokalemia effect (Roza and Berman, 1971; Koch et al., 2003). As a potassium channel antagonist, barium increases intracellular and decreases extracellular potassium by blocking the efflux of cellular potassium and increasing the sodium-potassium-ATPase pump activity (Payen et al., 2011). It is possible that the increased intracellular potassium concentrations may result in a decreased resting membrane potential; however, there is also evidence of a barium-induced neuromuscular blockade and membrane depolarization (Phelan et al., 1984; Thomas et al., 1998). In addition, since barium has chemical properties similar to calcium, they can interact through biochemical pathways involving calcium binding proteins and compete for binding sites (IPCS, 1990). Hypertensive effects of barium in rats as reported by Perry et al. (1989) may have been due to inadequate calcium levels in the diet.

10.0 Classification and assessment

The International Agency for Research on Cancer (IARC) has not classified barium as to its carcinogenicity. The U.S. EPA (2005) concluded that barium is considered not likely to be carcinogenic to humans via oral intake. Other agencies have concluded that there is no evidence that barium is carcinogenic via the oral route (IPCS, 2001; WHO, 2016). Several animal studies found no increase in tumours following long term exposure to barium in drinking water at levels as high as 2500 mg/L (60–75 mg/kg bw per day in rats; 160–200 mg/kg bw per day in mice) (Schroeder and Mitchener, 1975a: 1975b; McCauley et al, 1985; NTP, 1994).

Nephropathy in mice is considered to be the most sensitive health effect associated with chronic oral exposure to soluble salts of barium. In humans, renal failure has been observed following exposure to high levels of barium in poisoning events (see Section 9.1). The chronic mouse study by the NTP (1994) was chosen as the key study for deriving a health-based value (HBV) for barium in drinking water for the following reasons: it used an adequate number of animals (60/sex/dose); administration of barium was via drinking water; histopathological analysis indicated that the observed renal lesions were morphologically different compared to the spontaneous degenerative renal lesions commonly observed in aging mice; and, mice appear to be the most sensitive of the animal species tested exhibiting the lowest NOAEL for kidney effects (75 mg/kg bw per day). Additionally, a dose-response relationship was observed with a statistically significant number of mice in the high dose group exhibiting mild to severe cases of nephropathy (along with a significant increase in mortality due to treatment-related renal lesions),

and within the second highest dose group, one female and two males (out of 60) exhibited mild to moderate chemical-related nephropathy.

Hypertension has also been reported in animals and humans following exposure to barium; however, the evidence is conflicting. In humans, the dose-response data is insufficient to support an association between chronic barium exposure and hypertension. Results from epidemiological studies are limited either by their small sample sizes, short durations of exposure, poor exposure characterization, inadequate controlling of important risk factors for hypertension, or a combination thereof. In animals the results are equivocal with the positive findings potentially being influenced by an experimental diet low in calcium which has been identified as a possible risk factor for hypertension in humans. As a result the data on hypertensive effects were considered inadequate for deriving a HBV.

Benchmark dose (BMD) modelling was performed using the nephropathy incidence in mice as reported in the 2-year NTP (1994) study at a 10% and 5% increased incidence over background rates (the benchmark response; BMR). Male and female mouse data were modeled separately as well as combined with both average dose and individual gender doses giving similar modeling results. Of the models that provided a reasonable fit (via evaluation of goodness of fit p-value > 0.1; BMD/BMDL ratio < 5; and visual inspection of the curve), the model providing the best fit (i.e., lowest Akaike Information Criterion [AIC]) as well as the most conservative BMD/BMDL values was the multistage 3 model for male mice. A BMR of 5% was selected due to the following statistical and biological considerations: the study design provides sufficient statistical power (e.g., 50–100 animals/dose/sex); the BMR falls near the low-end of the observable dose range; the BMD and BMDL values are similar; and the health endpoint is severe. As the lower 95% confidence limit on the benchmark dose for a 5% response ($BMDL_5$) of 58 mg/kg bw per day for male mice is lower than the corresponding values for females, and males and females combined, this has been selected as the point-of-departure (POD) for the calculation of the HBV for barium in drinking water.

Limited information is available on the age-related differences in susceptibility to barium. Although adults were symptomatic, children did not appear to be affected in two food poisoning incidents involving barium carbonate (Lewi and Bar-Khayim, 1964; Deng et al., 1991); however, the lack of examination of children and uncertainty regarding their barium intake limits the interpretation of these results. Age-related differences in the absorption of ingested barium are reported for both animals and humans. Studies by Taylor et al. (1962) and Cuddihy and Griffith (1972) indicate that oral absorption of barium in younger animals may be an order of magnitude greater than older animals; additionally, the ICRP (1993) estimates the oral absorption of soluble barium to be 60% in infants, 30% in 1–15 years old and 20% in adults. With increased uptake of barium and higher bone remodelling rates in infants and children compared to adults, there is greater potential for barium accumulation in bone, however, the significance of this not known and requires further investigation.

Using the $BMDL_5$ identified above, a tolerable daily intake (TDI) can be calculated as follows:

$$\text{TDI} = \frac{58 \text{ mg/kg bw per day}}{300}$$

$$= 0.19 \text{ mg/kg bw per day}$$

where:

- 58 mg/kg bw per day is the lower 95% confidence limit on the benchmark dose ($BMDL_5$) for increased incidence of nephropathy in male mice as described above; and
- 300 is the uncertainty factor (10 for interspecies and 10 for intraspecies variation, as well as 3 for database deficiencies including the lack of a 2 generation reproduction toxicity study).

Using this TDI, the HBV for barium in drinking water for non-cancer effects is derived as follows:

$$\text{HBV} = \frac{0.19 \text{ mg/kg bw/day} \times 70 \text{ kg} \times 0.20}{1.5 \text{ L/day}}$$

$$= 2.0 \text{ mg/L (rounded)}$$

where:

- 0.19 mg/kg bw per day is the TDI, as derived above;
- 70 kg is the average body weight for an adult (Health Canada, 1994);
- 0.2 is the allocation factor for drinking water since food represents the main source of exposure and drinking water represents a significant but lesser source of exposure (see Section 5.0); and
- 1.5 L/day is the drinking water intake rate for an adult.

10.1 International considerations

The U.S. EPA (1995) established a maximum contaminant level (MCL) of 2 mg/L based on the possibility of increased blood pressure in humans. In a more recent evaluation, the U.S. EPA IRIS derived a RfD of 200 µg/kg bw per day for nephrotoxicity based on the benchmark dose lower 95% confidence limit ($BMDL_5$) of 63 mg/kg bw per day derived from a 2-year mouse study (U.S. EPA, 2005); using this recent evaluation, the U.S. EPA updated the drinking water equivalent level (DWEL) for barium to 7 mg/L (U.S. EPA, 2012c).

The WHO (2016) established a drinking water guideline value of 1.3 mg/L for barium based on the same uncertainty factor (300) and $BMDL_5$ of 63 mg/kg bw per day as determined by the U.S. EPA (2005). An allocation factor of 20%, an adult body weight of 60 kg and a drinking-water consumption rate of 2 L/day were used in calculating the final guideline value.

The Australia government has established a drinking water guideline of 2.0 mg/L based on a NOAEL of 0.2 mg/kg bw/day from Brenniman and Levy (1985) for no observed adverse effects on blood pressure and kidney disease (NHMRC, 2011).

11.0 Rationale

Barium is present in many drinking water sources both naturally and as a result of human activities. The barium levels in Canadian drinking water will vary greatly depending on geological formations as well as anthropogenic activities, including oil and gas exploration and the use of fertilizers and pesticides. Barium exists as a mixture of over 20 naturally occurring radioisotopes with various levels of radioactivity. The focus of this document is limited to barium's chemical properties. Based on barium's chemical properties, exposure to barium from

drinking water would only be a concern from ingestion — it is not expected to be a concern through either inhalation or dermal absorption.

IARC has not classified barium as to its carcinogenicity. The U.S. EPA concluded that barium is not likely to be carcinogenic to humans via ingestion, and other international agencies agree that there is no evidence showing that barium could cause cancer via ingestion.

Kidneys are considered to be the major target for barium toxicity. In humans, renal failure has been observed following exposure to high levels of barium in poisoning events; in animals, kidney effects are considered the most sensitive health effect associated with chronic oral exposure especially in mice, the most sensitive species.. For these reasons, an HBV of 2.0 mg/L was derived to be protective of the general population, based on kidney effects from a study in mice.

A MAC of 2.0 mg/L is proposed for barium in drinking water. The proposed MAC is protective of potential health effects, can be reliably measured by available analytical methods and is achievable by municipal and residential scale treatment technologies. As part of its ongoing guideline review process, Health Canada will continue to monitor new research in this area and recommend any change to the guideline that is deemed necessary.

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Appendix A: List of acronyms

AIC	Akaike Information Criterion
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMR	benchmark response
BW	body weight
CCME	Canadian Council of Ministers of the Environment
CDC	Centers for Disease Control
CI	confidence interval
CSA	Canadian Standards Association
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EPA	Environmental Protection Agency (U.S.)
HBV	health-based value
HRL	health risk limit
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
IPCS	International Programme on Chemical Safety
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MCL	maximum contaminant level (U.S.)
MDL	method detection limit
ND	not detected
NHANES	National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
NRC	National Research Council
NSF	NSF International
NTP	National Toxicology Program (U.S.)
OR	odds ratio
PHG	public health goal (U.S.)
POD	point of departure
PPM	parts per million
PQL	practical quantification limit
RO	reverse osmosis
RR	relative risk
SCC	Standards Council of Canada
SEM	standard error of the mean
SMR	standardized mortality ratio
TDI	tolerable daily intake
TDS	total diet study
UF	uncertainty factor
WHO	World Health Organization

Appendix B: Provincial and territorial anticipated impacts

Please note that this information is not available in both official languages because the source of the information is not subject to the Official Languages Act.

Prince Edward Island

Newfoundland and Labrador

Nova Scotia

New Brunswick

Quebec

Ontario

Manitoba

Saskatchewan

Alberta

British Columbia

Yukon

Northwest Territories

Nunavut

4 Parameters - Chemical

4-H Lead

Reference/Action:

- Oral presentation on the main comments received during the public consultation period, as well as the main changes made to the guideline technical document on lead in drinking water in order to address public consultation comments
- Status: The draft document on lead went through peer-review, ending in January 2015. Comments from peer-reviewers were addressed, the document was revised and approved for a 2-month public consultation by CDW at the May 2015. The consultation ended March 15th 2017, after which all relevant comments were addressed. The revised document was provided to CDW members 8 weeks prior to the fall 2017 meeting for their review. We are now seeking CDW's final approval of the document.
- Sent 8 weeks prior to fall CDW meeting: The revised guideline technical document on lead in drinking water.
- For CDW discussion/approval.

Notes:

4 Parameters - Chemical

4-I Other chemical

Reference/Action:

- Other parameters /issues to discuss, including pesticides
- For information only

Notes:

5 Secretariat Projects

5-A CHMS cycle 4 results

Reference/Action:

- Oral presentation by Annie St-Amand from the Chemical Surveillance Bureau at Health Canada, on the cycle 4 results of the Canadian Health Measures Survey (CHMS)
- For information only

Notes:

5 Secretariat Projects

5-B CNPHI update

Reference/Action:

- Oral presentation on the Drinking Water Advisories Application of the Canadian Network for Public Health Intelligence (CNPHI)
- For information only

Notes:

5 Secretariat Projects

5-C BWA in small water supplies

Reference/Action:

- Verbal update on boil water advisories in small water supplies
- For information only

Notes:

5 Secretariat Projects

5-D Parliamentary business

Reference/Action:

- Verbal update on Bill C-326, Motion M-69, as well as recommendation #37 from the Report of the Standing Committee on Environment and Sustainable Development regarding CEPA.
- For information only

Notes:

5 Secretariat Projects

5-E Update on GRC conference on DBPs

Reference/Action:

- Verbal update on the 2017 Gordon Research Conference on DBPs in drinking water by Dr. Anca-Maria Tugulea (Exposure and Biomonitoring Division) and Richard Carrier.
- For information only

Notes:

5 Secretariat Projects

5-F National drinking water conference

Reference/Action:

- Verbal update on the status of the national drinking water conference
- For information only

Notes:

5 Secretariat Projects

5-G Sampling integrity

Reference/Action:

- Verbal update and CDW discussion on sampling integrity
- Context: At the spring 2017 CDW meeting, members raised some concerns about sampling integrity for monitoring and are seeking guidance for consistency. The Secretariat would like members to discuss in order to help find solutions.
- For CDW discussion

Notes:

5 Secretariat Projects

5-H Ra-228

Reference/Action:

- Oral presentation on Ra-228 in Canada by Dr. Jing Chen, from the Radiation Protection Bureau, Health Canada.
- For information only

Notes:

5 Secretariat Projects

5-I Radiological Qs & As – WHO document

Reference/Action:

- Oral presentation on the recent WHO Qs & As document by Dr. Jing Chen, from the Radiation Protection Bureau, Health Canada.
- For information only

Notes:

5 Secretariat Projects

5-J Research group update

Reference/Action:

- Oral presentation by Dr. Anca-Maria Tugulea (Exposure and Biomonitoring Division) on drinking water related research at the Environmental Health and Research Bureau (EHSRB)
- For information only

Notes:

6 Committee Liaison Reports

6-A CRCP/CACP report

Reference/Action:

- Verbal update with respect to various activities of the Canadian Regulatory Committee for Plumbing (CRCP) and the Canadian Advisory Committee on Plumbing (CACP) meeting held in August, 2017.
- For information only

Notes:

6 Committee Liaison Reports

6-B Certification body reports

Reference/Action:

- Oral presentation on certification activities within the area of drinking water material standards. Accredited certification organizations will be attending the meeting and available for questions related to the activities reported. They may be handing out information material to members on issues they wish to bring forward.
- For information only

Notes:

6 Committee Liaison Reports

6-C CHE report

Reference/Action:

- Verbal update on CHE activities
- For information only

Notes:

6 Committee Liaison Reports

6-D WHO report

Reference/Action:

- Verbal update on WHO-related activities
- For information only

Notes:

6 Committee Liaison Reports

6-E CCME report

Reference/Action:

- Verbal update on CCME activities by Philippa Cureton from Environment Canada
- For information only

Notes:

6 Committee Liaison Reports

6-F FNIHB report

Reference/Action:

- Kristina Taracha will provide a verbal update on First Nations and Inuit Health Branch activities related to drinking water
- For information only

Notes:

6 Committee Liaison Reports

6-G SDWFNA and regulations

Reference/Action:

- Verbal update by Sophie-Natacha Robichaud from INAC (Indigenous and Northern Affairs Canada) and Tina Sheppard from FNIHB on the status of the Safe Drinking Water for First Nations Act and regulations
- For information only

Notes:

7 Member's Reports

Reference/Action:

- Verbal update by all CDW members

Notes:

8 Future Meetings

Reference/Action:

- Future meetings
- Status: spring 2018 meeting: May 1–3, 2018; fall 2018 meeting: November 6–8, 2018.
- Need to find date for spring 2019 meeting
- For CDW discussion/decision

Notes:

Fishwick, David HLTH:EX

From: Zemanek, Michael HLTH:EX
Sent: September 18, 2017 1:40 PM
To: HLTH PPH Health Protection
Subject: FW: Follow up - Release of Health Canada's Fourth Report on Human Biomonitoring / Suivi – Diffusion du Quatrième rapport sur la biosurveillance humaine
Attachments: ATTFCG9H.pptx; CHMS C4 Briefing - EN Deck.pptx; CHMS C4 Briefing - Qs and As.docx; CHMS Chemical List Cycles 1 - 6.xlsx

FYI....information on the 4th Report on Human Biomonitoring from Health Canada

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From: Val Marshall [mailto:Val.Marshall@hc-sc.gc.ca]
Sent: Monday, September 18, 2017 11:46 AM
To: Lambert, Tim HLTH:EX; Merry.Turtiak@gov.ab.ca; tmacaulay@health.gov.sk.ca; chuck.bosgoed@gov.sk.ca; susan.roberecki@gov.mb.ca; Marion.Schnebelen@msss.gouv.qc.ca; charles.cauchon@mddelcc.gouv.qc.ca; karen.white-masry@gnb.ca; Scott.Lloy@gnb.ca; ktfraser@gov.pe.ca; angelaburridge@gov.nl.ca; Kami_Kandola@gov.nt.ca; Erin_Kelly@gov.nt.ca; WJoy@GOV.NU.CA; XT:Hanley, Brendan HLTH:IN; Sherri.young@gov.yk.ca; Frederic.beauregardtellier@ec.gc.ca; peter_workman@gov.nt.ca; Don.Labossiere@gov.mb.ca; tom.wong@hc-sc.gc.ca; rwneale@gov.pe.ca; bill.rideout@novascotia.ca; Paquin, Lisa C ENV:EX; Tony.Amalfa@ontario.ca; Tim.Fletcher@ontario.ca; vincent.gagnon-lefebvre@mddelcc.gouv.gc.ca; David Morin; debra.hopkins@gov.ab.ca
Cc: Suzanne Leppinen; Val Marshall; Jacquie.vanmarck@gov.yk.ca; Benson, Stacey HLTH:EX; Vincent.Gagnon-Lefebvre@mddefp.gouv.qc.ca; Kerri.Timoffee@canada.ca; daniel.richard@mddelcc.gouv.qc.ca; Brenna.McLennan@gov.ab.ca; Tom Wong; Zemanek, Michael HLTH:EX; Anna Albovias; Monica Brown; Patricia Pelletier; Annie St-Amand; Kate Werry
Subject: Follow up - Release of Health Canada's Fourth Report on Human Biomonitoring / Suivi – Diffusion du Quatrième rapport sur la biosurveillance humaine

Le texte français suit

Good day,

Thank you for your recent participation in a WebEx session on the release of the biomonitoring results from the fourth cycle of the Canadian Health Measures Survey. Please find attached the presentation delivered during the WebEx, as well as a document containing questions posed during the sessions and the answers provided.

The report and background information are available on Health Canada's biomonitoring website (canada.ca/biomonitoring).

If you have any additional questions or comments, please contact Annie St-Amand (annie.st-amand@hc-sc.gc.ca).

Best regards,

Bonjour,

Nous vous remercions pour votre participation récente à la séance d'information WebEx sur la diffusion des résultats de biosurveillance du quatrième cycle de l'Enquête canadienne sur les mesures de la santé. Vous trouverez ci-joint le document présenté à la séance, ainsi qu'un document contenant les questions posées et les réponses données durant les séances.

Le rapport et des renseignements généraux se trouvent sur le site Internet de Santé Canada portant sur la

biosurveillance (canada.ca/biosurveillance).

Si vous avez des questions ou des commentaires additionnels, veuillez communiquer directement avec Annie St-Amand (annie.st-amand@hc-sc.gc.ca).

Cordialement,

(See attached file: ATTFCG9H.pptx) (See attached file: CHMS C4 Briefing - EN Deck.pptx)

(See attached file: CHMS C4 Briefing - Qs and As.docx) (See attached file: CHMS Chemical List Cycles 1 - 6.xlsx)

Patricia Pelletier, P. Eng
Director, Environmental Health Science and Research Bureau
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*N.B.: **Monday & Tuesday, September 18 & 19, my Lotus Notes account will be transitioning to Outlook.** I won't be able to access my emails during these 2 days. During the transition you may reach me by phone (613-946-7481) or, for urgent requests only, please email Monica Brown (monica.brown@canada.ca). / **Lundi le 18 et mardi le 19 septembre mon compte Lotus Notes sera en transition vers Outlook.** Pendant ces 2 jours je ne pourrai accéder à mes courriels. Pour me joindre vous pourrez me contacter par téléphone (613- 946-7481) ou, pour les demandes urgentes, veuillez envoyer un courriel à Monica Brown (monica.brown@canada.ca).*

Health Canada Santé Canada

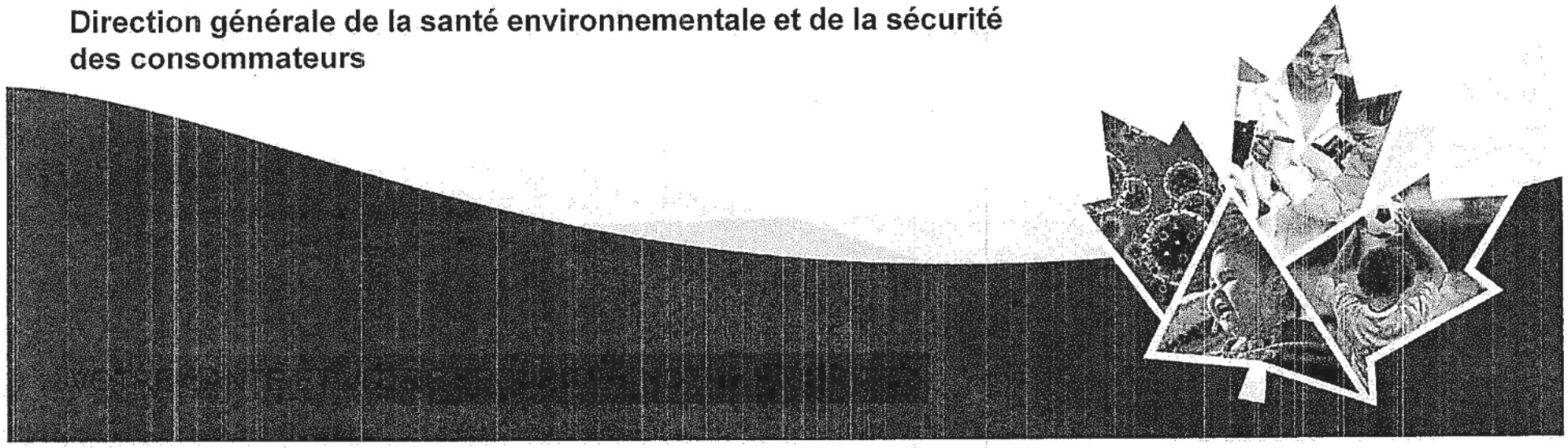
Canada

Séance d'information sur la publication des données de biosurveillance de l'Enquête canadienne sur les mesures de la santé (2014-2015)

24 août 2017

Bureau de la science et de la recherche en santé environnementale

Direction générale de la santé environnementale et de la sécurité des consommateurs



Objectifs de la séance d'information

(1) Annoncer la publication du *Quatrième rapport sur la biosurveillance humaine des substances chimiques de l'environnement au Canada* de Santé Canada

(2) Présenter certains résultats du volet de biosurveillance de l'Enquête canadienne sur les mesures de la santé (ECMS 2014-2015)

Produits de Santé Canada

24 août 2017

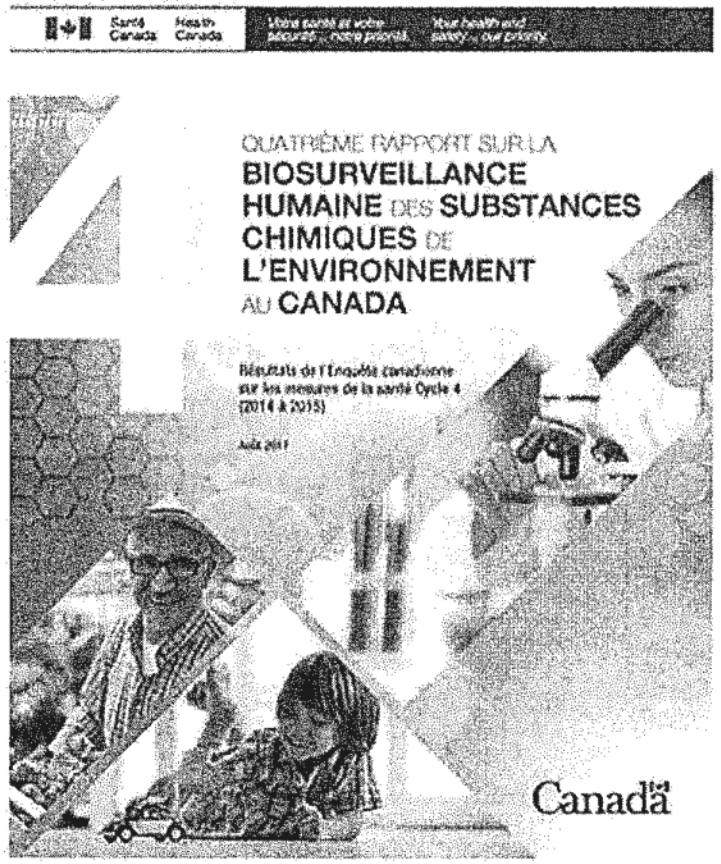
- *Quatrième rapport sur la biosurveillance humaine des substances chimiques de l'environnement au Canada*
- Résumé révisé du *contenu du volet biosurveillance de l'Enquête canadienne sur les mesures de la santé : Cycles 1 à 4 (2007 à 2015)*
- Disponible en formats HTML et PDF à : canada.ca/biosurveillance

Automne 2017

- Tableaux de données disponibles sur le portail du Gouvernement ouvert: ouvert.canada.ca

Quatrième rapport sur la biosurveillance humaine des substances chimiques de l'environnement au Canada

24 août 2017

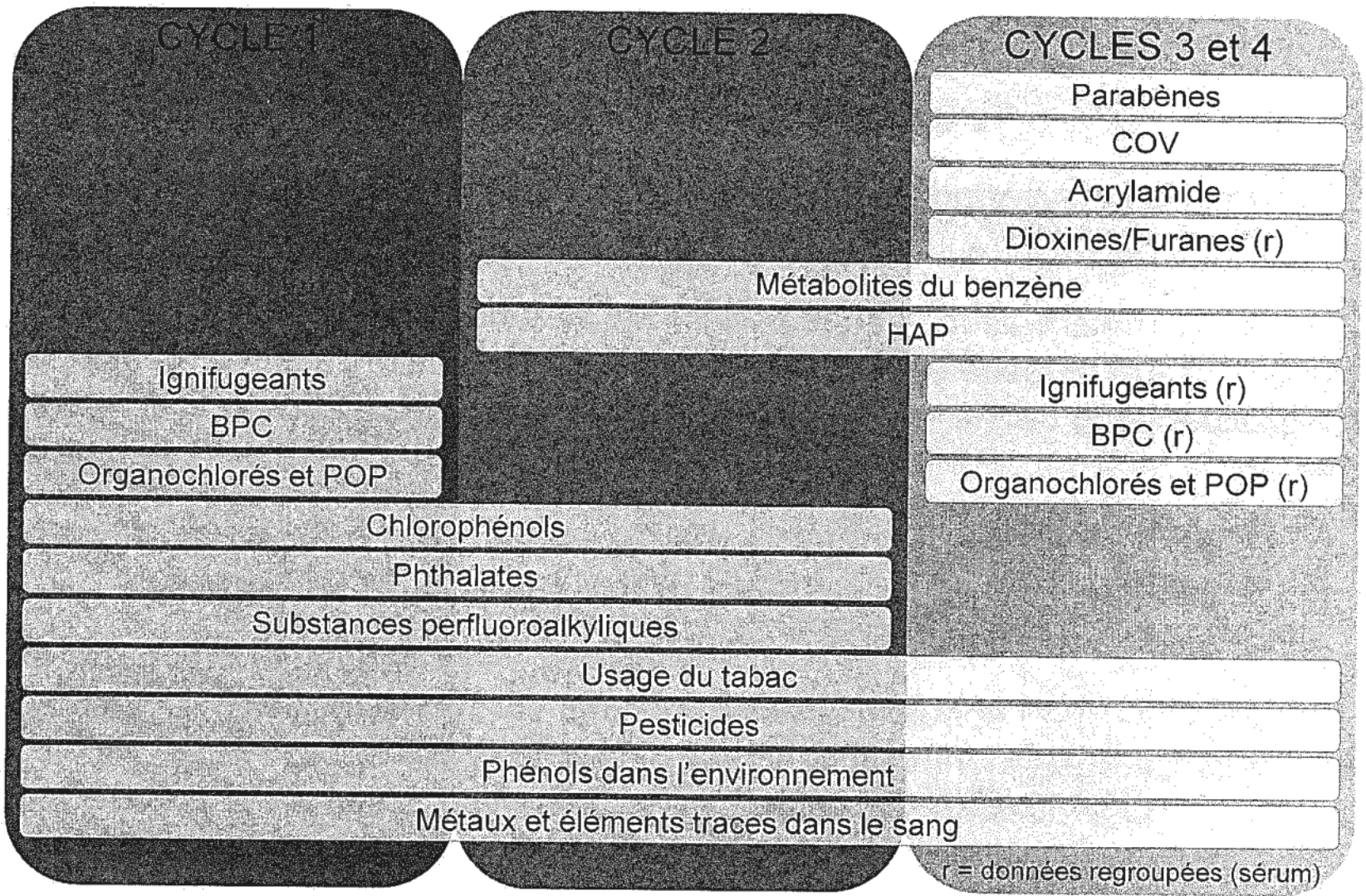


- Quelles sont les nouveautés dans le *Quatrième rapport?*
  - Présentation des données les plus récentes (2014-2015) sur 54 substances chimiques de l'environnement
  - Actualisation des données sur 48 substances chimiques qui figuraient dans le *Troisième rapport*
  - Présentation de nouvelles données sur six produits chimiques :
    - Parabènes
    - Métabolites du chlorpyrifos et du malathion
- Les données sont présentées pour la population canadienne totale, et sont également subdivisées selon le groupe d'âge et le sexe.
- Le rapport n'examine pas les risques ni les résultats sur le plan de la santé.

Aperçu des résultats

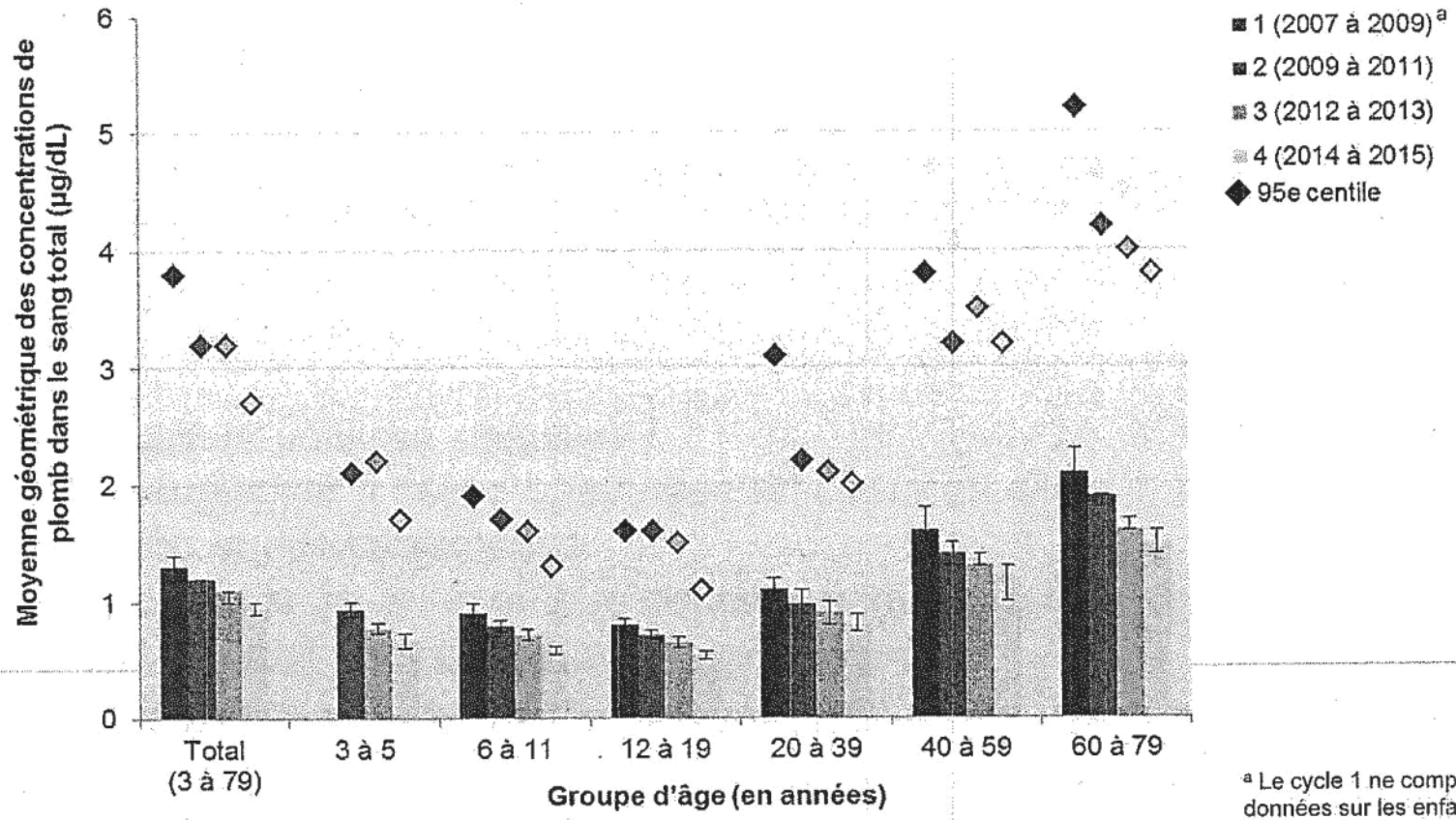
- De façon globale, les concentrations de substances chimiques de l'environnement mesurées chez les Canadiens se situent dans des plages semblables à celles déclarées dans le passé au Canada (2007-2013) et à l'échelle internationale.
- Tendances relatives à la concentration sanguine de plomb – les concentrations moyennes ont chuté, passant de 1,3 µg/dL durant le cycle 1 (2007-2009) à 0,95 µg/dL durant le cycle 4 (2014-2015).
- Tendances relatives à la concentration de mercure – aucun changement significatif dans les concentrations moyennes n'a été observé entre 2007-2009 et 2014-2015 chez la population adulte canadienne (20 à 79 ans).
- Taux de détection des parabènes dans l'urine de la population canadienne :
  - Méthylparabène : 92 %
  - Propylparabène : 79 %
  - Éthylparabène : 35 %
  - Butylparabène : 17 %

Biosurveillance des substances chimiques dans le cadre de l'ECMS



Concentration de plomb dans le sang – Cycles 1 à 4 (2007-2015)

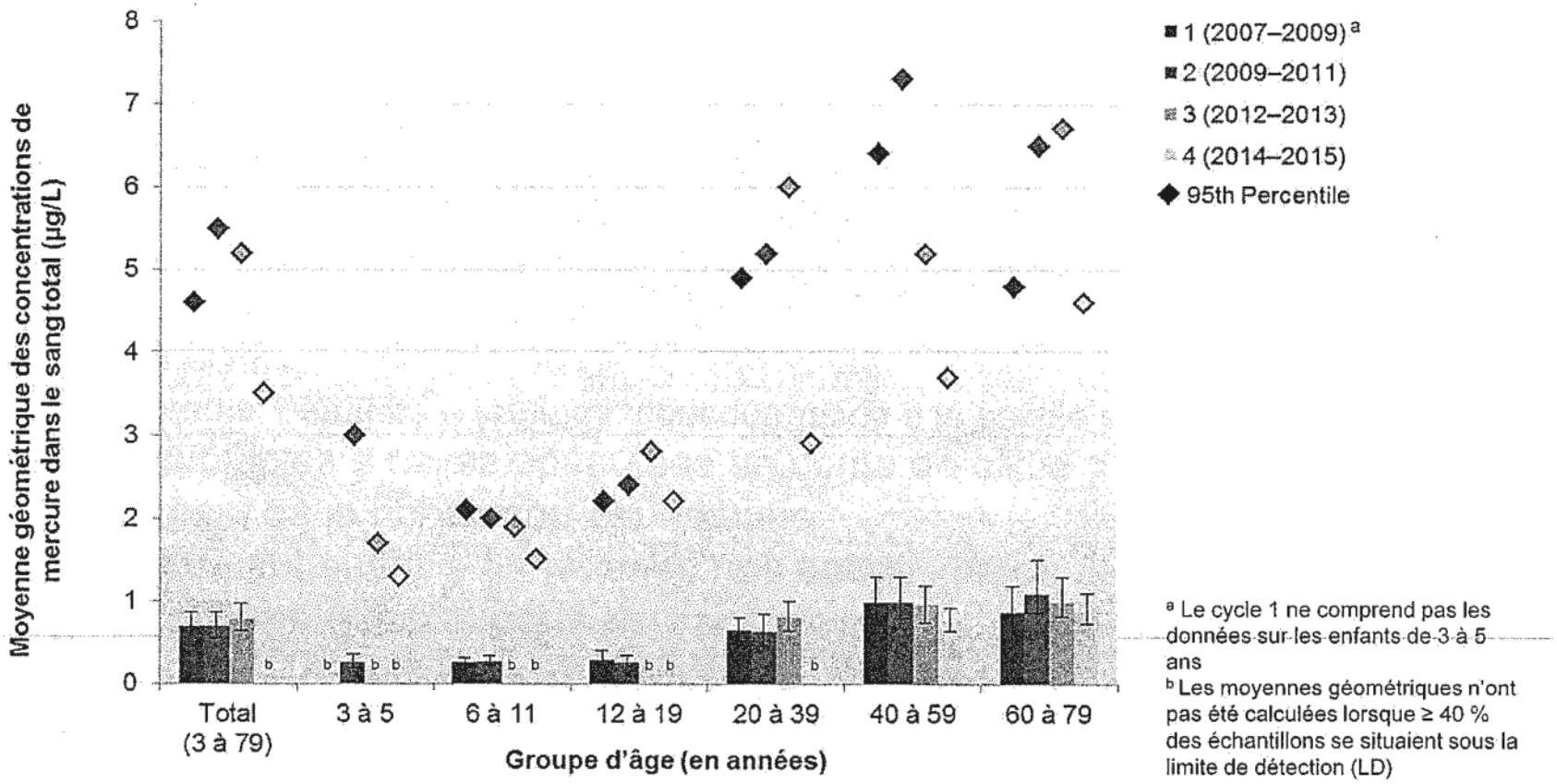
- Mesure fondamentale (incluse dans tous les cycles)
- Taux de détection supérieur à 99 %, avec une concentration moyenne de 0,95 µg/dL au sein de la population canadienne
- Tendances semblables à celles observées au cours du cycle 3 :
  - adultes > enfants; hommes > femmes; concentrations à la baisse au cours des 40 dernières années



[a] Le cycle 1 ne comprend pas les données sur les enfants de 3 à 5 ans

Concentration de mercure dans le sang – Cycles 1 à 4 (2007-2015)

- Mesure fondamentale (incluse dans tous les cycles)
- Taux de détection de 55 %, avec une concentration moyenne de 0,70 µg/L au sein de la population adulte canadienne
- Tendances semblables à celles observées au cours du cycle 3 :
  - adultes > enfants; hommes = femmes

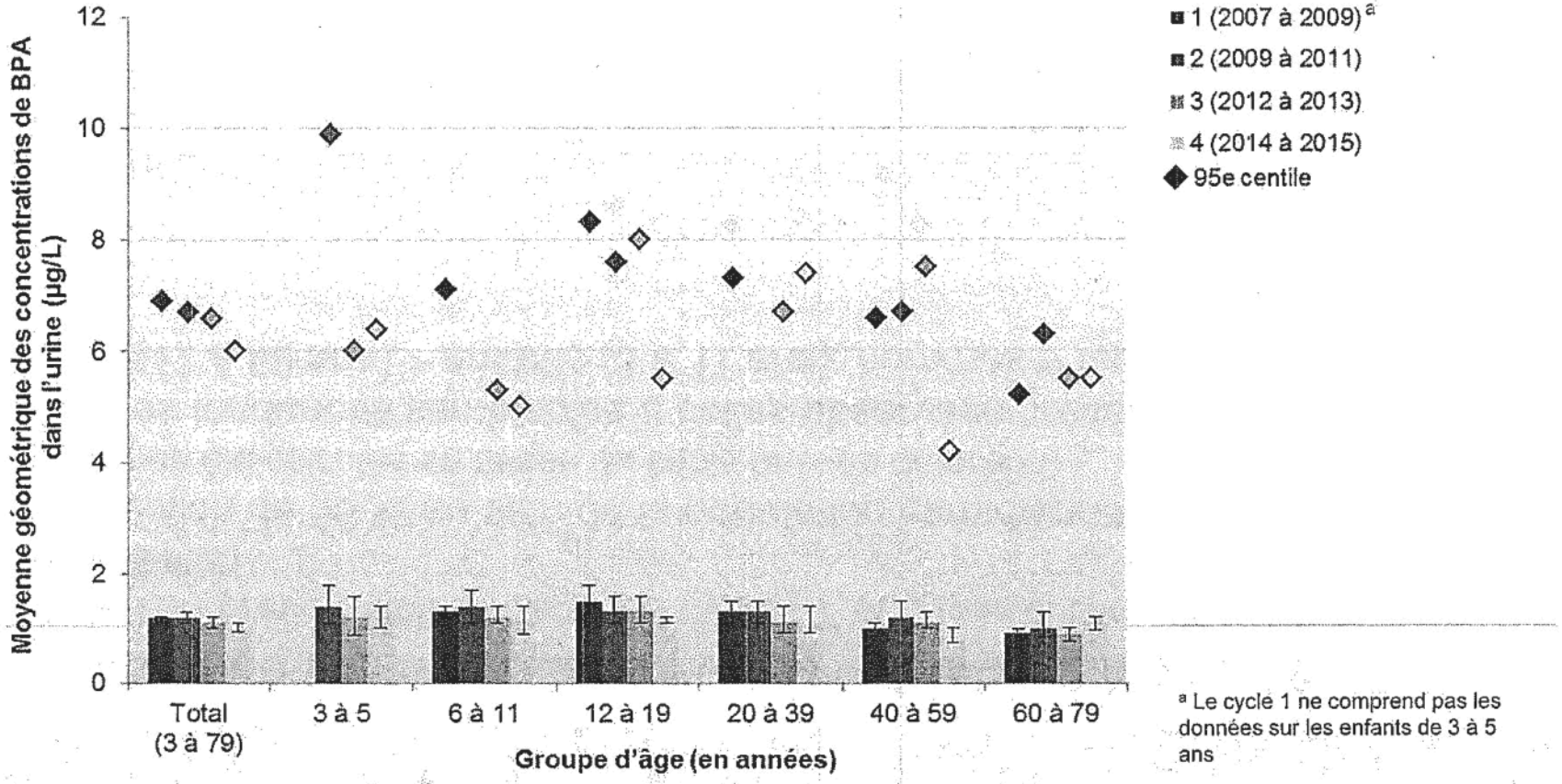


[a] Le cycle 1 ne comprend pas les données sur les enfants de 3 à 5 ans

[b] Les moyennes géométriques n'ont pas été calculées lorsque ≥ 40 % des échantillons se situaient sous la limite de détection (LD)

Concentration de BPA dans l'urine – Cycles 1 à 4 (2007-2015)

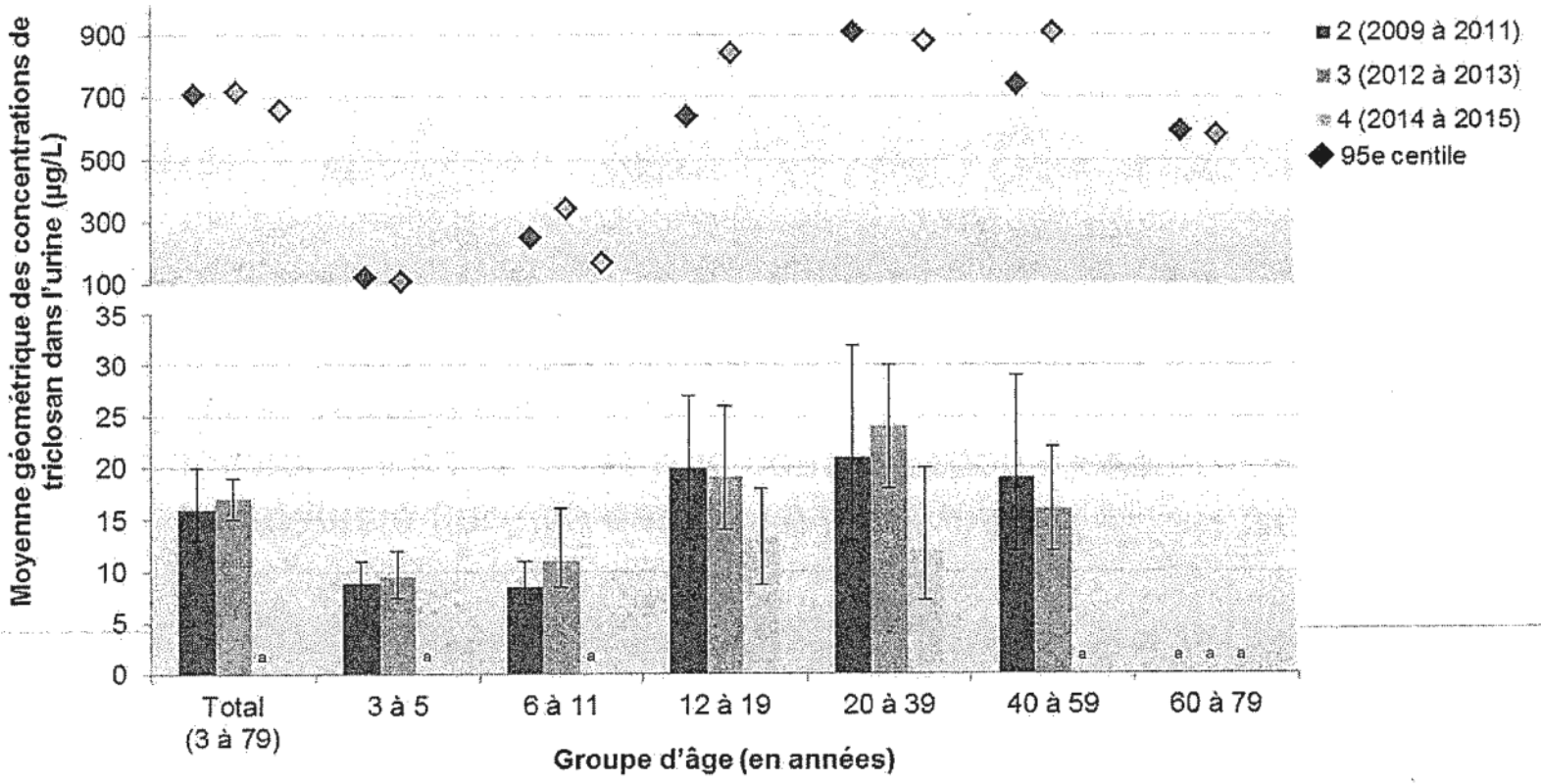
- Mesure fondamentale (incluse dans tous les cycles)
- Taux de détection de 93 %, avec une concentration moyenne de 1,0 µg/L au sein de la population canadienne
- On prévoit des tendances semblables à celles observées au cours du cycle 3 :
  - enfants > adultes; hommes > femmes



[a] Le cycle 1 ne comprend pas les données sur les enfants de 3 à 5 ans

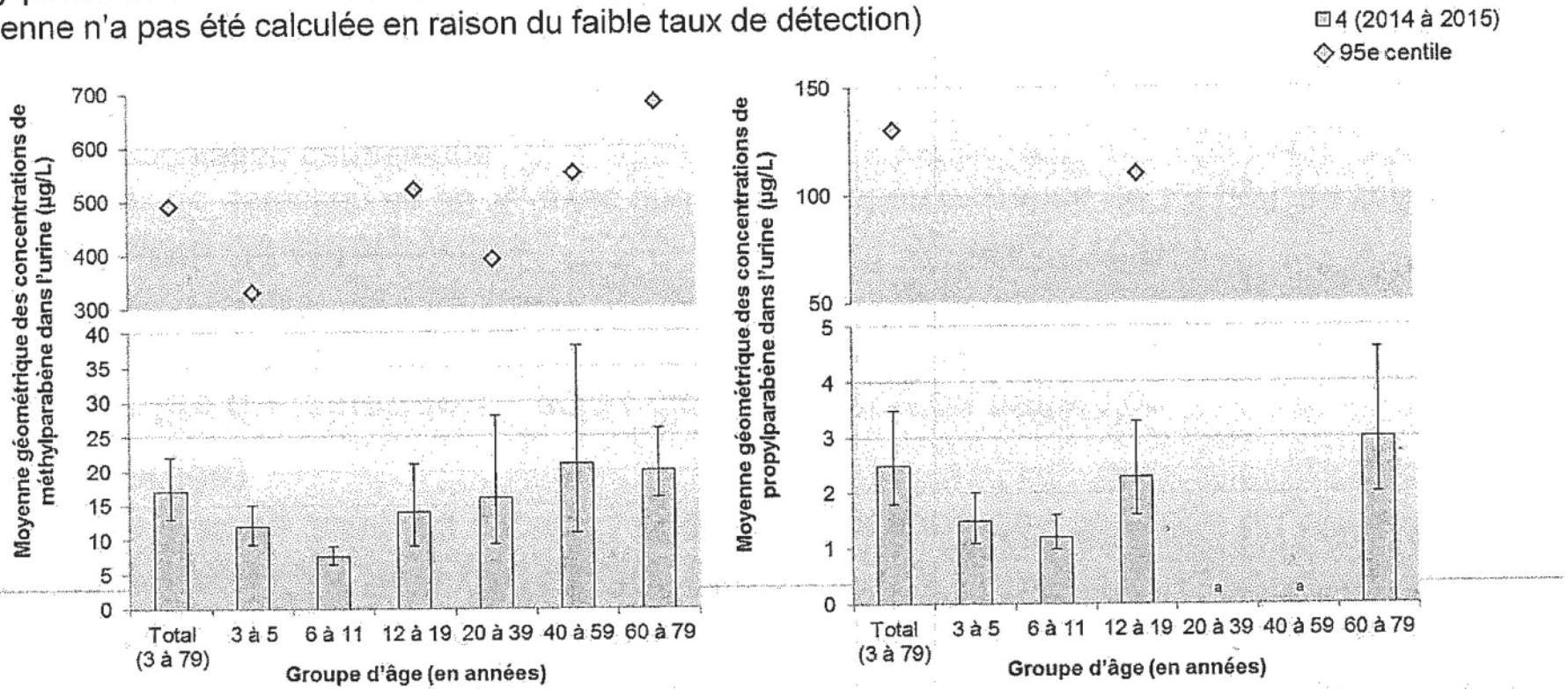
Concentration de triclosan dans l'urine – Cycles 2 à 4 (2009-2015)

- Mesure que l'on prévoit inclure dans les cycles 7 et 8 (pas encore mesurée au cours des cycles 1, 5 et 6)
- Taux de détection de 55 % au sein de la population canadienne (la concentration moyenne n'a pas été calculée en raison du faible taux de détection)
- On prévoit des tendances semblables à celles observées précédemment :
  - <u>adultes</u> (12 à 59 ans) > enfants (3 à 11 ans); hommes = femmes



Concentration de parabènes dans l'urine – Cycle 4 (2014-2015)

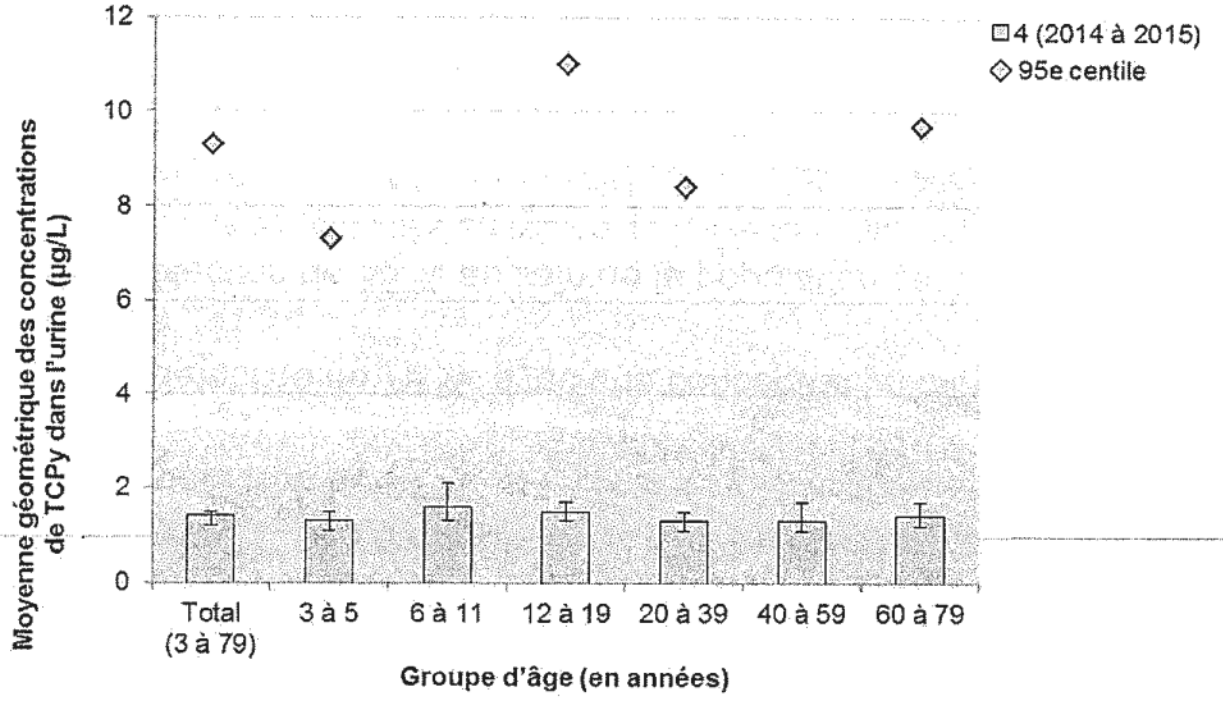
- Mesure incluse dans les cycles 3 à 6 (la publication des données du cycle 3 a été retardée)
- Méthylparabène : taux de détection de 92 %, avec une concentration moyenne de 17 µg/L au sein de la population canadienne
- Propylparabène : taux de détection de 79 %, avec une concentration moyenne de 2,5 µg/L au sein de la population canadienne
- Éthylparabène : taux de détection de 35 % au sein de la population canadienne
- (la concentration moyenne n'a pas été calculée en raison du faible taux de détection)
- Butylparabène : taux de détection de 17 % au sein de la population canadienne (la concentration moyenne n'a pas été calculée en raison du faible taux de détection)



[a] Les moyennes géométriques n'ont pas été calculées lorsque ≥ 40 % des échantillons se situaient sous la limite de détection (LD)

Concentration de métabolites de pesticides organophosphorés dans l'urine – Cycle 4 (2014-2015)

- Mesure incluse dans les cycles 3 et 4 (la publication des données du cycle 3 a été retardée)
- **Métabolite du malathion** – acide dicarboxylique de malathion
  - Taux de détection de 17 % au sein de la population canadienne (la concentration moyenne n'a pas été calculée en raison du faible taux de détection)
- **Métabolite du chlorpyrifos** – 3,5,6-Trichloro-2-pyridinol (TCPy)
  - Taux de détection de 99 %, avec une concentration moyenne de 1,4 µg/L au sein de la population canadienne



Renseignements importants sur l'analyse des données

- L'ECMS vise à fournir des estimations à l'échelle nationale sur la concentration d'une gamme de substances chimiques de l'environnement mesurées chez des Canadiens.

- En combinant les données de plusieurs cycles, il est possible à l'heure actuelle de réaliser certaines analyses régionales (p. ex. Ontario, Québec).

- Au fur et à mesure que d'autres cycles seront terminés, il pourrait être possible de réaliser d'autres analyses régionales.

- Il pourrait être possible de comparer les données des groupes autochtones et non autochtones (quoique les comparaisons seraient très limitées, puisque l'ECMS n'inclut pas les données sur les membres des Premières Nations vivant dans des réserves).

- Il est possible d'analyser les données selon l'origine ethnique, car les participants ont été invités à fournir leurs origines culturelles et ethniques (p. ex. origine sud-asiatique ou arabe) et à indiquer s'ils étaient nés au Canada ou ailleurs.

- Les femmes enceintes ont été incluses dans l'ECMS (c.-à-d. état autoclaré).

ECMS – données à venir

- **Cycles 3 et 4 – données regroupées (sérum)**
  - Des analyses de données sont en cours; leur publication est prévue pour 2018.
  - Les échantillons de sérum ont été combinés pour optimiser le volume d'échantillonnage et permettre la réalisation d'une analyse à haute résolution.
  - 52 substances chimiques (p. ex. BCP, organochlorés, dioxines, furanes et PBDE).

- **Cycle 5**
  - La collecte de données est en cours (janvier 2016 à décembre 2017), et la publication des résultats est prévue pour 2019.
  - 96 substances chimiques (dont 35 % sont de nouvelles substances).

- **Cycle 6**
  - Mêmes substances que pour le cycle 5.
  - La collecte de données devrait commencer en janvier 2018.

- **Cycles 7 et 8**
  - La planification est en cours pour les cycles 7 et 8, y compris l'élaboration des méthodes pour les nouvelles substances chimiques.
  - La collecte de données devrait commencer en janvier 2020.

Produits de statistique Canada

22 février 2017

- Publication de l'ensemble de données sur les concentrations en fluorure et en composés organiques volatils (COV) mesurées dans l'eau du robinet, les concentrations en fluorure mesurées dans l'urine et les concentrations en COV mesurées dans le sang.
- Annonce dans *Le Quotidien* comprenant un résumé des données sur les concentrations de fluorure mesurées dans l'eau du robinet et l'urine.

24 août 2017

- Publication de l'ensemble de données sur la biosurveillance et transfert aux Centres de données de recherche (CDR)
- Annonce dans *Le Quotidien* comprenant les analyses des tendances relatives au cadmium, au plomb et au mercure
- Tableaux de données pour certaines substances chimiques accessibles en ligne

Automne 2017 (*selon les prévisions*)

- Publication de l'ensemble de données sur l'air intérieur
- Fiches de renseignements sur la santé sur les parabènes et l'arsenic

Remarque : Les ensembles de données complets pour la période de 2007 à 2015 sont accessibles par le biais des Centres de données de recherche de Statistique Canada.

Pour en savoir plus

Santé Canada
canada.ca/biosurveillance

Des questions?
Annie.St-Amand@hc-sc.gc.ca

Gouvernement ouvert
ouvert.canada.ca

Statistique Canada
ECMS (Information au sujet de l'Enquête)
http://www23.statcan.gc.ca/imdb/p2SV_f.pl?Function=getSurvey&SDDS=5071

Le Quotidien (publication des données de l'ECMS)
www.statcan.gc.ca/dai-quo/

Centres de données de recherche (accès aux données)
https://crdcn.org/fr

Renseignements généraux – Données de biosurveillance humaine de l'ECMS

DIAPOSITIVES ADDITIONNELLES

Enquête canadienne sur les mesures de la santé (ECMS) – Aperçu

- Enquête nationale sur la santé dirigée par Statistique Canada, en partenariat avec Santé Canada et l'Agence de la santé publique du Canada.
- Sert à recueillir des renseignements sur l'état de santé général et le mode de vie des Canadiens en vue de fournir de l'information sur les maladies chroniques et infectieuses, la condition physique, l'alimentation et d'autres facteurs qui ont une incidence sur la santé.
- L'ECMS comprend aussi un **volet de biosurveillance** qui mesure les concentrations de substances chimiques de l'environnement chez les Canadiens :
  - Cycle 1 (2007-2009) : 92 substances chimiques (+ 50 dans un échantillon de sérum combiné)
  - Cycle 2 (2009-2011) : 91 substances chimiques
  - Cycle 3 (2012-2013) : 56 substances chimiques + 52 dans un échantillon de sérum combiné
  - **Cycle 4 (2014-2015) : 54 substances chimiques + 52 dans un échantillon de sérum combiné**

Biosurveillance des substances chimiques de l'environnement dans le cadre de l'ECMS – Objectifs

- Fournir des données représentatives à l'échelle nationale sur une gamme de substances chimiques mesurées chez les Canadiens aux fins de comparaison avec des sous-populations canadiennes et d'autres pays.

- Fournir des données de référence permettant de suivre les tendances sur les concentrations de substances chimiques de l'environnement mesurées au fil du temps.

- Fournir des données permettant d'étudier les liens entre les substances chimiques de l'environnement et d'autres mesures (p. ex. tension artérielle, alimentation).



Jalons de l'ECMS

Rapport de biosurveillance – cycle 1 (août 2010)

Rapport de biosurveillance – cycle 2 (avril 2013)

Rapport de biosurveillance – cycle 3 (juillet 2015)

2007 2008 2009 2010 2011 2012 2013 2014 2015 2016

Cycle 1
mars 2007 – fév. 2009
15 sites
6 à 79 ans (n = 5 600)
92 (+ 50) subst. chimiques

Cycle 2
août 2009 – nov. 2011
18 sites
3 à 79 ans (n = 6 400)
91 subst. chimiques

Cycle 3
janv. 2012 – déc. 2013
16 sites
3 à 79 ans (n = 5 700)
56 subst. chimiques + 52 dans un échantillon combiné

Cycle 4
janv. 2014 – déc. 2015
16 sites
3 à 79 ans (n = 5700)
54 subst. chimiques + 52 dans un échantillon combiné

Rapport de biosurveillance – cycle 4 (août 2017)

2016 2017 2018 2019 2020 2021 2022 2023 2024

Cycle 5
janv. 2016 – déc. 2017
16 sites
3 à 79 ans (n = 5 700)
155 subst. chimiques
Rapport prévu pour 2019

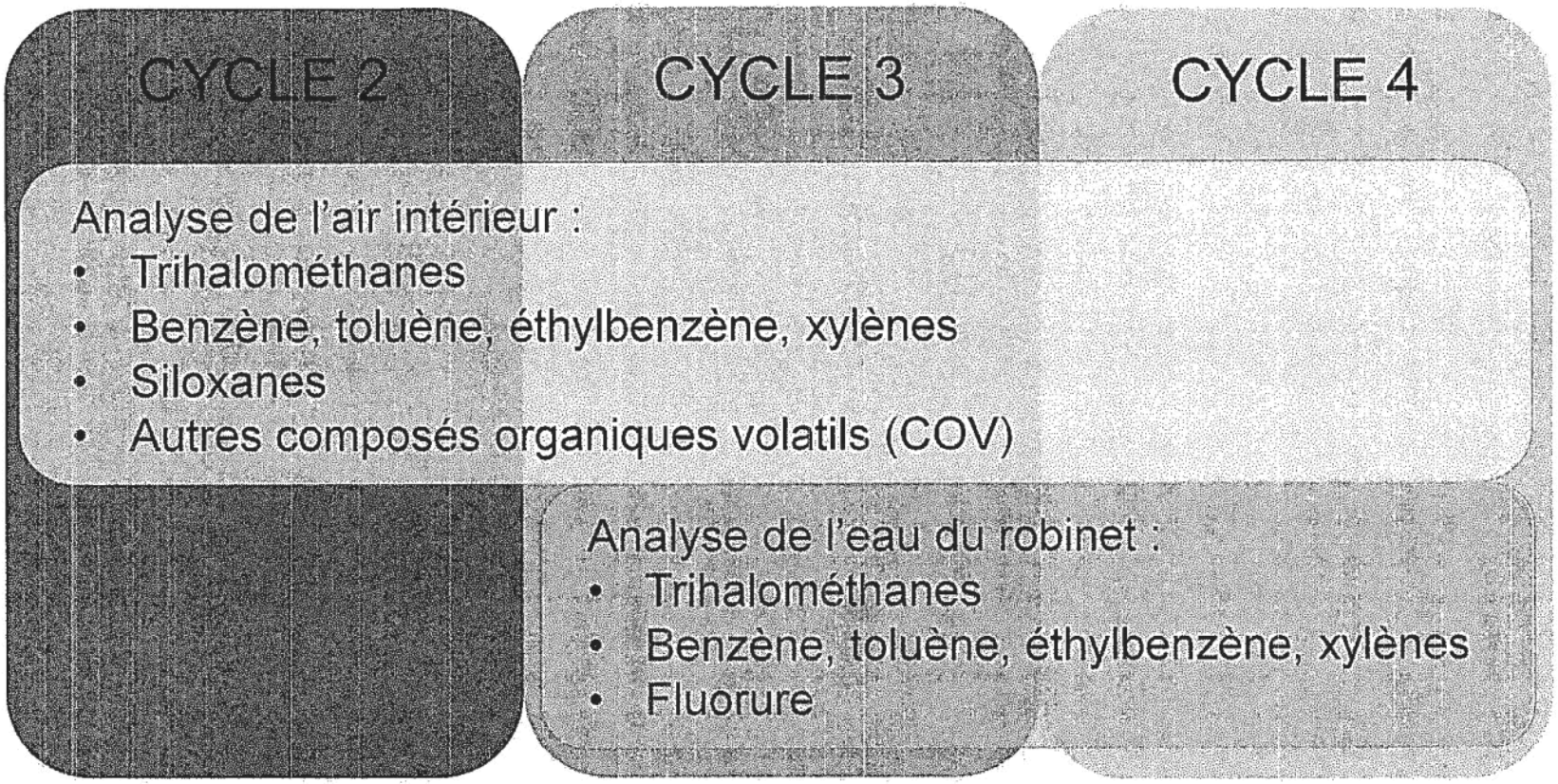
Cycle 6
janv. 2018 – déc. 2019
16 sites
3 à 79 ans (n = 5 700)
Tendances semblables à celles du cycle 5
Rapport prévu pour 2021

Cycle 7
janv. 2020 – déc. 2021
16 sites
3 à 79 ans (n = 5 700)
Subst. chimiques à confirmer
Rapport prévu pour 2023

Cycle 8
janv. 2022 – déc. 2023
16 sites
3 à 79 ans (n = 5 700)
Tendances semblables à celles du cycle 7
Rapport prévu pour 2025

SANTÉ CANADA >

Biosurveillance des substances chimiques de l'environnement dans le cadre de l'ECMS



Health Canada Santé Canada

Canada

Briefing on Release of Biomonitoring Data from the Canadian Health Measures Survey (2014-2015)

August 24, 2017

Séance d'information sur la parution des données de biosurveillance de l'Enquête canadienne sur les mesures de la santé (2014-2015)
24 août 2017

Environmental Health Science Research Bureau
Bureau de la science et de la recherche en santé environnementale
Healthy Environment and Consumer Safety Branch
Direction générale de la santé environnementale et de la sécurité des consommateurs



Purpose of the Briefing
Objectifs de la séance d'information

(1) To announce the publication of Health Canada's *Fourth Report on Human Biomonitoring of Environmental Chemicals in Canada*

Annoncer la parution du *Quatrième rapport sur la biosurveillance humaine des substances chimiques de l'environnement au Canada* de Santé Canada

(2) To highlight results from the biomonitoring component of the Canadian Health Measures Survey (CHMS 2014-2015)

Présenter certains résultats du volet de biosurveillance de l'Enquête Canadienne sur les mesures de la santé (ECMS 2014-2015)

Health Canada Products
Produits de Santé Canada

August 24, 2017
24 août 2017

- *Fourth Report on Human Biomonitoring of Environmental Chemicals in Canada*
  Quatrième rapport sur la biosurveillance humaine des substances chimiques de l'environnement au Canada

- Revised *Biomonitoring Content Summary for the Canadian Health Measures Survey: Cycles 1-4 (2007-2015)*
  Résumé révisé du contenu du volet biosurveillance des substances chimiques de l'environnement : Cycles 1 à 4 (2007-2015)

- Available in HTML and/et PDF at: canada.ca/biomonitoring
  Disponible en formats HTML et PDF à: canada.ca/biosurveillance

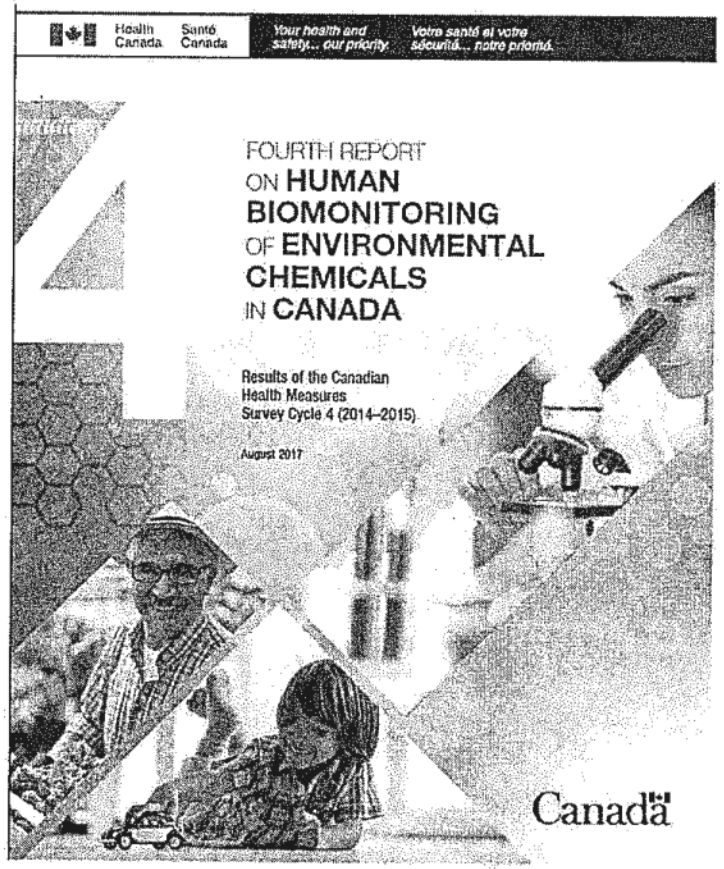
Fall 2017
Automne 2017

- Data tables available on Open Government portal: open.canada.ca
  Tableaux de données disponibles sur le portail du Gouvernement ouvert: ouvert.canada.ca

4th Report on *Human Biomonitoring of Environmental Chemicals in Canada*

August 24, 2017

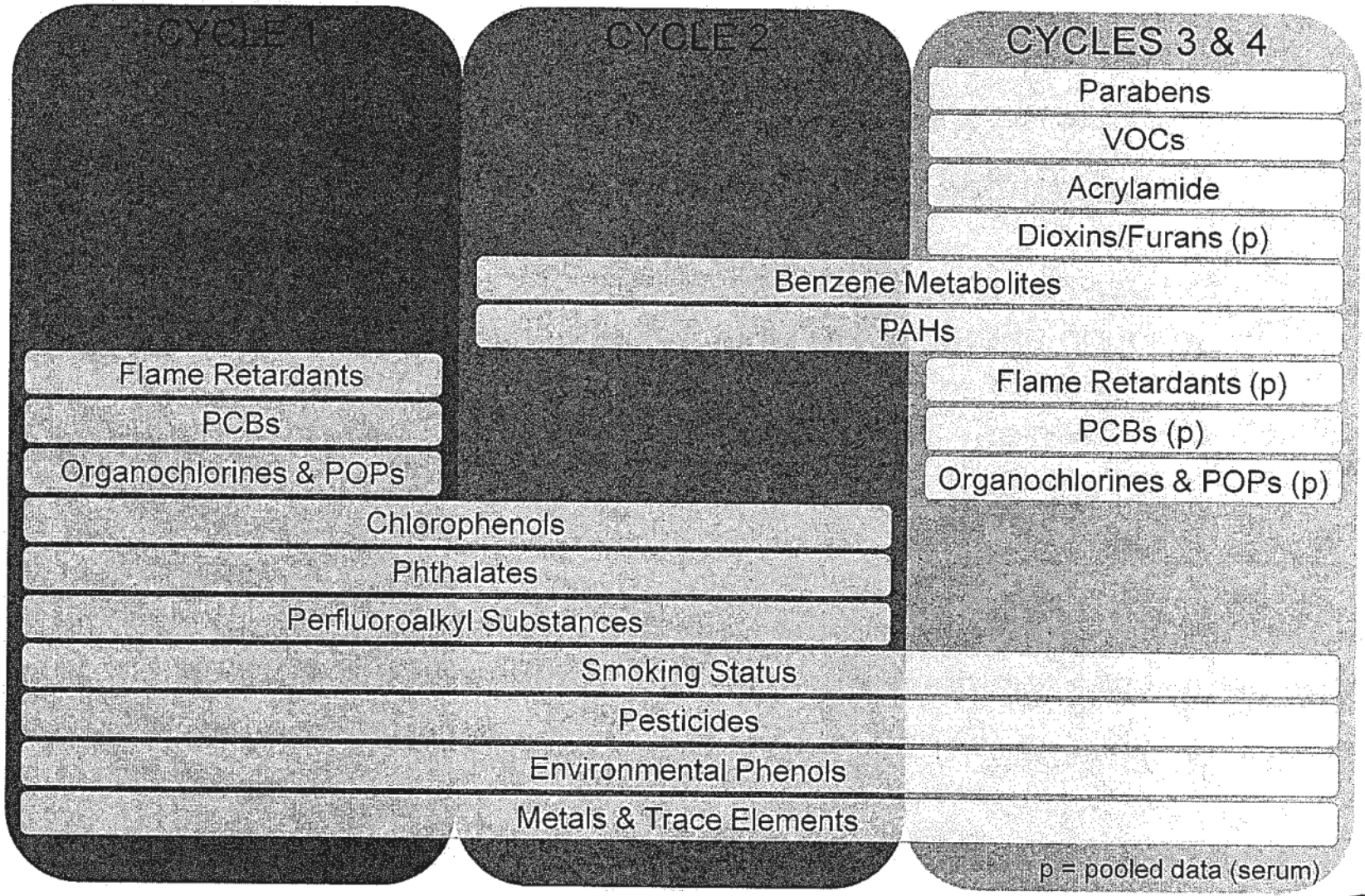
- What's new in the *Fourth Report?*
  - Most recent data (2014-2015) for 54 environmental chemicals
  - Updated data for 48 chemicals previously included in the *Third Report*
  - New data for six chemicals:
    - Parabens
    - Malathion and chlorpyrifos metabolites
- Data are shown for the total Canadian population and are further sub-divided by age group and sex
- The report does not examine health risks or outcomes



Highlights of Results

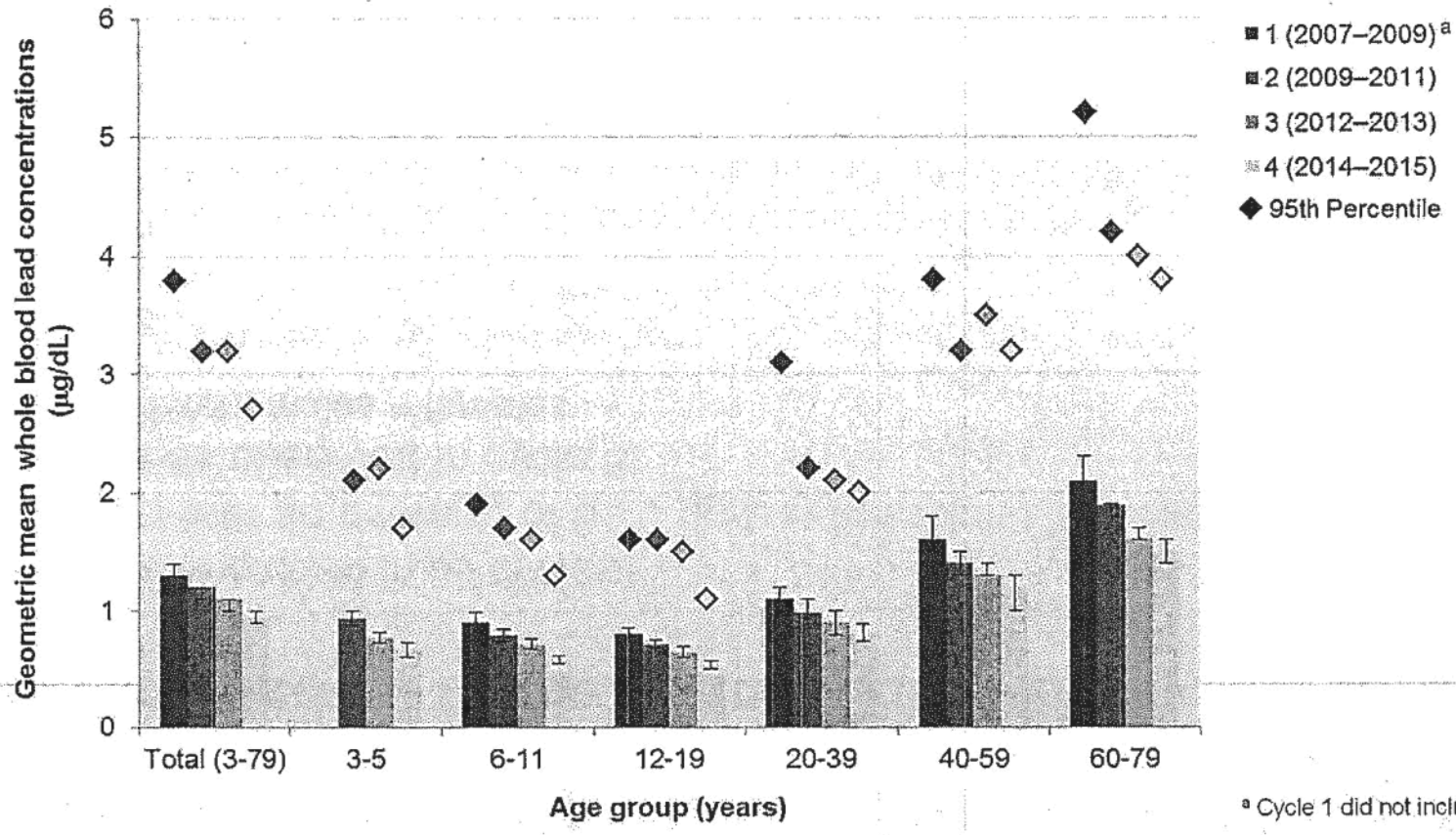
- Overall, levels of environmental chemicals in Canadians are within similar ranges as those previously reported in Canada (2007-2013) and internationally
- Blood lead level trends – averages have declined from 1.3 µg/dL in cycle 1 (2007-2009) to 0.95 µg/dL in cycle 4 (2014-2015)
- Mercury level trends – no significant change in average concentrations from 2007-2009 to 2014-2015 for the Canadian adult (20-79) population
- Parabens detection rate in urine of the Canadian population:
  - Methyl paraben: 92%
  - Propyl paraben: 79%
  - Ethyl paraben: 35%
  - Butyl paraben: 17%

CHMS Biomonitoring Chemicals



Lead in Blood – Cycles 1 to 4 (2007-2015)

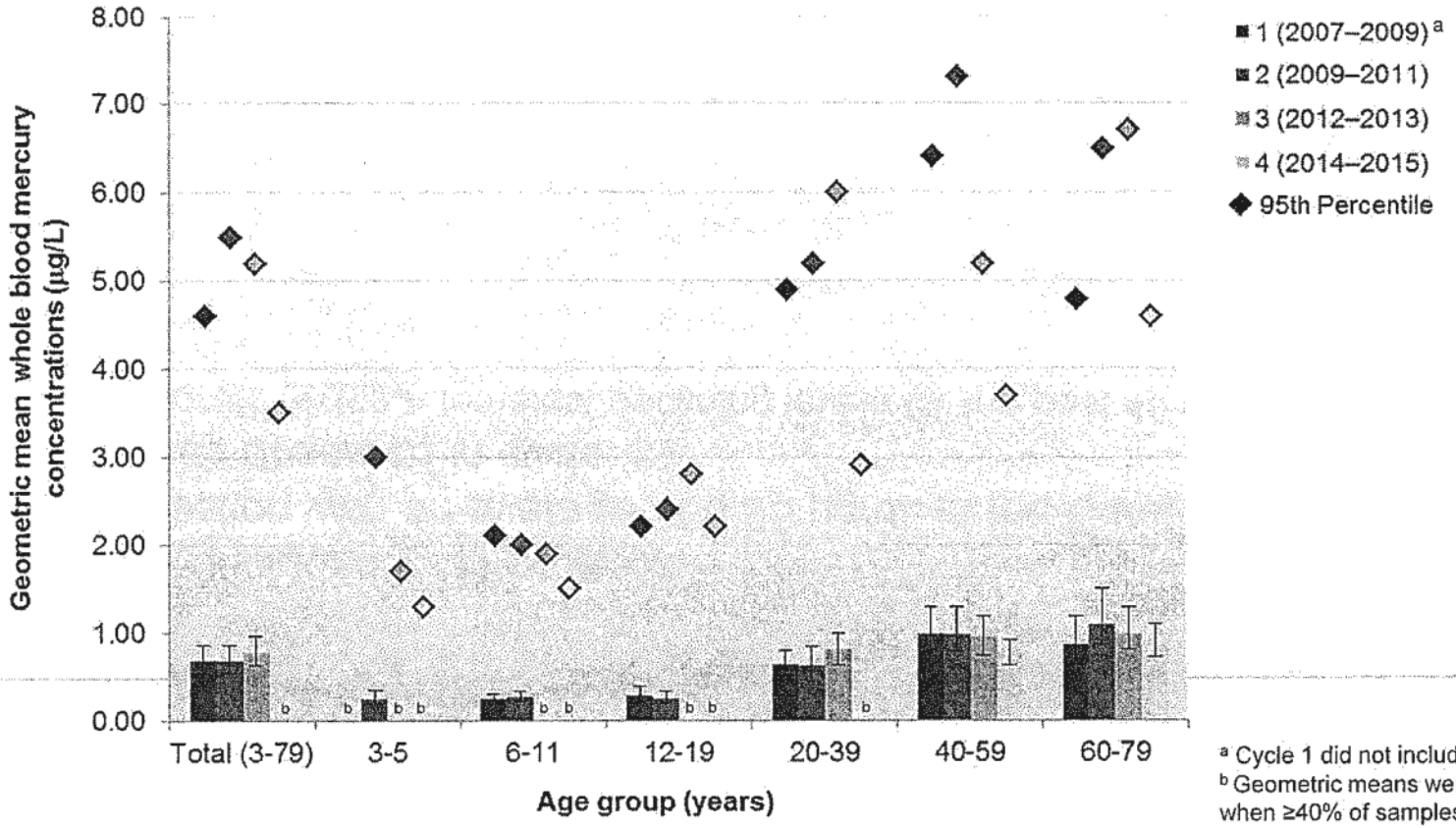
- Core measure (included in all cycles)
- Over 99% detection with an average of 0.95 µg/dL in the Canadian population
- Similar trends as observed in cycle 3:
  - adults > children; males > females; declining levels for the past 40 years



[a] Cycle 1 did not include 3-5 year olds

Mercury in Blood – Cycles 1 to 4 (2007-2015)

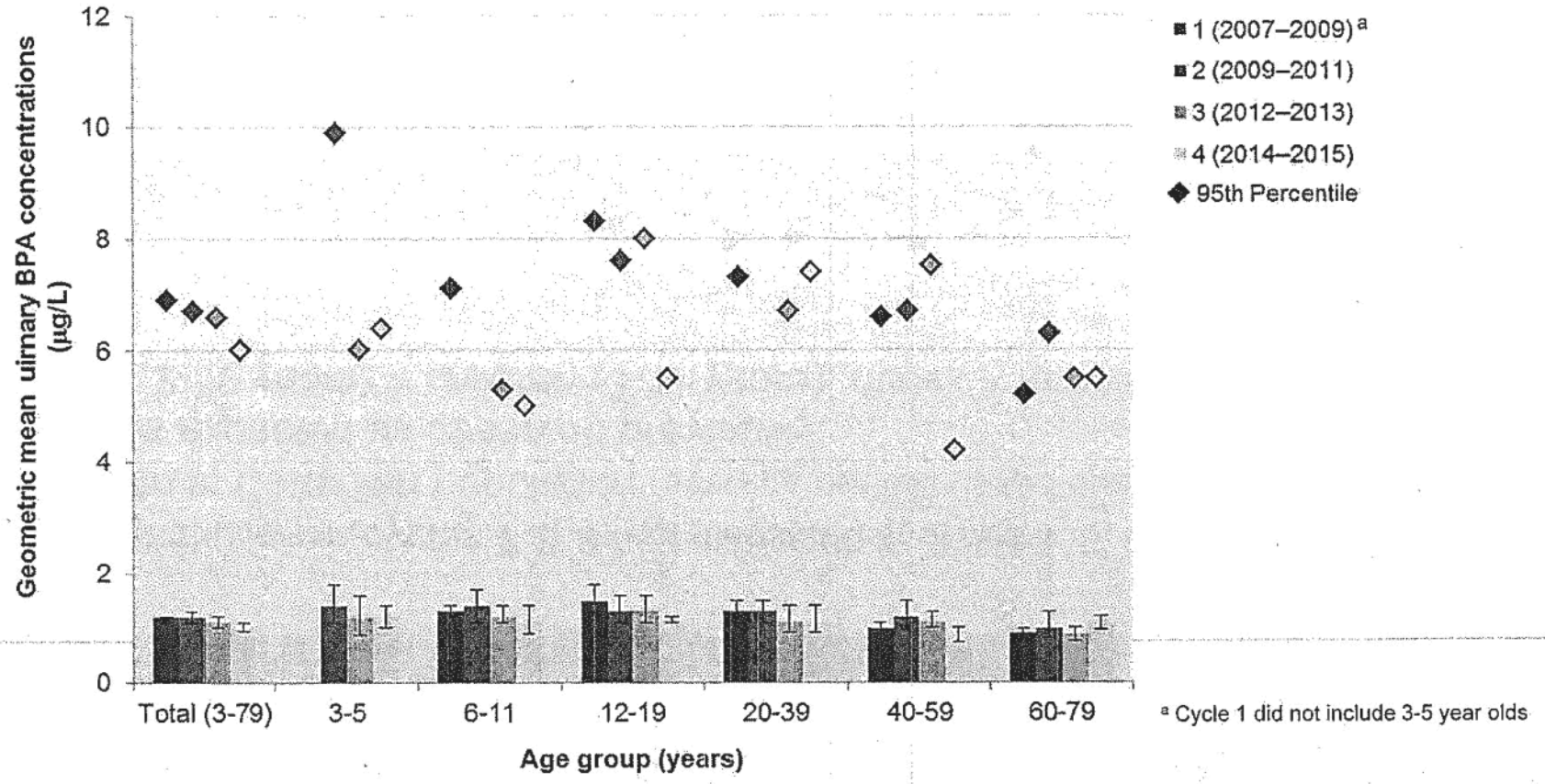
- Core measure (included in all cycles)
- 55% detection with an average of 0.70 µg/L in the adult Canadian population
- Similar trends as observed in cycle 3:
  - adults > children; males = females



[a] Cycle 1 did not include 3-5 year olds
[b] Geometric means were not calculated when ≥40% of samples were below the LOD

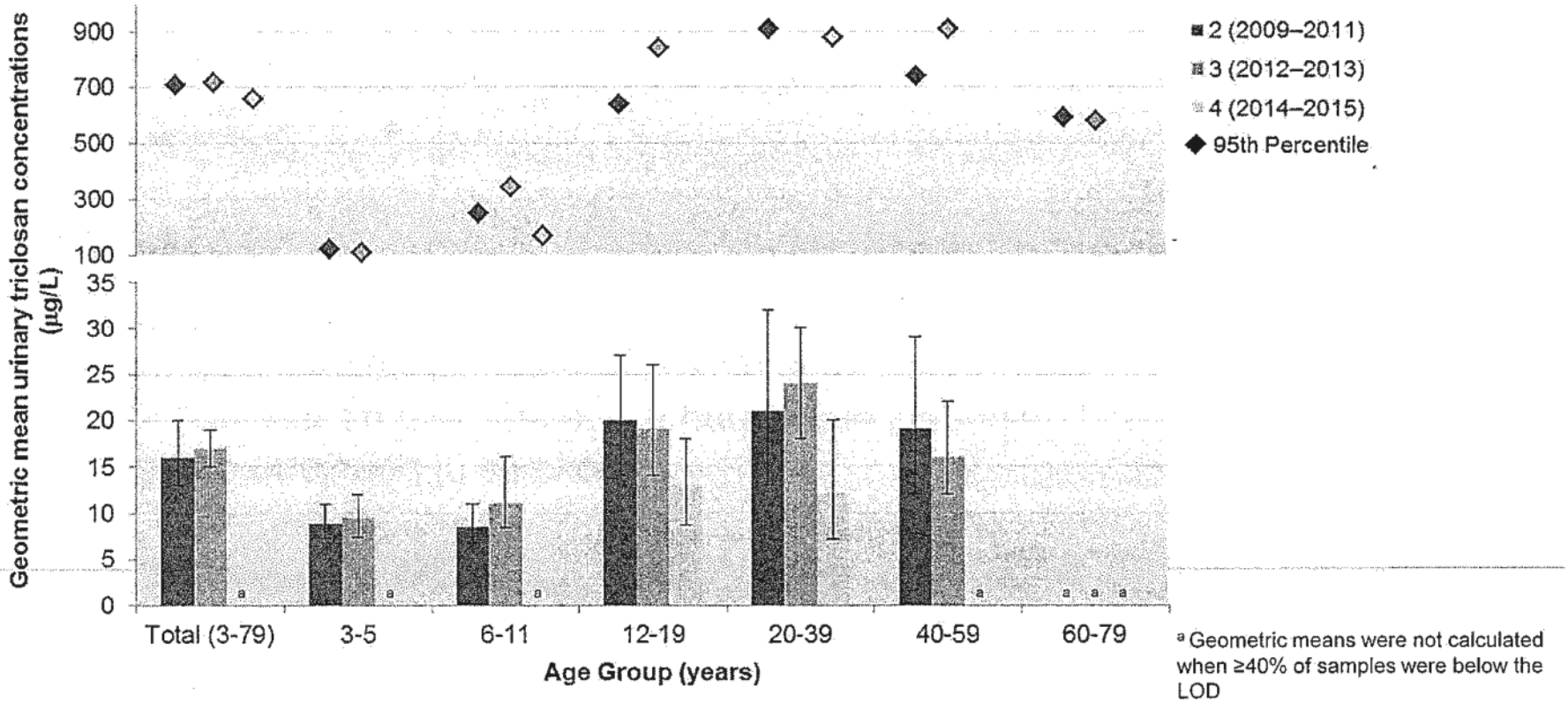
BPA in Urine – Cycles 1 to 4 (2007-2015)

- Core measure (included in all cycles)
- 93% detection with an average of 1.0 µg/L in the Canadian population
- Similar trends expected as observed in cycle 3:
  - children > adults; males > females



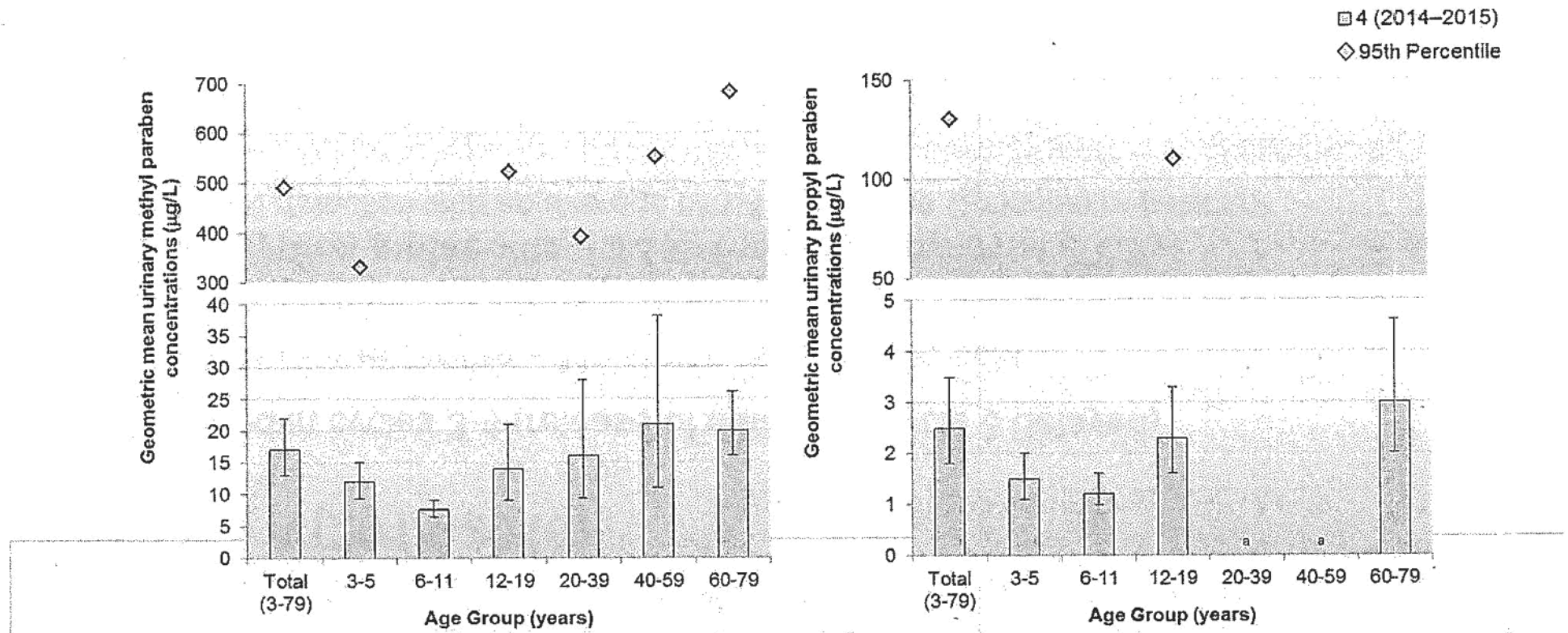
Triclosan in Urine – Cycles 2 to 4 (2009-2015)

- Planned for inclusion in cycles 7 & 8 (not measured in cycles 1, 5, 6)
- 55% detection in Canadian population (average not calculated due to low detection)
- Similar trends expected as observed previously:
  - adults (12-59 years) > children (3-11 years); males = females



Parabens in Urine – Cycle 4 (2014-2015)

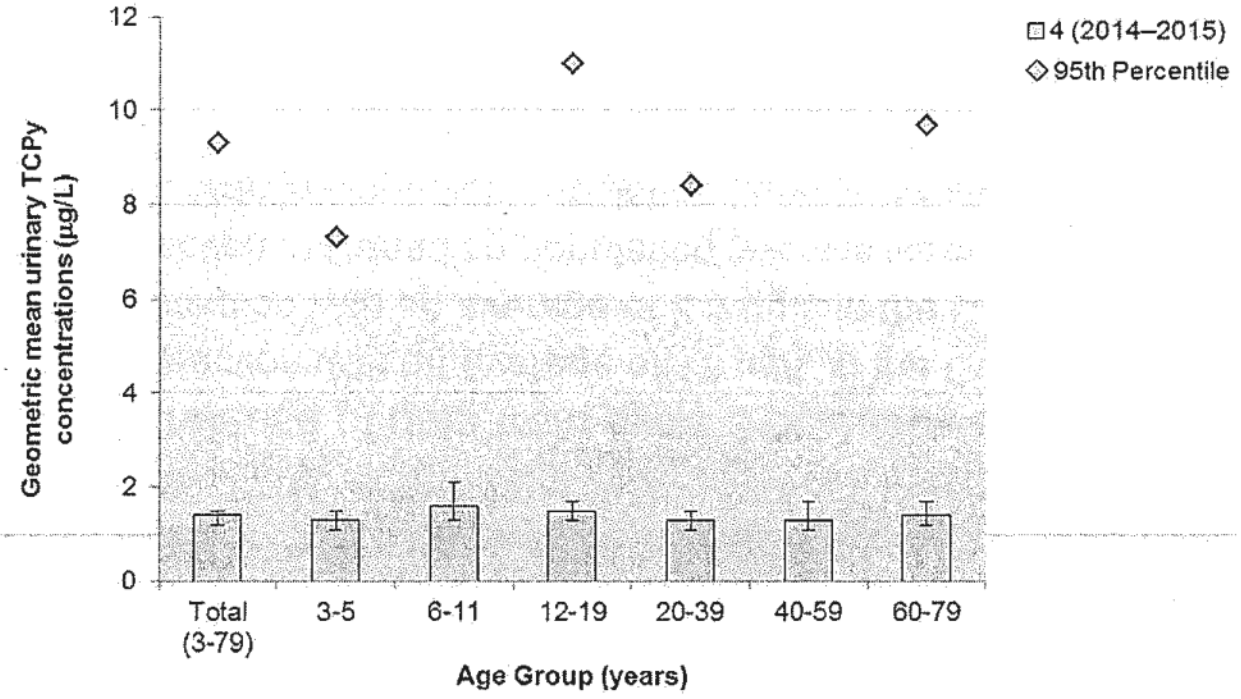
- Included in cycles 3-6 (release of data from cycle 3 delayed)
- Methyl paraben: 92% detection with an average of 17 µg/L in the Canadian population
- Propyl paraben: 79% detection with an average of 2.5 µg/L in the Canadian population
- Ethyl paraben: 35% detection in Canadian population (average not calculated due to low detection)
- Butyl paraben: 17% detection in Canadian population (average not calculated due to low detection)



[a] Geometric means were not calculated when ≥40% of samples were below the LOD

Organophosphate Pesticide Metabolites in Urine – Cycle 4 (2014-2015)

- Included in cycles 3-4 (release of data from cycle 3 delayed)
- **Malathion metabolite** – Malathion dicarboxylic acid
  - 17% detection in Canadian population (average not calculated due to low detection)
- **Chlorpyrifos metabolite** – 3,5,6-Trichloro-2-pyridinol (TCPy)
  - 99% detection with an average of 1.4 µg/L in the Canadian population



Key information on Data Analysis

- CHMS is designed to give national estimates for a range of environmental chemicals in Canadians
- By combining data from multiple cycles, it is currently possible to conduct some regional analyses (e.g. ON, QC)
- As more cycles are completed, it may be possible to do more regional analyses
- It may be possible to make comparisons between Aboriginal and non-Aboriginal groups (though very limited, since CHMS does not include residents living on First Nations Reserves)
- Data can be analysed by ethnic origin since participants were asked to identify their cultural and ethnic backgrounds (e.g. South Asian, Arab) and whether they were born in Canada or elsewhere
- Pregnant women were included in the CHMS (i.e. self reported)

Future Data from the CHMS

- **Cycle 3 & 4 – pooled data (serum)**
  - Data analyses are underway with release anticipated in 2018
  - Pooled serum was used to maximize the sample volume and allow for high-resolution analysis
  - 52 chemicals (e.g. PCBs, organochlorines, dioxins, furans, and PBDEs)

- **Cycle 5**
  - Data collection is underway (Jan 2016 – Dec 2017) with release anticipated in 2019
  - 96 chemicals (35% new)

- **Cycles 6**
  - Same chemicals as cycle 5
  - Data collection scheduled to start in January 2018

- **Cycles 7 & 8**
  - Planning for cycles 7 & 8 is currently underway including method development for new chemicals
  - Data collection scheduled to start in January 2020

Statistics Canada Products

February 22, 2017

- Release of tap water dataset for fluoride and volatile organic compounds (VOCs), urine data for fluoride and blood data for VOCs
- Announcement in *The Daily* with summary of tap water and urine fluoride data

August 24, 2017

- Release of biomonitoring dataset and transfer to RDC
- Announcement in *The Daily* with trend analyses for cadmium, lead and mercury
- Data tables for certain chemicals available online

Fall 2017 (*anticipated*)

- Release of indoor air dataset
- Health fact sheets for parabens and arsenic

Note: complete datasets for 2007 to 2015 are available through Statistics Canada's Research Data Centres

For More Information/ Pour en savoir plus:

Health Canada/ Santé Canada:

canada.ca/biomonitoring

canada.ca/biosurveillance

Questions?
Annie.St-Amand@hc-sc.gc.ca

Open Government/ Gouvernement ouvert :

open.canada.ca

ouvert.canada.ca

Statistics Canada/ Statistique Canada:

CHMS (info about Survey)/ ECMS (Informations à propos de l'Enquête):

http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=5071
http://www23.statcan.gc.ca/imdb/p2SV_f.pl?Function=getSurvey&SDDS=5071

The Daily (CHMS data releases)/ *Le Quotidien (publication de données de l'ECMS):*

www.statcan.gc.ca/dai-quo/

Research Data Centres (access to data)/ Réseau canadien des Centres de données de recherche (accès aux données)

crdcn.org

https://crdcn.org/fr

Background information - Human Biomonitoring in CHMS

ADDITIONAL SLIDES

Canadian Health Measures Survey (CHMS) – Overview

- National health survey led by Statistics Canada, in partnership with Health Canada and the Public Health Agency of Canada
- Collects information on the general health and lifestyles of Canadians to provide information on chronic and infectious disease, physical fitness, nutrition, and other factors that influence health
- Also includes a **biomonitoring component** which measures environmental chemicals in Canadians:
  - Cycle 1 (2007-2009): 92 environmental chemicals (+ 50 in pooled serum)
  - Cycle 2 (2009-2011): 91 environmental chemicals
  - Cycle 3 (2012-2013): 56 environmental chemicals + 52 in pooled serum
  - **Cycle 4 (2014-2015): 54 environmental chemicals + 52 in pooled serum**

CHMS Environmental Chemical Biomonitoring – Objectives

- Provide nationally-representative data for a range of environmental chemicals in Canadians for comparison with sub-populations and with other countries
- Provide baseline data for tracking trends in environmental chemical levels over time
- Provide data to explore relationships between environmental chemicals and other measures (e.g. blood pressure, nutrition)



CHMS Milestones

Cycle 1 biomonitoring report (August 2010)

Cycle 2 biomonitoring report (April 2013)

Cycle 3 biomonitoring report (July 2015)

2007 2008 2009 2010 2011 2012 2013 2014 2015 2016

Cycle 1	Cycle 2	Cycle 3	Cycle 4
Mar 2007 – Feb 2009 15 sites 6-79 years (n = 5,600) 92 (+ 50) chemicals	Aug 2009 – Nov 2011 18 sites 3-79 years (n = 6,400) 91 chemicals	Jan 2012 – Dec 2013 16 sites 3-79 years (n = 5,700) 56 chemicals + 52 in pooled serum	Jan 2014 – Dec 2015 16 sites 3-79 years (n = 5,700) 54 chemicals + 52 in pooled serum

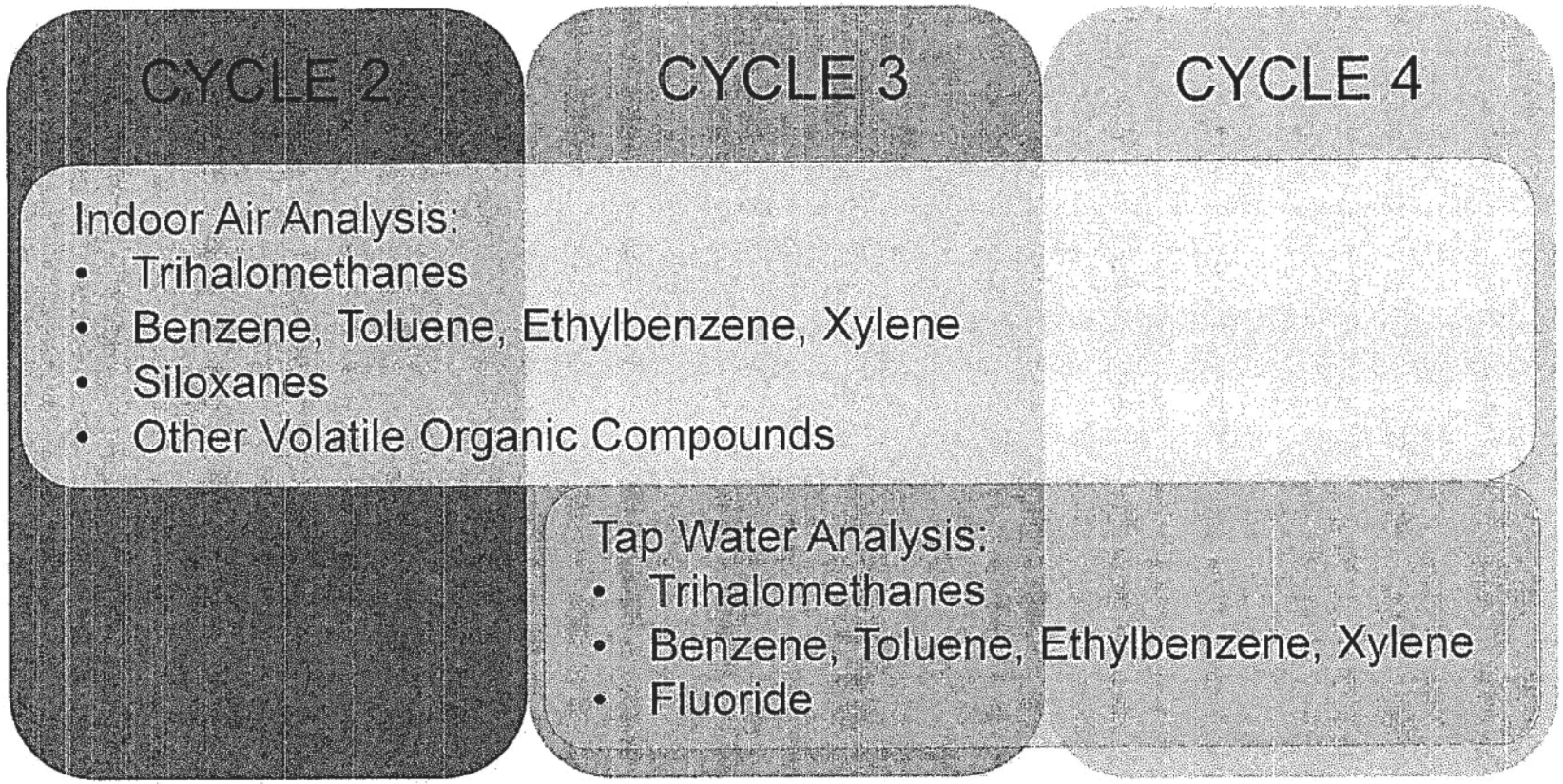
Cycle 4 biomonitoring report (August 2017)

2016 2017 2018 2019 2020 2021 2022 2023 2024

Cycle 5	Cycle 6	Cycle 7	Cycle 8
Jan 2016 – Dec 2017 16 sites 3-79 years (n = 5,700) 155 chemicals Report planned for 2019	Jan 2018 – Dec 2019 16 sites 3-79 years (n = 5,700) similar to Cycle 5 Report planned for 2021	Jan 2020 – Dec 2021 16 sites 3-79 years (n = 5,700) chemicals TBD Report planned for 2023	Jan 2022 – Dec 2023 16 sites 3-79 years (n = 5,700) similar to Cycle 7 Report planned for 2025

HEALTH CANADA >

CHMS Environmental Monitoring



Fishwick, David HLTH:EX

From: Vezina, Anne (HC/SC) <anne.vezina@canada.ca>
Sent: September 22, 2017 8:04 AM
To: 'Gould, Kevin (DH/MS)'; Vezina, Anne (HC/SC); 'angelina.polegato@novascotia.ca'; 'Caroline.Robert@mddelcc.gouv.qc.ca'; Fishwick, David HLTH:EX; 'donald.reid@gov.ab.ca'; 'Peter_Workman@gov.nt.ca'; 'ghsomers@gov.pe.ca'; 'hkhan@gov.nl.ca'; 'Kim.Philip@gov.mb.ca'; 'pat.brooks@gov.yk.ca'; 'sam.ferris@wsask.ca'; 'Satish.Deshpande@ontario.ca'; 'MLeBlanc-Havard@GOV.NU.CA'
Cc: Carreau, Greg (HC/SC); Giddings, Michele (HC/SC); McFadyen, Stephanie (HC/SC); Carrier, Richard (HC/SC); Lemieux, France (HC/SC); Morisset, Veronique (HC/SC); Enright, Wendy (HC/SC); Zuric, Jelena (HC/SC); Labib, Sarah (HC/SC); Martinova, Nadia (HC/SC)
Subject: RE: Revised PFOS and PFOA documents
Attachments: PFOS 2017-0804 (with Kevin edits) 2017-09-20.pdf; PFOA 2017-0804 (with Kevin edits) 2017-09-20.pdf

Good morning Kevin,
Below are the responses to your comments on the revised PFOS and PFOA documents. Attached are the revised PFOS and PFOA documents with highlighted changes made since the last versions sent after the CDW meeting, to address the latest comments.
I cc'd CDW members for them to see the latest changes. If you or any CDW members have concerns with these changes, please let me know as soon as possible.
Thank you,
Anne

From: Gould, Kevin (DH/MS) [mailto:Kevin.Gould@gnb.ca]
Sent: Monday, August 21, 2017 9:08 AM
To: 'Anne Vezina'; angelina.polegato@novascotia.ca; Caroline.Robert@mddelcc.gouv.qc.ca; David.Fishwick@gov.bc.ca; donald.reid@gov.ab.ca; Peter_Workman@gov.nt.ca; ghsomers@gov.pe.ca; hkhan@gov.nl.ca; Kim.Philip@gov.mb.ca; pat.brooks@gov.yk.ca; sam.ferris@wsask.ca; Satish.Deshpande@ontario.ca; MLeBlanc-Havard@GOV.NU.CA
Cc: Greg Carreau; Michele Giddings; Stephanie McFadyen; Richard Carrier; France Lemieux; Veronique Morisset; Wendy Enright; Jelena Zuric; Sarah Labib; Nadia Martinova
Subject: RE: Revised PFOS and PFOA documents
Hi Anne.

- I am still personally having a bit of a hard time getting my head wrapped around this approach and what it <u>really means</u> (see note 3.0 and 9.0 below). I am fine to move ahead with approval, because, based on the discussion at the last CDW meeting, I understand the reasoning for the additional text – <u>but</u> it seems to me the outcome of this will be that whenever we have a hit of PFOS/PFOA we will automatically be screening for other PFAS and then following up with Health Canada for more information. Is this what we want? Section 3.1 Source Characterization, essentially states this as the approach for sites contaminated from AFFF.
  Our intention was not to prescribe automatic screening for other PFAS and automatic follow-up with Health Canada for more information; rather our intention was to acknowledge that in a spill situation or if the source of PFOS/PFOA contamination is suspected to be from the use of AFFF, other PFAS may also be found and that it is an option to contact Health Canada for more information regarding possible health risks associated with exposure. We did not intend for jurisdictions to think they have to contact us each and every time they detect other PFAS. Therefore, we have modified the statement in section 3.0 to indicate the following:
  "If other PFAS are found, jurisdictions have the option of contacting Health Canada for more information related to their possible health risks".
  If jurisdictions should choose to contact us, we have Screening Values available for a suite of other PFAS, which we are in the process of updating. Additionally, keeping track of other PFAS that are detected across Canada will help in the long run.

- Also, could this concern about additivity also not be applied to HAA, etc? Is it possible that the approach being used in this document could raise doubt with the approach we currently use in others – like HAA for example? The situation with HAAs is different than the situation with PFOS and PFOA, since the HAAs do not fit the criteria for additivity based on the framework we employed in the PFOS and PFOA documents. More specifically, HAAs induce different health effects and operate via different modes of action.

For your consideration, I am also providing you a summary of comments I received:

- 2.4 I agree with the wording change, and the concept of what is meant by additivity is well explained. However, I thought that the Guideline statement in section 1.0 was less clear as to this meaning. I'd suggest the following revision in 1.0:

*"...the sum of the ratios of the detected concentrations to the **corresponding** MACs for PFOS and PFOA should not exceed 1."* This may be just a difference in semantics, but personally I find this wording clearer than the original.

We agree. The text in section 1.0 has been modified to reflect your suggestion, as follows:

"... the sum of the ratios of the detected concentrations to the corresponding MACs for PFOA and PFOA should not exceed 1."

- 3.0 The added text seems reasonable: since a spill could lead to considerably higher levels and longer-term impacts than other possible sources, characterizing what other co-contaminants might also be present would be a reasonable part of the approach in such a case, in my opinion. The downside to this, however, is **what to do re risk management** should you find other PFAS, given that they do not have guideline values, so the "contact Health Canada" clause would almost certainly come into play.

Please see our response to comment #1.

- 6.2 The added text seems unnecessary, as the same could be said of any organic analytical method targeting any class of compounds – all of them will have a "discrete list" of other measurable compounds that are related to the target analytes. I think perhaps the addition might have been prompted by a desire to highlight that current methods for measuring PFOA or PFOS can also measure some – but not all – additional PFAS, but I'm not sure why this was considered necessary

  We agree and have removed this statement from section 6.2.

  The motivation for including this statement ("Current analytical methodologies are designed to measure a discrete list of PFAS, including PFOS/PFOA) was prompted by a comment that the limitations in available analytical methodologies could be an issue from a regulatory standard-setting aspect and compliance schemes as the levels of the other PFAS may be low but their presence together could have an impact if they share a similar mode of action (for which there is little information to indicate that is the case). Although we agree that this is a good point and an area that requires further research, it is outside the scope of these documents.

- 9.0 The added text seems abrupt and out of context, as it is the first statement in a section entitled "Health Effects" but instead immediately starts talking about limitations of toxicity studies. If this additional text is desired, it might work better as a footnote, or at least placed after the former first paragraph, with a segue something like "It should however be noted that PFOA/PFOS typically occurs as part of a mixture with other PFAS... while the vast majority of the toxicity studies focus on the individual compounds... etc."

  Thank you for this suggestion. We agree and have moved the text to be the 2nd paragraph with a segue statement as suggested:

  "It should however be noted that PFOS/PFOA can be found as part of a mixture with other PFAS...."

- 11.0 The added text seems to be just a statement of the facts concerning limitations, and what is recommended given these (i.e. for now, consider additivity for only PFOA + PFOS even though we know that other PFAS exist), so it seems fine to me.

- However, I would note that the phrasing is a bit redundant, with the end of the new text and the beginning of the old right after it saying the same thing, viz: "... current science only supports the use of an additive approach for PFOS and PFOA. Although current science does not justify the use of this approach for other PFAS, it does support additivity for PFOA and PFOS..."
- I'd suggest consolidating this to something like "... current science supports the use of an additive approach for PFOS and PFOA, but it does not justify the use of this approach for other PFAS."

  Thank you for pointing this out. We have modified the text to reflect your suggestion, as follows:

"Given the similarity of the health effects used to establish the MACs for PFOS and PFOA, and the extensive characterization of their toxicity and toxicokinetics, as well as the limited information on the risks and uncertainties of other PFAS, current science supports the use of an additive approach for PFOS and PFOA, but it does not justify the use of this approach for other PFAS."

Thank you,

Kevin Gould, P.Eng.
Public Health Engineer
Healthy Environments Branch, New Brunswick Department of Health
Office of the Chief Medical Officer of Health
Tel: (506) 444-4096

From: Anne Vezina [mailto:anne.vezina@hc-sc.gc.ca]
Sent: August-09-17 10:24 AM
To: angelina.polegato@novascotia.ca; Caroline.Robert@mddelcc.gouv.qc.ca; David.Fishwick@gov.bc.ca; donald.reid@gov.ab.ca; Peter_Workman@gov.nt.ca; ghsomers@gov.pe.ca; hkhan@gov.nl.ca; Gould, Kevin (DH/MS); Kim.Philip@gov.mb.ca; pat.brooks@gov.yk.ca; sam.ferris@wsask.ca; Satish.Deshpande@ontario.ca; MLeBlanc-Havard@GOV.NU.CA
Cc: Greg Carreau; Michele Giddings; Stephanie McFadyen; Richard Carrier; France Lemieux; Veronique Morisset; Wendy Enright; Jelena Zuric; Sarah Labib; Nadia Martinova
Subject: Revised PFOS and PFOA documents

CDW folks,

The Guideline Technical Documents on PFOA and PFOS were discussed and approved for posting by the majority of the members at the last CDW meeting. Some changes were made to the documents since the meeting to help alleviate some of the concerns raised by Ontario. All changes made since your approval are highlighted in the attached document: *(See attached file: PFOA 2017-0804 (post CDW final approval).pdf)(See attached file: PFOS 2017-0804 (Post CDW final approval).pdf)*

Could you please have a look at the latest changes and let me know by **August 25th** if you have any concerns? If not, we will move forward with the next steps.

Thank you,

Anne

Anne Vézina
Coordinator of the F/P/T Committee on Drinking Water
Coordonatrice du Comité F/P/T sur l'eau potable
Water and Air Quality Bureau
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Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Perfluorooctanoic Acid (PFOA)

Prepared by the
Federal-Provincial-Territorial Committee on
Drinking Water
of the
Federal-Provincial-Territorial Committee on
Health and the Environment

Health Canada
Ottawa, Ontario

August, 2017

This document may be cited as follows:

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The document was prepared by the Federal-Provincial-Territorial Committee on Drinking Water of the Federal-Provincial-Territorial Committee on Health and the Environment.

Any questions or comments on this document may be directed to:

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Healthy Environments and Consumer Safety Branch
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269 Laurier Avenue West, Address Locator 4903D
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Canada K1A 0K9

Tel.: 613-948-2566
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E-mail: water_eau@hc-sc.gc.ca

Other Guideline Technical Documents for the Guidelines for Canadian Drinking Water Quality can be found on the following web page: www.healthcanada.gc.ca/waterqualite

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Perfluorooctanoic Acid

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) for perfluorooctanoic acid (PFOA) in drinking water is 0.0002 mg/L (0.2 µg/L), based on exposure solely to PFOA.

As the toxicological effects of PFOA and perfluorooctanoyl sulfonate (PFOS) are considered to be additive, the sum of the ratios of the detected concentration to the MAC for PFOS and PFOA should not exceed 1.

2.0 Executive summary

PFOA is a man-made compound that does not occur naturally in the environment. It is used in the manufacture of stain/water-resistant coatings for various consumer products and in specialized chemical applications, such as fire-fighting foams, hydraulic fluids, and carpet spot removers. Environmental concentrations, and therefore potential exposure levels, may be higher in areas near facilities using high amounts of PFOA and near locations with extinguished fires if PFOA-containing fire-fighting foams were used.

This guideline technical document reviews and assesses all identified health risks associated with PFOA in drinking water. It incorporates available studies and approaches and takes into consideration the availability of appropriate treatment technology. Based on this review, the drinking water guideline for PFOA is a maximum acceptable concentration (MAC) of 0.0002 mg/L (0.2 µg/L), based on the general population.

2.1 Health effects

PFOA and its salts have been classified as possibly carcinogenic to humans (Group 2B) by the International Agency for Research on Cancer (IARC), based on limited epidemiological evidence demonstrating associations between PFOA and testicular and renal cancers, and on limited evidence in experimental animals. Non-cancer effects occurring at the lowest level of exposure to PFOA in animals include liver effects, reproductive and developmental effects and changes in serum lipid levels.

Both cancer and non-cancer endpoints were considered in the derivation of the MAC for PFOA in drinking water. The non-cancer approach, based on liver effects in rats, was used to calculate a MAC that is protective of human health from both cancer and non-cancer effects. Because PFOA remains in the human body longer than it does in rats, an approach that accounts for this difference was used in the derivation of the MAC for PFOA in drinking water.

2.2 Exposure

Canadians can be exposed to PFOA in food, consumer products, dust, and drinking water. Exposure is mainly from food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Although PFOA is not regularly monitored at water treatment plants in Canada, the analysis has been performed for a few locations. When detected in drinking water, it is usually found at levels below 0.003 µg/L.

2.3 Analysis and treatment

To date, the United States Environmental Protection Agency has not approved any methods for the analysis of PFOA in drinking water. There are some methods that can be used to measure PFOA in drinking water at levels well below the MAC.

The selection and effectiveness of a treatment strategy for PFOA removal is driven by several factors, including source water chemistry, concentration of PFOA and/or other perfluoroalkyl substances and pre-existing treatment processes. Conventional treatment is not effective for PFOA removal. Other treatment methods are promising, although full-scale studies are limited. Activated carbon adsorption can achieve treated water concentrations of PFOA below the MAC. However, proper operation of the system is essential to ensure that the performance of granular activated carbon (GAC) is not affected by the presence of natural organic matter in the source water. Membrane filtration techniques (reverse osmosis and nanofiltration) and anion exchange may also be effective. Although there are no residential treatment devices certified to remove PFOA, it is expected that the same treatment technologies would also be effective at the residential scale.

2.4 Additivity

The health effects of PFOA and PFOS are similar and well documented. Recent scientific evidence shows that PFOS and PFOA affect the same organ in similar ways. Thus, when PFOS and PFOA are found together in drinking water, the best approach to protect human health is to consider both chemicals together when comparing to the ~~screening guideline~~ values. This is done by adding the ratio of the observed concentration for PFOA to its MAC with the ratio of the observed concentration for PFOS to its MAC; if the result is below or equal to one, then the water is considered safe for drinking. Science currently does not justify the use of this approach for other PFAS.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

PFOA and perfluorooctane sulfonate (PFOS) are typically found in groundwaters and surface waters impacted by aqueous film-forming foam (AFFF) (i.e., fire-fighting foams). They may also be found in groundwaters and surface waters contaminated by: discharges from industrial facilities; effluents from wastewater treatment plants treating domestic or industrial waste; storm water runoff; or applications of biosolids from a municipal wastewater treatment plant to agricultural land. Like other groundwater contaminants, PFOA can reach drinking water wells through migration of a contaminated groundwater plume. It can also reach surface waters from air emissions of industrial facilities. Particle-bound volatile perfluoroalkyl substances (PFAS) including PFOA may be carried from disposal sites by the wind and deposited on land or surface water, thus explaining their presence in remote locations and in waters not impacted by a point source. PFOA migrates very slowly through the soil to groundwater.

PFOA salts are used as a processing aid in the production of fluoropolymers which are used in joining and sealing materials, which may contain trace amount of PFOA. Some of these materials may be used in distribution systems. The use of distribution system components that are certified to NSF/ANSI 61 would minimize the leaching of PFOA into drinking water.

Given the potential health effects from PFOS and PFOA, and the limited information on the risks and uncertainties of other PFAS, in the case of spill situations, a more thorough evaluation may be required to determine what substances are present. If other PFAS are found, jurisdictions can contact Health Canada for more information related to their possible health risks.

For drinking water supplies that occasionally experience short-term exceedances above the MAC, it is suggested that a plan be developed and implemented to address these situations. For more significant long-term exceedances that cannot be addressed through treatment, it is suggested that alternative sources of drinking water be considered.

3.1 Monitoring

It is important to note that the analysis for PFOA is highly specialized and should be conducted by a laboratory that is accredited or that has a stringent quality assurance/quality control (QA/QC) program in place to ensure data quality.

3.1.1 Source charcterization

Utilities should characterize their source water to assess PFOA and PFOS concentrations, particularly if source waters are impacted by firefighting training areas, military bases, airports, manufacturing sites and/or waste disposal sites. Once contamination is detected, the source should be sampled semi-annually to confirm that the sum of the ratios of the observed concentration to the MAC for PFOA and PFOS does not exceed 1. If treatment is required, the source should be sampled in conjuction with compliance monitoring. Utilities that have baseline data showing the absence of PFOA and PFOS may conduct less frequent monitoring.

If the main source of contamination is suspected to be from the use of AFFF, utilities may want to consider monitoring for other PFAS, including shorter chain compounds such as perfluorobutanoic acid and perfluorobutane sulfonate. These other PFAS are likely to co-occur at AFFF-impacted sites and are typically more mobile. As such, they can serve as an early warning sign of PFOA and PFOS contamination of a groundwater source.

3.1.2 Operational monitoring

Treatment systems should be specifically designed, operated and maintained for removal of PFOA and PFOS. The operational monitoring frequency will depend on the treatment technology the utility employs. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance. Utilities that use a GAC system for PFOA and PFOS removal may require quarterly monitoring of the treated water in order to assess the performance of the GAC system and to determine the timing of the regeneration or replacement. Utilities should also be aware that ozone or advanced oxidation processes (AOPs) may oxidize polyluorinated pecursors present in the source water, which could result in an increased concentration of PFOA in the finished water.

3.1.3 Compliance monitoring

When treatment is in place for PFOA and PFOS removal, semi-annual monitoring of the treated water is recommended. Samples should be collected after treatment, but prior to distribution, typically at the entry point to the distribution system. Paired samples of source and treated water should be taken to confirm the efficacy of the treatment. The sum of the ratios of the measured concentration to the MAC for PFOA and PFOS should not exceed 1.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Perfluorooctanoic acid (PFOA) is an anthropogenic compound with a chain length of eight carbons, of which seven are perfluorinated. It belongs to the class of chemicals known as perfluorocarboxylic acids (PFCAs), one of a broader class of chemicals known as perfluoroalkyls (PFAs) (Environment Canada and Health Canada, 2012), or perfluoroalkyl substances (PFAS). In this report, the term "PFOA" may refer to the free acid ($C_8HF_{15}O_2$; CAS number 335-67-1; 414.07 g/mol) or its conjugate base ($C_8F_{15}O_2^-$; CAS number 45285-51-6). The term APFO (ammonium perfluorooctanoate) refers to the ammonium salt ($C_8F_{15}O_2^- NH_4^+$; CAS number 3825-26-1), its principal salt, and K^+PFOA refers to the potassium salt (CAS number 2395-00-8). The main synonyms of PFOA are pentadecafluorooctanoic acid, perfluorooctanoate, C8, FC-143, pentadecafluoro1-octanoic acid, pentadecafluoro-n-octanoic acid, perfluorocaprylic acid, perfluoroctanoic acid, perfluoroheptanecarboxylic acid and octanoic acid.

PFOA is highly soluble in water, with estimates as high as 3,500 mg/L in neutral to alkaline pH and 9,500 mg/L in pure water, and as low as 0.7 mg/L at acidic pH (Kauck and Diesslin, 1951; Barton et al., 2007; Environment Canada and Health Canada, 2012). Solubility depends on the acid dissociation constant (pKa) of the acid form. Data for pKa indicate values ranging from –0.5 to 4 (Kissa, 1994; Burns et al., 2008; Goss, 2008; ATSDR, 2009; Goss and Arp, 2009; Environment Canada and Health Canada, 2012), and it was suggested that with such a low pKa value, the environmental partitioning of PFOA will be dominated by the anionic form (Goss, 2008).

PFOA has combined hydrophobic and hydrophilic properties over different portions of its molecule (Environment Canada and Health Canada, 2012). Due to this particularity, PFOA is thus expected to behave differently than traditional hydrophobic chemicals. The octanol:water partition coefficient (K_{ow}) cannot be determined directly (because multiple layers are formed in octanol/water) and the parameters usually estimated from the K_{ow} (e.g., K_{oc}, bioconcentration factor) cannot be calculated using this method (ATSDR, 2009; Environment Canada and Health Canada, 2012). The values of $LogK_{ow}$ estimated by modelling range from 3.62 to 6.30 (Arp et al., 2006; Jasinski et al., 2009; Environment Canada and Health Canada, 2012).

PFOA is essentially non-volatile, with a vapour pressure of 2.24×10^{-5} atm at 20°C (Barton et al., 2007; ATSDR, 2009; Environment Canada and Health Canada, 2012). Its Henry's law constant was estimated at 2.4×10^{-5} atm-m^3/mol (Barton et al., 2007).

Precursors of PFOA (polyfluoroakyl phosphate diesters, fluorotelomers, perfluorinated phosphonic acids) represent an indirect source of PFOA in the environment (Ellis et al., 2004; D'Eon et al., 2009; Lee, 2010).

The main producers of PFOA are located principally in the United States, Europe and Asia. Industrial information obtained in 2004 indicates no known manufacturers of perfluoroalkyl and fluoroalkyl substances in Canada; however, APFO was imported into Canada in quantities ranging between 100 and 100,000 kg (Environment Canada and Health Canada, 2012). Regulations established under the *Canadian Environmental Protection Act, 1999* prohibit the manufacture, use, sale, offer for sale, or import of PFOA or its salts, unless designed for specific uses (Government of Canada, 2012). APFO is mainly used as a commercial polymerization aid for fluoropolymer manufacturing. Fluoropolymers are used in the manufacture of stain/water-resistant coatings for textiles and carpets, hoses, cable and gaskets, non-stick coatings on cookware and personal care products. APFO is also used in aqueous fluoropolymer dispersions that are used in paints and in photographic film additives as well as within the aerospace industry

(e.g., it may be a component of aqueous film-forming foams [AFFFs] for firefighting; Environment Canada and Health Canada, 2012). Fluorochemicals (potential PFOA precursors) are also used in the treatment of food packaging materials (Environment Canada and Health Canada, 2012) such as microwaveable popcorn bags (Dolman and Pelzing, 2011). The term PFOA is not interchangeable with commercial mixtures containing PFOA, as these mixtures are often not well characterized and could include any product that contains even a small amount of PFOA (Environment Canada and Health Canada, 2012).

4.1 Sources to water

A source of PFAS in water is the discharge of AFFF for extinguishing fires. Discharge of AFFF was presumed to have resulted in increased levels of PFAS in water surrounding the Toronto International Airport, based on spatial and temporal trends of PFAS in water (Awad et al., 2011). Although the study focused on PFOS contamination, as this was the primary PFAS in the AFFF used at the location, PFOA-containing AFFFs could plausibly also result in similar increased concentrations of PFOA in water near discharge sites. Data supporting the possibility of contamination in the vicinity of firefighting training areas include measurements of elevated PFOA concentrations in groundwater near a Michigan air force base (Moody et al., 2003), at a firefighting training ground in Australia (Baduel et al., 2015), and in private drinking water wells proximate to an industrial site in Cologne, Germany (Weiß et al., 2012).

Elevated PFOA concentrations measured in surface water downstream from fluorochemical manufacturing plants have also been used as indications of the potential for industrial sources of PFOA in water (Hansen et al., 2002; Frisbee et al., 2009).

Mass balance studies of PFAS at wastewater treatment plants commonly report similar or higher PFOA concentrations in effluents in comparison to raw influents, suggesting that the degradation of other fluorinated organic compounds (i.e., fluoropolymers) into PFOA may take place during wastewater treatment (Clarke and Smith, 2011) and that conventional wastewater treatment plants are not effective in removing PFAS (Ahrens, 2011). PFOA was detected in effluent wastewater treatment facilities at concentrations ranging from 0.007 to 0.055 µg/L in Canada (Environment Canada and Health Canada, 2012) and at average concentrations ranging from 0.080 to 0.12 µg/L in effluents of seven different locations in the U.S. (Quinones and Snyder, 2009).

Although measures are in place in North America and Europe to restrict the production, use and/or the major exposure risks to PFAS (primarily PFOS, but to some extent PFOA), the ubiquitous use of PFAS within the built environment still causes their transfer to biosolids (sludge) (Clarke and Smith, 2011). The use of biosolids as fertilizers may thus represent a source of soil and water contamination with PFOA (Clarke and Smith, 2011). Elevated concentrations of PFOA were found in surface and well water in Decatur, Alabama, after biosolids from a municipal wastewater treatment plant (at which waste from local fluorochemical facilities were received) were applied in agricultural fields (Lindstrom et al., 2011).

4.2 Environmental fate

The elevated water solubility of PFOA and the negligible volatility of its ionized species suggest that PFOA species will partition primarily to the aquatic environment (Environment Canada and Health Canada, 2012).

PFOA may be found in air, surface water, sediment, groundwater and soil around the world (including the Arctic). Two long-range transport pathways have been proposed to explain this ubiquity (Post et al., 2012). The first pathway involves the atmospheric transport of volatile

precursors (e.g., fluorotelomer alcohol) and their oxidation to PFOA (and other PFAS) and further deposition onto land or water. The second pathway involves a long-range aqueous transport of the anionic forms of emitted perfluorinated carboxylates, such as PFOA, from the vicinity of industrial sources via the surface water currents (Butt et al., 2010; Post et al., 2012).

Experimental values of $LogK_{oc}$ vary between 1.2 and 4.5 (Dekleva, 2003; Higgins and Luthy, 2006; Prevedouros et al., 2006; ATSDR, 2009; Environment Canada and Health Canada, 2012; Zareitalabad et al., 2013). Data suggest that the sorption of PFOA can be described reasonably as a partitioning-like process with an average $LogK_{oc}$ of 2.8 (Zareitalabad et al., 2013).

PFOA may bioaccumulate in tissues of aquatic and terrestrial living organisms. Bioaccumulation data for different species of marine and terrestrial ecosystems indicate that PFOA has a low to moderate potential to accumulate in aquatic species (on a whole-body basis), while accumulation may be higher in certain organs/tissues (e.g., liver, blood) (Environment Canada and Health Canada, 2012). Briefly, the PFOA log bioaccumulation factors (BAFs) ranged from 0.02 to 0.63 for trout and from 9.6 to 19.4 for Pacific oysters. Log bioconcentration factors (BCFs) were estimated at 4.0 for the rainbow trout (carcass), 3.1–9.1 for carp, 1.8 for fathead minnows (whole body) and 0.8–3.0 for Pacific oysters. PFOA may also biomagnify in certain food webs (e.g., polar bears) (Environment Canada and Health Canada, 2012).

Under environmental conditions, PFOA does not hydrolyze, photolyze or biodegrade, and is considered extremely persistent in the environment (OECD, 2006; Environment Canada and Health Canada, 2012). PFOA is also resistant to microbial degradation (Liou et al., 2010). Moreover, biodegradation of precursor compounds could lead to increasing concentrations of PFOA in the environment (Ahrens, 2011; Clarke and Smith, 2011). Considering its empirical and physico-chemical properties, it was concluded that PFOA and its salts meet the persistence criteria in water, soil, sediment and air (half-lives of $\geq$ 182 days in soil and water, $\geq$ 365 days in sediment and $\geq$ 2 days in air) (Environment Canada and Health Canada, 2012).

The adsorption of PFAS onto natural sediments with varying organic carbon and iron oxide content, onto kaolinite, alumina and geothite was investigated in aqueous solution (Higgins and Luthy, 2006; Johnson et al., 2007; Pan and Yu, 2010; Tang et al., 2010; Wang et al., 2011; Xiao et al., 2011; 2015). Higgins and Luthy (2006) and Johnson et al. (2007) reported that the adsorption of PFAS on sediments collected from various riverines and lacustrine sites was influenced by the organic carbon, rather than the mineral content, of the sediment. Other studies demonstrated that the adsorption of PFOA/PFOS onto minerals was influenced by pH, ionic strength and the type of the cations present in the aqueous solution (Tang et al., 2010; Wang et al., 2011; Xiao et al., 2011).

5.0 Exposure

Canadians can be exposed to perfluorinated compounds present in food, consumer products, dust and drinking water. The major sources of perfluorinated compounds are expected to be food and consumer products, including solution-treated carpeting and treated apparel (Tittlemier et al., 2007); however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water.

The estimated total daily intake of PFAS (estimates not provided for individual PFAS) in Canadians was reported to be 410 ng/day for the general population of Canada (Tittlemier et al., 2007). Drinking water ingestion, estimated at 0.3 ng/day, contributed only a minor amount to the overall estimated exposure. Although some exposure data are available, they are considered

insufficient to justify modifying the default allocation factor for drinking water of 20%. This default allocation factor for drinking water is used as a "floor value" when drinking water is not a major source of exposure (Krishnan and Carrier, 2013); therefore, this value is applicable for PFOA, even though water is expected to be only a minor contributor to PFOA exposure for the general population.

5.1 Water

Although PFOA is not regularly monitored at water treatment plants in Canada, the analysis has been performed for a few locations. PFOA was not detected (method detection limit [MDL] of 0.51 ng/L) in raw or finished water from samples obtained in 2012 from two water treatment plants in Calgary (Alberta Environment and Water, 2013). In Quebec, raw and treated water samples were obtained monthly between April 2007 and March 2008 from seven sites (a total of 84 raw and treated water samples each). PFOA was detected in 75% of treated samples (MDL of 0.3–0.6 ng/L), with a median value of 2.5 ng/L and a maximum value of 98.0 ng/L. The detection rate and median concentrations were higher in treated water than in raw water, for which the detection rate and median were 55% and 2.0 ng/L, respectively (Berryman et al., 2012). The reported PFOA concentration in 5 tap water samples from Niagara-on-the-Lake, Ontario, was 2.1 ng/L (Mak et al., 2009). Lower concentrations of PFOA (0.2 ng/L) were reported in tap water from Calgary and Vancouver (Tanaka et al., 2006).

In a national survey of emerging contaminants in drinking water (including PFOA) performed by Health Canada, treated and raw water from groundwater and surface water sources (rivers and lakes) was monitored in winter and summer at 35 locations in 2009 and 30 locations in 2010. PFOA was detected (MDL of 0.023 ng/L) in 68% of raw water samples and 64% of treated water samples in summer 2009, with averages of 0.067 ng/L and 0.071 ng/L, respectively (median values of 0.050 and 0.060 ng/L, respectively). PFOA concentrations were slightly lower in winter 2009, with an average of 0.057 ng/L in detected raw samples (59% detection) and 0.056 ng/L in detected treated samples (55% detection). Detection rates for PFOA were lower in the 2010 locations, with detection rates in the summer of 18% in raw water (average of 0.066 ng/L and median of 0.030 ng/L) and 15% in treated water (average of 0.046 ng/L and median of 0.025 ng/L), and in winter of 33% in raw water (average of 0.055 ng/L and median of 0.040 ng/L) and 27% in treated water (average of 0.05 ng/L and median of 0.030 ng/L) (Health Canada, 2013a). Maximum levels of 0.220 ng/L and 0.180 ng/L were detected in raw and treated water samples, respectively.

PFOA levels in Etobicoke Creek, Ontario (a tributary of Lake Ontario) ranged from not detected (limit of quantification: 9 ng/L) to 11.3 µg/L following a fire alarm malfunction that released flame retardants containing PFAS (Moody et al., 2002). Interestingly, PFOA was also found upstream of the spill site at 0.02 µg/L.

5.1.1 Co-occurrence with other PFAS

Limited data show that PFOA is co-detected with other substances in several locations across Canada. In all of these studies, PFOS and PFOA were the predominant PFAS detected. PFOA is co-detected with:

- PFOS, perfluorohexane sulfonate (PFHxS), perfluoroethanesulfonate (PFEtS), perfluorooctanesulfonamide (PFOSA), perfluoroundecanoic acid (PFUDA), perfluorodecanoic acid (PFDA), perfluorononanoic acid (PFNA), perfluoroheptanoic acid (PFHpA), perfluorohexanoate (PFHxA), perfluoro-n-pentanoic acid (PFPeA), and

perfluorobutanoate (PFBA) in tap water in Niagara-on-the-Lake, Ontario (Mak et al., 2009);

- PFOS, PFNA and PFUDA in treated and raw water in Québec (Berryman et al., 2012~~Ministère du Développement durable, de l'Environnement, de la Faune et des Parcs, 2012~~);
- PFOS, PFBA, PFPeA, PFHxA, PFHpA, PFNA, PFBS, and PFHxS in groundwater at former fire-fighting training areas in British Columbia, Alberta, Nova Scotia, and Ontario (Paterson et al., 2008; Environmental Sciences Group, 2015);
- PFOS and PFDA in Nova Scotia and Ontario, and PFUDA, PFDoA, and PFOSA in Nova Scotia (Environmental Sciences Group, 2015).

5.1.2 Leaching from drinking water materials

Polymers and elastomers used as joining and sealing materials in water distribution systems may contain trace amount of PFOA. PFOA salts are used as a processing aid in the production of fluoropolymers such as polytetrafluoroethylene (e.g.,Teflon®) and in fluoroelastomers (e.g., Viton®). An important consideration for reducing exposure to PFOA is to address leaching from these materials by specifying that they meet health-based standards. NSF/ANSI Standard 61 (Drinking Water System Components—Health Effects) limits the leaching of PFOA into drinking water. The standard ensures that materials meet health-based leaching requirements and are safe for use in potable water applications by specifying the single product allowable concentration (SPAC) for contaminants. Although the current SPAC for PFOA is 0.0003 mg/L (NSF/ANSI, 2016a), it is presently under review by NSF International to reflect up-to-date science. Polymers and elastomers used as joining and sealing materials in water distribution systems that meet NSF/ANSI Standard 61 would be expected to leach very low concentrations of PFOA into drinking water.

5.2 Food

Food is generally considered to be the main source of exposure to PFOA for the majority of the Canadian population, but exposure from food is still well below what is considered unsafe to humans. PFOA was measured in a selection of Canadian food composite samples (samples from the Canadian Total Diet Study [TDS]) conducted in 2004 and additional samples collected within 1992 and 2001) to estimate the dietary intake. PFOA was detected in 3 out of 54 food composites. The detected PFOA concentrations (on a w.w. basis) were 0.74 ng/g (pizza; the sample was above the limit of detection but below the limit of quantitation), 2.6 ng/g (roast beef) and 3.6 ng/g (microwave popcorn). Values were used to estimate the average dietary daily exposure of Canadians; food was estimated to contribute 250 ng/day of perfluorinated compounds, of which approximately 70 ng was attributed to PFOA (Tittlemier et al., 2007).

Store-bought and restaurant foods commonly consumed by Canadians were collected in Whitehorse (Yukon Territory, Canada) in 1998 and analyzed for PFAS. PFOA was detected in several composite samples (0.36–0.77 ng/g w.w. for cookies, processed cheese, peppers, canned lunchmeats, and pizza), but all measurements were below the limits of quantification (0.65–1.52 ng/g w.w.) (Ostertag et al., 2009a).

The concentrations of PFAS in the traditional foods of Inuit in Northern Canada was measured to estimate their dietary exposure. PFOA was infrequently detected (9% out of 68 samples) in the traditional foods collected from Chesterfield Inlet, Igloolik, Pond Inlet and Qiqiktarjuak in Nunavut, between 1997 and 1999. PFOA was detected in ringed seal (liver: 0.3 ng/g; blood: 0.1 ng/g), eider duck (whole body: 0.4 ng/g), caribou liver (baked: 0.7 ng/g; raw: 0.1

ng/g) and caribou stomach (raw: 0.8 ng/g); the other concentrations were below the detection limit (<0.1 to <0.6 ng/g) (Ostertag et al., 2009b).

PFOA is a processing aid in the manufacture of polytetrafluoroethylene (PTFE), which is used for many purposes, including non-stick cookware. Residual PFOA was detected in PTFE cookware and film (Begley et al., 2005); however, only minor transfer of PFOA from these products was observed in investigations on the migration into watery and fatty simulated foodstuff (Begley et al., 2005; Powley et al., 2005; Washburn et al., 2005; Sinclair et al., 2007). PFOA has also been detected in microwave popcorn bags (Begley et al., 2005; Sinclair et al., 2007; Dolman and Pelzing, 2011), and found in food contact papers treated with polyfluoroalkyl phosphate surfactant (PAPs) or di-perfluoro-alkyloxy-amino-acid (PAA) (Xu et al., 2013). The migration rates of PFOA from food contact papers treated with these compounds ranged from 7% to 92% for five different food simulants (Xu et al., 2013).

5.3 Air

The inhalation intake of PFOA for Canadians was considered negligible due to its low volatility (Tittlemier et al., 2007).

The levels of PFAS in outdoor air were determined in a Canadian study conducted in 2007 in Vancouver (Shoeib et al., 2011). PFOA samples were collected using outdoor passive samplers deployed in residential yards for approximately 3 months. PFOA was detected in 4 out of 6 samples (<0.47–9.2 pg/m^3; mean: 1.4 pg/m^3) (Shoeib et al., 2011). Similar concentrations were measured in the Canadian Arctic (Resolute Bay, Cornwallis Island, Nunavut) in 2004, with a mean concentration (gas and particulate phase of atmospheric air) of 1.4 pg/m^3 (Stock et al., 2007).

In indoor air, the levels of PFOA primarily depend on its concentration in air particulates and are thus related to the levels in indoor dust, as well as the number, type and age of the potential sources (e.g., carpeting, furniture and paint) (Fraser et al., 2012). To date, data on indoor air concentrations of PFOA are limited to those reported in the aforementioned residential study (Shoeib et al., 2011). The authors collected PFOA in indoor air using passive samplers deployed for approximately 4 weeks in bedrooms of 59 participants. PFOA was the dominant ionic PFAS, with a geometric mean concentration of 28 pg/m^3 (arithmetic mean: 113 pg/m^3, median: 21 pg/m^3, range: 3.4–2,570 pg/m^3).

5.4 Consumer products

Owing its use patterns, human exposure to PFOA would likely result from contact with, or the use of, certain consumer products (Health Canada, 2006). Estimates of the contribution of solution-treated carpeting and treated apparel to Canadians' daily intakes of total perfluorinated compounds were 120 ng/day and 12 ng/day, respectively (Tittlemier et al., 2007). As no Canadian data were available on exposure to PFOA in consumer products, data from other countries are summarized below.

PFOA has been measured in a variety of consumer products, including waterproofing agents, fluorotelomer-treated textiles, apparel and carpeting, aqueous firefighting foams, non-stick ware, industrial floor waxes and wax removers, latex paint, home and office cleaners, PTFE-coated dental floss and dental tape, and PTFE film/sealant tape (Begley et al., 2005; Washburn et al., 2005; Herzke et al., 2012). PFOA has also been measured in ski waxing blocks and glider powders, with occupational exposure to airborne PFAS measured during professional ski waxing (Freberg et al., 2010).

5.5 Soil and household dusts

The estimated contribution of dust to Canadians' daily intakes of total perfluorinated compounds was 28 ng/day (Tittlemier et al., 2007). The study did not estimate the total daily contribution of soil to perfluorinated compound exposure.

PFOA concentrations in dust from Canadian houses were reported to vary from <2.3 to 1,234 ng/g with a median value of 19.7 ng/g (mean: 106 ng/g). House age and fraction of floor covering were reported to be significantly correlated with the concentration of PFAS in dust—older houses and those with smaller fractions of the floor covered with carpet were characterized by lower concentrations of PFAS (Kubwabo et al., 2005).

In another Canadian study conducted in Vancouver, BC, PFOA was detected in all house dust samples analyzed for this compound (n = 132). The PFOA concentrations ranged from 1.9 to 1390 ng/g (median: 30 ng/g, mean: 97 ng/g) (Shoeib et al., 2011). PFOA levels in dust collected from homes in Toronto, Ontario (n=19) ranged from <0.98 ng/g to 4000 ng/g (median: 69 ng/g, mean: 270 ng/g) (Goosey and Harrad, 2011). Another Canadian study investigating PFAS levels in household dust in a family home in Edmonton, Alberta found PFOA in the housedust (550.0 ng/g) and carpets (16.0 – 153.0 ng/g) (Beesoon et al., 2012). The authors attributed the high levels of PFOS to carpet treatment with Scotchgard carpet protector.

No study reporting background PFOA levels in soils was located. Some data are available in soil surrounding perfluorochemical industrial facilities (as reviewed by ATSDR, 2009).

5.6 Human biomonitoring data

Human PFOA blood levels have been shown to be influenced by gender and age. The Canadian Health Measures Survey (CHMS), Cycle 1 (2007–2009) indicates that PFOA plasma levels in adult males (geometric mean [GM]: 2.94 ng/mL; 95% CI: 2.74–3.2~~15~~, 95th percentile: 6.0~~5.98~~ ng/mL, n=1376) are higher than in adult females (GM: 2.2~~17~~ ng/mL; 95% CI: 2.0~~1.99~~–2.4~~36~~, 95th percentile: 5.0~~4.99~~ ng/ml, n=1504) (Health Canada, 2010). This effect persisted in Cycle 2 (2009-2011) of the study ~~(2009–2011)~~ (Males—GM: 2.6 ng/mL, 95% CI: 2.4–2.9, 95th percentile: 6.0, n=511; Females—GM: 2.0 ng/mL, 95% CI: 1.8–2.2, 95th percentile: 4.4 ng/mL, n=506) (Health Canada, 2013b).

5.7 Multi-route exposure through drinking water

The multi-route exposure assessment process is not applicable for PFOA, due to the compound's high molecular weight and low volatility (Krishnan and Carrier, 2008); therefore, the relative contributions of exposure to PFOA from both inhalation and dermal routes during showering and bathing were not estimated. Based on the high molecular weight of 414.07 g/mol and the ionic properties of PFOA at pH levels typical in drinking water, volatility and dermal penetration are expected to be low. Moreover, dermal permeability coefficients measured in *in vitro* studies predict that PFOA is impermeable to skin under typical conditions (Fasano et al., 2005; Franko et al., 2012). Consequently, exposure to PFOA via inhalation and dermal routes during showering or bathing is expected to be negligible.

6.0 Analytical methods

To date, the United States Environmental Protection Agency has not approved any analytical methods for the analysis of PFOA in drinking water. There are some methods that can be used to measure PFOA in drinking water at levels well below the MAC. However, they require good quality control procedures to produce accurate results.

6.1 Available methods

EPA Method 537 ver. 1.1, International Standard Organization (ISO) Method, 25101 and 3M Method ETS-8-154.3 can all be used for the analysis of PFOA in drinking water (3M, 2008; ISO, 2009; U.S. EPA, 2009a). All methods use a solid phase extraction (SPE) technique followed by a liquid chromatograph (LC) coupled to electrospray ionization (ESI) tandem mass spectrometry (MS/MS) operated in negative ion mode. For the purpose of trace quantitation of PFOA in drinking water, the chromatographic conditions are selected such that all isomers (linear and branched) are co-eluted together.

In the EPA method, a water sample is fortified with labelled internal standards and passed through a SPE cartridge to extract target analytes in addition to their corresponding internal standards. The compounds are eluted from the SPE cartridge, concentrated and injected into a LC-MS/MS. The mass spectra and retention times of the analytes are identified by comparison to internal standards. The MDL for PFOA is 1.7 ng/L (0.0017 µg/L) and the Lowest Concentration Minimum Reporting Level (LCMRL) is 5.1 ng/L (0.0051 µg/L) (U.S. EPA, 2009a). PFOA has been included in the third Unregulated Contaminant Monitoring Rule (UCMR3), which stipulates that using Method 537 ver. 1.1, an MRL of 20 ng/L (0.02 µg/L) for PFOA must be achieved and reported by the utilities during monitoring (U.S. EPA, 2012b).

The results of an inter-laboratory trial (Taniyasu et al., 2013), conducted in 2006, were used to establish whether ISO Method 25101 was reliable for the analysis of PFOA and PFOS in environmental water samples, including drinking water. The intra- and inter laboratory precisions were in the range of 3–7% and 15–22%, respectively for PFOA for all environmental water samples analyzed. The recovery of the internal standards for PFOA ranged from 91 to 98%. These results confirmed that this analytical method was reliable and can be used for the analysis of PFOA in environmental water samples. The method uses SPE, LC-MS/MS and is applicable for the quantification of the linear and branched isomers of PFOA and PFOS. The branched isomers can be separated from the linear isomers by using specific chromatographic column and optimized conditions. ISO Method 25101 was found to be appropriate for determination of PFOA levels in unfiltered samples of drinking water, groundwater and surface water with concentrations in the range of 10 – 10,000 ng/L (0.01 – 10 µg/L) (ISO, 2009).

Method (ETS-8-154.3) was developed and validated by 3M for PFOA analysis in drinking water, groundwater and surface water samples. The analytical steps are similar to EPA Method 537 Ver 1.1 and the method has a limit of quantitation (LOQ) of 25 ng/L (0.025 µg/L) for PFOA (3M, 2008).

6.2 Analytical challenges

Current analytical methodologies are designed to measure a discrete list of PFAS, including PFOA. In spite of the significant improvements in analytical methods for the determination of PFAS in environmental water samples, challenges, uncertainties and drawbacks still remain. Major challenges associated with the trace quantitation of PFAS included matrix effects and a background contamination in the analytical blanks. In order to generate accurate data, quality control procedures (i.e., matrix spikes, duplicates, spike-recovery experiments, surrogate recovery checks) are critical. In addition, the use of isotope-labelled internal standards is a standard practice and must be used in the analysis of PFAS. In addition, PFOA analyses should be conducted by an accredited laboratory or by a laboratory with a stringent quality assurance/quality control (QA/QC) program in place to ensure data quality.

6.2.1 Matrix effect

Although LC-MS/MS is a highly selective and sensitive technique, it is susceptible to matrix effects which is one of the major uncertainties in the trace quantitation of PFOA in environmental water samples (Martin et al., 2004; Yamashita et al., 2004; Taniyasu et al., 2005; van Leeuwen et al., 2006; Arsenault et al., 2008). Matrix effects result from the co-extracted components from the sample, which affect the signal intensity of the target analyte and either suppress or enhance the spectral signal. The extent of the matrix interference varies, depending on the nature of the samples. Although the matrix interferences are negligible for drinking water and groundwater (ISO, 2009), the PFOA quantification requires efficient extraction and clean-up procedures. The aim of these procedures is to separate the compounds in the sample by their chemical and physical properties, to concentrate the target analyte and to purify the extract prior to the instrumental determination. The most frequently used technique for the extraction of PFASs from drinking water samples includes SPE cartridges with different packing material such as reverse phase (C18) cartridge (Loewen et al., 2005; Wolf and Reagen, 2011; Zainuddin et al., 2012), mixed hydrophobic/polar (Oasis HLB) cartridges (Yamashita et al., 2004; Taniyasu et al., 2005; Villaverde-de-Saa et al., 2015) and a weak anion exchange (WAX) cartridges (Taniyasy et al., 2005; 2013). Several studies conducted a liquid-liquid extraction (LLE) technique to extract and concentrate PFASs in different environmental aqueous matrices prior to LC-MS/MS (Gonzales-Barreiro et al., 2006; Szostek et al., 2006; Backe et al., 2013). A laboratory study (Gonzales-Barreiro et al., 2006) used an LLE to extract PFASs (C6-C12) from tap water. The recovery of the PFASs with a carbon chain greater than C8 was in the range 80-93%. The authors indicated that the method was less efficient in extracting short-chained PFASs when compared to the SPE technique (Gonzales-Barreiro et al., 2006).

The clean-up procedures involved a washing step after the sample enrichment on the SPE cartridge and a filtration to remove solids from the final extract (Yamashita et al., 2004; Larsen and Kaiser, 2007; van Leeuwen and Boer, 2007). Care should be taken to avoid contamination of the extract or losses of PFASs during the clean-up procedures. Prior to a SPE, a sample pre-treatment (filtration) may be required to facilitate extraction or to remove matrix constituent that will interfere with analyses (van Leeuwen and Boer, 2007; Ding et al., 2012).

The most suitable approach to assist in the quantification of PFASs is to use of isotopically-labelled internal standards (isotope dilution). It is important that the appropriate isotope-labelled internal standards are used for the quantitation of the corresponding native compound. Isotope-labelled internal standards will have the same retention time as the target analytes (excluding isomeric separation) and the monitoring of their signals will determine whether the analytes signal are suppressed or enhanced. The application of surrogates or isotopically-labelled internal standards early in the sampling or the sample preparation steps will compensate for the inefficiency/losses in the extraction and other sample preparation steps (Martin et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007). Wolf and Reagen (2011) reported that an addition of isotope-labelled internal standards prior to sample collection simplified the sample preparation procedures. The method demonstrated an accuracy of 105% and a precision of 12% for PFOA in laboratory Milli-Q water samples (Wolf and Reagen, 2012).

If isotope-labelled internal standards are not available, a standard addition quantitation, which involves spiking known quantities of a standard into the sample, is an alternative to use when matrix effects are unavoidable (Weremiuk et al., 2006; Furdui et al., 2007; van Leeuwen et al., 2009).

The use of MS/MS for analysis of PFOA enables the detection of product (daughter) ions. The transitions from m/z ratio 413 (parent ion $C_7H_{15}COO^-$) to m/z ratio 369 and 169 (daughter ions) are used for PFOA quantification (ISO, 2009; U.S. EPA, 2009a).

6.2.2 Background contamination in the analytical blanks

A known source of background contamination is the presence of fluoropolymers, such as polytetrafluoroethylene (PTFE) and perfluoroalkoxy compounds in various laboratory consumables. Ammonium perfluorooctanoate and ammonium perfluorononanoate are used as fluoropolymer processing aids and are common components in the laboratory products. These fluoropolymers may lead to quantifiable background levels in the analytical blanks especially when quantifying trace levels in water samples. Contacts with such laboratory materials and products during analysis of PFOA should be avoided (Martin et al., 2004; Yamashita et al., 2004; ISO, 2009).

Yamashita et al. (2004) studied the sources of background contamination at various analytical steps, including sample collection, extraction and sample clean up prior to the instrumental analysis. Polypropylene bottles used for sample collection and storage, in addition to different types of SPE cartridges and purified reagent water, were found to be sources of PFASs contamination in the analytical blanks. Taniyasu et al. (2005) and Berger et al. (2011) found that the polypropylene containers are unsuitable for collection and storage of water samples intended for analysis of long-chain PFCAs such as perfluoroundecanoic and perfluorododecanoic acids, because of the adsorption of the compounds on the containers' surface. The authors recommended the use of high density polyethylene or glass containers. However, ISO method 25101 and EPA Method 537 recommended against the use of glassware for sampling due to the potential adsorption of PFOA on the walls (ISO, 2009; U.S. EPA, 2009a). The storage and sample preservation steps prior to the instrumental analysis should prevent changes in composition of the sample matrix and the concentration of the analyte (van Leeuwen et al., 2007).

SPE cartridges can also be a source of contamination and the U.S. EPA (2009a) recommends that SPE devices be tested prior to using them for analysis to ensure that there is no contamination of the sample. Several studies were conducted with a direct injection (DI) of the water samples into liquid chromatograph column. The method avoids the use of additional materials and sample preparation processes, which may limit possible contamination and target compound losses (Schultz et al., 2006; Furdui et al., 2008; Dickenson and Higgins, 2013).

HPLC tubing, nylon filters, auto-sampler vial caps made of Teflon or Viton fluoropolymers, valve seals and degassers were identified as the potential sources of contamination of the instrumental blanks with PFOA (Yamashita et al., 2004; Taniyasu et al., 2005; Schultz et al., 2006; Larsen and Kaiser, 2007) and to lesser extent with PFOS (Yamashita et al., 2004). The instrumental background contamination can be reduced by replacing or bypassing the fluoropolymers parts such as a degasser (Arbuckle et.al, 2013) with offline degassing of mobile phases; replacing fluoropolymer components with stainless steel, polyetheretherketone (PEEK) tubing, installing an upstream guard column, extensively flushing of the LC system or reducing the LC-column equilibration time (Martin et al., 2004; Yamashita et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007; Nakayama et al., 2007; Shoemaker et al., 2009; Arbuckle et.al, 2013).

6.3 Analytical performance

Recent analytical improvements have been realized through the availability and use of high quality standards and stable isotope internal standards to compensate for the matrix effect

and for inefficiencies in the extraction procedure and/or other sample preparation steps (Yamashita et al., 2004; Lowen et al., 2005; Taniyasu et al., 2005; Nakayama et al., 2007; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). There are currently, a number of high quality analytical-grade standards that are commercially available and the list of these standards continues to expand (van Leeuwen et al., 2009, Berger et al., 2011).

In the early 2000s, quantification of PFASs was biased by the lack of proper analytical standards, isotopically labelled surrogates and reference material and there was a significant analytical variability between laboratories. Two inter-laboratory studies were conducted to analyze PFASs, including PFOA and PFOS, in environmental water samples and found a varying degree of accuracy. In the first study (van Leeuwen et al., 2006), conducted in 2004/2005, factors resulting in poor agreement between participating laboratories, were determined to be low PFOA/PFOS concentrations (below 20 ng/L) in water samples; the use of low purity standards, high matrix effect, and a high background contamination in the analytical blanks. The relative standard deviation (RSD) reported in the study was 118% for PFOA (van Leeuwen et al., 2006). In the second inter-laboratory study, the performance of the participating laboratories improved due to the minimization of the matrix effects; the use of higher quality (purity and isomeric composition) shared standards (provided by a single source), and the use of mass-labelled internal standards. The reported RSD value in this study was 32% for PFOA.

Methods using SPE and DI procedures followed by LC/ESI/MS/MS have been reported in the literature for the determination of PFAS, including PFOS in water samples (Yamashita et al., 2004; 2005; Taniyasu et al., 2005; 2013; Furdui et al., 2008; Hansen et al., 2010; Berryman et al., 2012; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). Details regarding the preconditioning procedures of the SPE cartridges, eluent, clean-up procedures, MS quantification parameters and QC procedures specific to each method are available in the cited reference.

A study reported a limit of detection (LOD) (signal-to-noise [S/N] = 3:1) of 0.28 ng/L and an LOQ (S/N= 10:1) of 0.94 ng/L using an SPE followed by LC-MS/MS for analyzing PFOA in surface water. A water sample of 500 mL was loaded on the Oasis WAX cartridge, a target fraction was eluted, dried under nitrogen gas and before the analysis the samples were filtered. The recovery value of 115±6% for PFOA was calculated by isotopically-labelled internal standards calibration (Sun et al., 2011; Li et al., 2011).

Villaverde-de-Saa et al. (2015), using an SPE followed by LC–MS/MS, developed a method for the determination of seven PFCAs (C6–C12) and PFOS in environmental waters samples. A water sample of 1.0 liter, fortified with internal standards, was loaded on the Oasis HLB cartridge. The method reported a LOD of 0.03 ng/L and a LOQ of 0.11 ng/L for PFOA, (LOD and LOQ were calculated as 3 and 10 times the standard deviation, respectively). The recovery value of 89±4% for PFOA was calculated by isotopically-labelled internal standards calibration.

Furdui et al. (2008) investigated the concentration of PFASs in water samples from the Great Lakes. The analysis of nine target contaminants including PFOA, were performed by directly injecting the samples into LC-MS/MS. Quantification was performed using internal standard correction and standard addition. An isotope dilution provides the most accurate and precise results. The method had a LOQ (signal-to-noise [S/N] =10:1) of 0.5 ng/L for PFOA (Furdui et al., 2008).

The province of Québec reported results of the monitoring PFASs at 16 sites, including seven drinking water treatment plants. A total of 226 water samples (84 raw, 84 treated and 58 surface water samples) were analyzed. Both raw and treated water were sampled monthly for a period of one year. Sampling of the surface water was limited through the year. The samples were

analyzed using C18 cartridges and LC-MS/MS in positive ionization mode. Reported DLs ranged from 0.5 to1.0 ng/L and 0.3 to 0.6 ng/L for untreated (250 mL analysed sample) and finished water (500 mL sample), respectively. In order to compensate and correct the instrumental variations and the matrix effect, isotopically-labelled internal standards were added prior to the LC (Berryman et al., 2012). Although the photoionization technique is less sensitive than the electrospray ionization, it is less prone to matrix effect (Martin et al., 2004).

Berger et al. (2004) compared different mass spectrometric techniques (time-of-flight [TOF] high resolution MS, triple-quadrupole tandem MS, and IT-MS) coupled with a high performance liquid chromatography (HPLC) for analysis of PFASs including PFOA. The instrument parameters such as vaporizer temperature, collision energy, and cone voltage fragmentation were optimized for each mass spectrometry technique. Negative electrospray ionization was selected as the ionization mode for all instruments. The study indicated that both TOF high resolution MS and triple-quadrupole tandem MS methods had higher sensitivities than IT-MS for all tested PFASs. Although IT-MS had a higher DL and smaller linear range, it provided the best results for tentative structure elucidation and qualitative analysis of branched PFASs isomers (Berger et al., 2004; Jahnke and Berger, 2009).

The analysis of PFASs in environmental water samples has been dominated by the use of LC coupled to MS or MS/MS, although other techniques such as ^{19}F nuclear magnetic resonance (NMR) and gas chromatography (GC)–MS have also been explored. ^{19}F NMR analysis is a less sensitive and non-specific method due to the determination of the presence of CF_2 and CF_3 moiety in the sample. Gas chromatography (GC) can be used to determine neutral and volatile PFASs and fluorotelomer alcohols. PFAS are derivatized in order to be amenable for GC analysis. However, the use of the derivatization techniques is limited for PFOS analysis due to the instability of the PFOS's derivatives (Moody et al., 2001; Villagrassa et al., 2006).

7.0 Treatment technology

The available data and calculated pKa (2.8) values indicate that PFOA is a strong acid which predominantly dissociates to a negatively charged form (anion) at environmentally relevant pH values (U.S. EPA, 2005; Lange et al., 2006; Prevedouros et al., 2006). Based on the physical-chemical properties of the ionized form (a negligible vapor pressure, a high solubility in water and moderate sorption to solids), Prevedouros et al. (2006) suggested that PFOA would accumulate in surface water. Given the hydrophobic and oleophobic nature of the fluorinated alkyl chain and the hydrophilic nature of the carboxylate group, hydrophobic and electrostatic effects likely influence PFOA adsorption (Higgins and Luthy, 2006; Xiao et al., 2011). The nature of the chemical structure of PFOA (i.e., strong carbon - fluorine (C-F) bonds) makes it resistant to hydrolysis and biodegradation as well as to several chemical treatment processes (Lange et al., 2006; ATSDR, 2009).

7.1 Municipal scale

Dickenson and Higgins (2013) evaluated the ability of wide range of full-scale treatment techniques to remove PFASs, including PFOA and PFOS, from raw water or potable water reuse plants. The treatment trains varied, but generally consisted of coagulation followed by physical separation, aeration, chemical oxidation, UV irradiation, and disinfection. Regardless of the treatment train applied, there was little or no decrease in PFOA and PFOS concentrations and the authors concluded that these treatment methods are not effective in removing PFASs.

GAC adsorption and membrane filtration techniques appear promising for removal of PFOA in drinking water, achieving treated water concentrations below 0.2 µg/L (Tang et al., 2006; Lampert et al., 2007; Wilhem et al., 2008; Deng et al., 2010; Takagi et al., 2011; Appleman et al., 2014). In order to achieve a PFOA concentration below 0.2 µg/L, the GAC system must be specifically designed and appropriately operated for PFOA removal in drinking water. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance by directly competing for adsorption sites and preloading (fouling) the GAC beds. Therefore, the effectiveness of GAC to remove PFOA in drinking water appears to be dependent on the regeneration frequency and/or replacement of the carbon (Kolstad 2010; Takagi et al., 2011; Appleman et al., 2014). Membrane filtration such as reverse osmosis (RO) and bench-scale nanofiltration (NF) studies demonstrated effective removal of all tested short-and long-chain PFASs including PFOA in drinking water. Although the RO process is effective, it is likely to be an expensive treatment method (Steinle-Darling et al., 2008); Quinones and Snyder, 2009; Appleman et al., 2013; Flores et al., 2013). Anion exchange resins may also be effective in removal of PFOA. However full-scale evaluation of this technology has not been conducted specifically for PFOA removal in drinking water.

The selection and effectiveness of each treatment strategy is driven by several factors, including source water chemistry, concentration of PFOA and/or other PFASs and pre-existing treatment processes. If long-chain PFASs are detected in the drinking water sources, the utility may consider the implementation of treatments such as GAC. However, utilities that have shorter chain PFASs in their raw water source may choose to implement RO or NF. The treatment technologies need to be designed specifically for PFASs removal and operated appropriately in order to achieve contaminants removal objectives in drinking water (Dickenson and Higgins, 2013).

The ability of various drinking water treatment processes and treatment trains to remove PFOS have been summarized by Dickenson and Higgins (2013) and Rahman et al. (2014). Appendix A summarizes the percentage removal of PFOA in full-scale plants where both raw and finished water concentrations were reported (Rahman et al., 2014). Data show that the treatment technologies employed by these plants (with the exception of GAC, RO and NF) did not appreciably remove PFOA. They also show that in some cases concentrations in the finished water were higher than in the raw water, likely due to the breakdown of precursor compounds to form PFOA during the treatment (Takagi et al., 2008; Shivakoti et al., 2010). Takagi et al. (2011) also postulated that these higher finished water levels may result from desorption from GAC filters used for long periods of time without reactivation and the leaching of these compounds from Teflon-coated treatment equipment.

7.1.1 Conventional treatment

Conventional drinking water treatment processes generally incorporate coagulation, flocculation, sedimentation, and filtration, followed by primary and secondary disinfection. Common coagulants used in drinking water include aluminum sulfate (alum), ferric hydroxide, ferric chloride, polyaluminum chloride and coagulant aid polymers. Filtration media can consist of sand (single media); sand and anthracite (dual media); or sand, anthracite, and garnet (multi or mixed garnet media). GAC may also be used as the filter media.

Conventional full-scale drinking water treatment techniques have been found ineffective in removing PFOA from source waters. Samples collected from several full scale conventional treatment plants indicated essentially no difference in the PFOA concentrations between plant influent and concentrations in water following the coagulation, sedimentation, and sand filtration

steps (Loos et al., 2007; Shivakoti et al., 2009; Takagi et al., 2011; Thompson et al., 2011). Similarly, Eschauzier et al. (2012) reported that slow- and rapid- sand filtrations were ineffective for PFOS and PFOA removal. The inability of conventional water treatment to remove PFOA and PFOS may be due to their extremely low concentrations in water and their hydrophilicity which renders them unamenable to removal by conventional treatment processes (Rahman et al., 2014). These findings are in agreement with recently conducted bench-scale studies of the removal of PFOA from water (Deng et al., 2011; Xiao et al., 2013).

Jar tests (Xiao et al., 2013) achieved an approximately 3% removal of an influent concentration of 0.083 µg/L (83 ng/L) of PFOA, with an alum dose of 30 mg/L and pH of 7.9. A removal efficiency below 10% was reported under a range of alum doses ranging from 10 to 60 mg/L and pH levels ranging from 6.5 to 8.0. Removal rates of approximately 25% were observed using enhanced coagulation with alum doses greater than 60 mg/L and pH 4.5 – 6.5. In general, the removal efficiencies were below 35% under the examined coagulation conditions (alum doses 3-110 mg/L and pH 4.5-8.0). Ferric chloride coagulation exhibited similar results. The authors indicated that removal rates were lower for PFOA than PFOS in both conventional and enhanced coagulation conditions, possibly due to PFOA having a lower molecular size and a potential for being less hydrophobic.

However, Deng et al. (2011) demonstrated that the addition of powdered activated carbon (PAC) before the coagulation process was capable of enhancing the removal efficiency of PFOA in water after the coagulation. In the experiments, an initial PFOA concentration of 21.2 µg/L was decreased to 5.8 µg/L with a polyaluminium chloride (PACl) dose of 10 mg/L. A concentration below 1.0 µg/L was measured in the finished water after the addition of 10 mg/L of PACl and PAC doses up to 16 mg/L, to the initial PFOA concentrations in the range of 0.5-3.0 mg/L. The study found that the concentration of PFOA in the finished water decreased with increasing initial turbidity and PACl dose, and increased with increasing pH or temperature

7.1.2 Adsorption

Adsorbents typically used in drinking water treatment include activated carbon, activated alumina, zeolites, clays, metal oxides, hydroxides, and carbonates (AWWA, 2011; U.S. EPA, 2012). GAC is used in a fixed bed, while PAC is generally added directly to the raw water as a powder or mixed with water to form a slurry.

Several laboratory studies of PFOA and PFOS adsorption kinetics indicate that PAC reached sorption equilibrium in 4 hours while GAC reached equilibrium in 168 hours, (Yu et al., 2009) and that PFASs removal percentages were generally higher for PAC than for GAC (60–90% versus 20–40%, respectively) for 10 minutes adsorption time (Hansen et al., 2010). These results may be due to PAC's smaller particle size, and higher specific surface area per volume of carbon when compared to GAC (Yu et al., 2009; Hansen et al., 2010). If PFASs are present in the raw water year round, Rahman et al. (2014) suggested that GAC adsorption may be the preferred method for PFASs removal, while PAC may be more appropriate for short-term spill response remediation.

7.1.2.1 GAC

Full-scale evaluations of the effectiveness of GAC adsorption for the removal of PFOA in drinking water sources have been mixed. Several full-scale studies, specifically designed and operated for PFASs removal in drinking water, observed successful removal of PFOA by GAC with a long empty bed contact time (EBCT) and an appropriate regeneration regime (MDH, 2008a; Wilhem et al., 2008; Rumsby et al., 2009; Little Hocking Water Association, 2010;

Appleman et al., 2014). Other water treatment plants found similar levels of PFOA in both source and finished water, suggesting that GAC treatment only partially removes this contaminant, if at all. These treatment plants were not specifically designed for PFASs removal in drinking water. As the GAC had been in place for a variable period of time, it was likely that the preloading by NOM had deteriorated the GAC performance leading to similar PFOA levels in the influent and treated water (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012, Flores et al., 2013).

A full-scale GAC treatment system with a flow rate of 1.5 m^3/minute was specifically designed for PFASs removal in groundwater. The system used two GAC contactors in a lead/lag configuration with an EBCT of 13 minutes each. The lead vessel operated for approximately 10 months and treated 30,129 BVs before the concentration of PFOA exceeded 0.05 µg/L. The GAC unit was capable of reducing an influent PFOA concentration in the range of 0.45–0.83 µg/L to below 0.05 µg/L, in the treated water from the lag vessel, for 72,775 BVs (approximately 22 months). At that point, the lead vessel water reached 0.25 µg/L PFOA, its carbon was replaced with virgin media and the vessel was put in the lag position (Appleman et al., 2014). Another full-scale 400 gpm (1.5 m^3/minute) GAC treatment system proved effective for the removal of PFOA in surface water, with an influent concentration decreasing from 0.9 µg/L to below the DL of 0.01 µg/L in the treated water. An increase in PFOA concentration in the treated water was observed after approximately 3 months with levels exceeding the treated water goal of 0.1 µg/L after 5 months of operation (Wilhelm et al., 2008; Rumsby et al., 2009).

The behaviour and fate of PFASs, including PFOA and PFOS, was assessed by analyzing influent and treated water from several drinking water treatment plants that included GAC in the treatment train. These plants were not specifically designed for PFASs removal in drinking water. The hydraulic retention time of individual treatment steps was considered when the efficiency of each these steps was assessed (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013). The studies found that only the GAC step was capable of removing PFASs in drinking water. Removal of approximately 50% of PFOA was reported when a GAC process was included in the treatment train (Eschauzier et al., 2012; Flores et al., 2013). The paragraphs below provide more details on some of these studies.

A full-scale 5 million gallons per day (MG/D) treatment plant, designed to remove trace levels (ng/L) of organic contaminants in surface water, consisted of river bank filtration, softening, UV/H_2O_2, biologically-active GAC filtration and six GAC contactors. The GAC system operated in parallel mode with an EBCT of 10.5 minutes. Water samples analyzed before and after the GAC system demonstrated reduction of an influent PFOA concentration of 9.7 ng/L to below 5 ng/L (Appleman et al., 2014).

Eschauzier et al. (2012) monitored the concentrations of PFOA and PFOS in a drinking water treatment train consisting of coagulation, rapid sand filtration, dune passage, softening, ozonation and GAC treatment. Only the GAC step was effective for PFASs removal. The system used two-stage GAC contactors in a lead/lag configuration. Of the 40 filters, 20 were used in parallel mode as a first stage and the other 20 were used as a second stage filter. Each GAC filter operated at a flow rate of 348 m^3/hour and an EBCT of 20 minutes, resulting in a total EBCT of 40 minutes. Each virgin GAC filter was installed as a second stage filter and was switched to the first stage after 15 months of operation. After another 15 months, the carbon was reactivated and put back in service as a second stage filter. The GAC system achieved approximately 50% reduction on the average influent PFOA concentration of 8.8 ng/L in the feed water to the first GAC stage (Eschauzier et al., 2012). Flores et al. (2013) reported similar results for the removal

of PFOA (45%) in a water treatment plant, which had 24 GAC contactors installed and that were regenerated approximately once a year.

Takagi et al. (2008, 2011) investigated the behaviour, fate and removal efficiency of PFOA and PFOS in drinking water treatment processes from several drinking water treatment plants that included GAC in the treatment train. The removal efficiency of PFOA and PFOS were less than 50% in many of the water treatment plants. A negative removal rate in certain plants suggested that desorption from GAC filters, used for long periods of time without reactivation, may be responsible for these observations. The negative removal rates could also result from the formation of PFOA and PFOS from the degradation of the precursor compounds found in the raw water (Takagi et al., 2011). However, greater than 90% removal of PFOA was observed for 4 months in a 1.5 MLD water treatment plant after the replacement of its activated carbon in the GAC unit. The treatment train consisted of coagulation/sedimentation, rapid sand filtration and two GAC contactors (coal and coconut-shell carbon) in parallel mode. Both GAC contactors were capable of reducing the PFOA concentrations in the range of 25–44 ng/L to below the LOQ of 0.7 ng/L for 4 months. The concentration of the GAC filtered water gradually increased to13 ng/L at the end of the 8 month study period (Takagi et al., 2011).

Rapid small-scale column tests (RSSCTs) are a common bench scale test used to evaluate GAC. Using RSSCTs, Appleman et al. (2013) compared the effectiveness of three different types of GAC for removal of several PFASs including PFOA and PFOS. The column experiments were conducted with an EBCT of 0.38 minutes using deionized water and surface water [dissolved organic carbon (DOC) of 1.7 mg/L], both spiked with 1.0 µg/L of each PFASs. The tests were run for a total of 125,000 BVs (approximately 33 days). Carbon performance varied based on the type of carbon and water chemistry, with GAC being more effective at removing PFASs in deionized water. Of the three carbons, F300 achieved the best results. In the experiments conducted with deionized water, a concentration greater than 0.02 µg/L PFOA (2% of influent concentration C0) was observed at approximately 30,000 BVs (8 days) and a filtered water concentration of 0.05 µg/L (5% of C0) was measured after 56,000 BVs. However, the filtered water concentration reached 0.2 µg/L (20% of C0) after 11,000 BVs (3 days) and full (100%) breakthrough was observed at a run length of 26,000 BVs in spiked surface water. Although RSSCTs are not suitable for evaluating the effect of preloading/fouling of GAC columns by DOC, the observed rapid breakthrough in the spiked natural water demonstrated that the presence of DOC affects the GAC performance in the removal of PFASs by directly competing for adsorption (Appleman et al., 2013).

The efficiency of PFOA removal by GAC adsorption is impacted by NOM in source water which competes for the carbon adsorption site and will adsorb irreversible, causing the carbon's capacity for the target compound to be reduced. When the adsorption capacity of the GAC is exhausted, it must be removed from the contactor and replaced with fresh or reactivated carbon. GAC is used in a fixed bed reactor, as a substitute for existing filtration media (i.e., sand) in a conventional filter, as a layer in a multi-media rapid filter, or in a separate contactor. The reactor can be located at the beginning of the treatment train in a dual-media or sand-replacement mode, or later in the treatment train as a second-stage contactor. The rate of GAC exhaustion will vary substantially for the same water source depending in which configuration GAC will be employed. A dual media (GAC and sand) is used when turbidity removal and the adsorption/removal of the contaminants are combined in a single unit process. The dual media filter (typically located after sedimentation) is likely to be exposed to higher DOC concentrations, and this filter will be exhausted faster. A GAC contactor located at the end of a treatment train will likely experience slower preloading/fouling, since the treatment steps prior to a GAC contactor will reduce the

DOC influent concentrations. GAC contactors in lead/lag configuration have also been shown to achieve a PFOA concentration below 0.2 µg/L in treated water (Appleman et al., 2014; Little Hocking Water Association, 2010). This treatment strategy will assist in completely utilizing the entire GAC capacity and reducing operating cost (i.e., carbon replacement cost) (Crittenden et al., 2012).

Close monitoring of PFOA breakthrough (treatment objective) is necessary for efficient operation of GAC unit. Studies indicated that PFOA was successfully removed from drinking water when a frequent regeneration or replacement (3 to 6 months) of the GAC was performed (e.g., Wilhelm et al., 2008; Rumsby et al., 2009; Takagi et al., 2011). Takagi et al. (2011) observed that GAC regenerated over periods greater than one year were not effective in removing PFOA and PFOS and suggested regenerating the carbon 2 to 3 times per year. A GAC replacement at approximately every 3 months was needed to achieve PFOA removal to below 0.004 µg/L in a system where the influent PFOA concentrations ranged from 1.9 to 15 µg/L (Little Hocking Water Association, 2010). A full-scale 2,500 gpm GAC treatment plant, using two GAC contactors in series observed breakthrough of PFOA and PFOS after 286 days and 550 days, respectively. With the replacement of the GAC at the earliest time of PFOA breakthrough, the system was able to treat 1.9 million gallons of water for 23 months (MDH, 2008a; Kolstad, 2010).

Eschauzier et al. (2012) observed that the removal efficiencies of PFASs by GAC increased with increasing carbon chain length and that sulfonate compounds were removed for a longer period of time than the carboxylate compounds. Shorter-chained PFASs (especially perfluorobutanoic acid [PFBA] and perfluorobutane sulfonate [PFBS]) were not removed by GAC. These findings were in agreement with previous batch experiments showing that the sorption of PFASs on activated carbon decreased with decreasing the carbon chain-length and perfluorosulfonates adsorbed stronger than perfluorocarboxylates with the same carbon chain length (Ochoa-Herrera and Sierra-Alvarez, 2008; Hansen et al., 2010; Dudley et al., 2012; Appleman et al., 2014). Branched isomers of PFOS and PFOA were found to be less sorbable to GAC than linear isomers. Desorption of shorter chain PFASs due to competition for sorption sites with longer chain PFASs or NOM (i.e., DOC) may result in higher levels of shorter chain PFASs in the treated water (Eschauzier et al. (2012).

7.1.2.2 PAC

No full-scale data were reported on the efficacy of PFOA removal by PAC. Most published studies on the efficacy of PAC were conducted at the bench-scale. PFOA concentrations in some of these bench-scale studies were order of magnitude higher than the concentration observed in natural waters. However, trends observed for PAC in terms of preferential adsorption (chain-length dependence) and competition with NOM were similar to that documented for GAC (Hansen et al., 2010; Dudley et al., 2012).

Dudley et al. (2012) evaluated the adsorbability of ten PFASs with different carbon chain lengths (from C4 - C10) on commercially available PACs (coconut shell, lignite, wood, and bituminous coal) and superfine PACs (S-PACs) obtained by wet-milling the commercially obtained PACs. Sulfonate substances were found to be more adsorbable than carboxylate substances and sorption kinetics were faster with S-PACs when compared to PACs. The removal efficiencies of PFAS increased with increasing carbon chain length (i.e., negligible removal of C4 compounds but greater than 90% removal for C7-C10 compounds). The presence of NOM was found to decrease the effectiveness of PFAS removal by PAC in batch studies. The authors also

concluded that significant removal of smaller chain PFASs may not be achievable at practical PAC dosages (Dudley et al., 2012).

Yu et al. (2009) investigated the sorption kinetics and isotherms of PFOA and PFOS on PAC, GAC and an anion-exchange resin. The anion exchange resin had the highest sorption capacity for PFOA while PAC was found to be the adsorbent of choice for PFOS. Another laboratory experiment found 88% and 25% removal of PFOA by PAC and GAC, respectively, based on an initial concentration of 1.4 µg/L in groundwater. The study also observed that PFOS sorption on PAC was faster than on GAC, suggesting that the sorption kinetics were influenced by the size of the activated carbon (Hansen et al., 2010). Qu et al. (2009) inferred that PAC could be used as an effective adsorbent for the removal of PFOA from water because the removal efficiency increased from 51.1% to 99.9% when the PAC doses were increased from 0.1 g/L to 10 g/L (initial PFOA concentration of 20 mg/L).

7.1.3 Membrane filtration

There are four main types of membrane filtration processes in drinking water treatment applications: microfiltration (MF), ultrafiltration (UF), nanofiltration, and reverse osmosis. Low pressure membranes such as MF and UF are not capable of rejecting PFASs since their pores sizes are larger than the effective diameter of the PFASs molecules (~1 nm) (Tsai et al., 2010; Rahman et al., 2014). Bench-scale studies indicated that the membrane molecular weight cut-off (MWCO) of NF/RO is probably the most important factor for removal of PFASs for these technologies. In general, NF membranes have a lower rejection (95%) than RO (greater than 99%), which is consistent with the fact that NF membranes have larger pores (Tang et al., 2006, 2007; Steinle-Darling and Reinhard, 2008; Lipp et al., 2010; Appleman et al., 2013; Rahman et al., 2014).

The available scientific information on the removal of PFOA and PFOS from drinking water supplies by membrane filtration is limited to one full-scale RO drinking water utility (Flores et al., 2013) and several indirect potable water reuse plants (Quinones and Snyder, 2009; Appleman et al., 2014). Due to the physical location of these indirect potable water reuse plants, they were considered to be major potential contributors to the drinking water facilities' source water in the conducted studies (Quinones and Snyder, 2009).

Although a full-scale conventional treatment was reported as being ineffective for PFOA removal in surface water; 92% removal of PFOA was achieved when RO followed the conventional treatment train (Flores et al., 2013). The RO system's feed water was filtered by the conventional treatment process and blended with untreated groundwater. Feed water PFOA concentration ranged from 15 to 26 ng/L (average 21 ng/L) and the RO system was capable of reducing these PFOA concentrations to an average of 2.1 ng/L (Flores et al., 2013).

Two indirect potable water reuse plants with RO units in their treatment trains were capable of reducing a PFOA concentration to below 55 ng/L in the RO treated water. Both RO systems had a flux rate of 12 gallons per square foot per day (gfd) (20 $L/m^2/h$) and water recovery in the range 80-85%. The feed PFOA concentrations to the RO units ranged from 9.5 to 200 ng/L (Dickenson and Higgins, 2013; Appleman et al., 2014). A survey of several drinking water utilities and indirect potable water reuse plants showed that the PFOA concentrations in the treated water were comparable to the levels found in the raw water samples in almost every case. However, removal was only observed in one planned potable reuse facility when an integrated membrane treatment consisting of MF and RO was employed. The membrane system was capable of rejecting a feed PFOS concentration of 15 ng/L to below 5 ng/L (Quinones and Snyder, 2009).

Bench-scale experiments evaluated the rejection behaviour of unfouled and fouled NF membranes on the removal of PFASs, including PFOA (Appleman et al., 2013). The study found that a polyamide thin film composite flat-sheet NF membrane was capable of rejecting all of tested compounds in the range of 93 to 99%. Greater than 97% rejection of an average influent PFOA concentration of 664 ng/L (LOQ of 20 ng/L) was observed in all experiments using virgin membranes and spiked de-ionized water; virgin membranes and spiked groundwater; and fouled membranes and spiked groundwater. The fouling layer on the NF membrane showed no negative effect on PFOA rejection (Appleman et al., 2013). Another bench-scale study was conducted on one RO (MWCO of 100 Da) and three NF (MWCO range of 200 – 360 Da) membranes for the removal of PFOA. The RO membrane achieved a 99.9% rejection of PFOA from the feed water concentration of 3500 ng/L with a permeate PFOA concentration in the range of 3–6 ng/L. The RO system was operated with a flux rate of 30–40 $L/m^2/h$ and a feed pressure of 8 bars (116 psi). All tested NF membranes achieved a rejection in the range of 95.5–99.8% of an average feed PFOA concentration of 3000 ng/L, with a flux rate of up to 70 $L/m^2/h$ and an operating pressure in the range of 4–7 bars (58-101 psi) (Lipp et al., 2010).

Although there is limited information on full-scale RO and only bench-scale NF treatment information, both technologies are considered effective for PFOA removal from drinking water (Appleman et al., 2014). The results of the NF studies are promising since NF is a less energy intensive process than RO. Testing of the selected NF membrane for PFOA removal at both pilot- and full-scale is an important step for utilities when considering this treatment process. Since the size exclusion is an important mechanism for PFASs rejection by NF membranes, consideration should be taken to select membranes with MWCO smaller than the size of PFOA.

Considerations when using RO treatment include disposal of the reject water and the potential for increased corrosivity of the treated water. RO rejects a significant portion of the influent water as contaminant-rich brine, and the concentrate discharge must be disposed of appropriately. The removal of contaminants can cause mineral imbalances that could increase the corrosive nature of the treated water. In most cases, post-treatment corrosion control measures need to be taken.

7.1.4 Ion exchange

PFOA is in an anionic form at ambient water pH values and therefore is expected to be amenable to removal by anion exchange resins (Senevirathna et al., 2010). Two primary mechanisms, hydrophobic and electrostatic interactions, were proposed for the removal of PFOA by ion exchange resins (Carter et al., 2010; Deng et al., 2010; Xiao et al., 2012).

Appleman et al. (2014) reported results for the only one known full scale application of ion exchange for the removal of PFASs. However, this system was not specifically designed for PFASs removal in drinking water. A 350 gpm full-scale ion exchange plant reduced the concentrations of PFOA in the range of 68–120 ng/L to an average concentration 24 ng/L in groundwater. A strong base anion resin impregnated with iron oxide used for arsenic removal was assessed for PFOA removal after the resin had been in use for 5 and 9 months. The highly porous strong base anion exchange resin, achieved greater than 75% removal of PFOA, partial removal of perfluoroheptanoic acid (PFHpA) (46%), and high removal of both PFOS (>92%) and perfluorohexanesulfonate (PFHxS) (97%). Shorter carbon chain compounds such as PFBA, and perfluorohexanoic acid (PFHxA) exhibited little to no removal. Results also indicated that perfluorosulfonic acids were preferably removed by anion exchange resin over the perfluorocarboxylic acids.

Exchange resins exhibit a degree of selectivity for various ions, depending on the concentration of ions in solution and the type of resin selected. Laboratory-scale evaluations of different types of resins (i.e., ion exchange resins, non-ion exchange resins) for removal of PFASs in water have been reported in the literature (Lampert et al., 2007; Carter et al., 2010; Deng et al., 2010; Senevirathna et al., 2011; Xiao et al., 2012; Chularueangaksorn et al., 2013). Batch kinetic tests conducted with a high initial PFOA concentration (mg/L) demonstrated a greater than 99% removal of PFOA in 25 hours of contact time using a commercial anion exchange resin, while another anion resin achieved only 37% removal. The study also observed that PFOS anions were preferably removed over PFOA anions in the ion exchange process (Lampert et al., 2007). In laboratory experiments, anion exchange resins demonstrated greater capacity for PFASs removal than non-ion exchange resins (Chularueangaksorn et al., 2013, 2014). Laboratory-scale fix-bed columns compared the performance of anion exchange and non-ion exchange resins. The tests were conducted with an influent concentration of 5 µg/L PFOA for 120 days of operation. The breakthrough goal of 0.5 µg/L was observed with run lengths of 119,880 BVs (111 days) and 68,040 BVs (60 days) by the anion exchange and non-ion exchange resins, respectively (Chularueangaksorn et al., 2013).

While findings showed that anionic resins had a higher capacity for PFOA than non-ion exchange resins (Deng et al., 2010; Chularueangaksorn et al., 2013, 2014), it was also observed that moderately polar non-ionic resins performed better than non-polar non-ionic resins for removal of PFOA from water (Xiao et al., 2012).

Studies indicate that the ion-exchange process is a promising technology (Dickenson and Higgins, 2013) for the removal of PFAS, including PFOA, from drinking water. However, additional studies on the, selectivity of the resins, kinetic limitations, the impact of DOC, regeneration rates, and the presence of competing ions such as sulfate and nitrate on removal efficiency are needed (Dickenson and Higgins, 2013; Rahman et al., 2013).

7.1.5 Oxidation, UV irradiation and advanced oxidation processes

Advanced oxidation processes (AOPs) have been developed for removal of contaminants that are resistant to more typical chemical oxidation treatment processes. They include the use of appropriate combinations of ultraviolet (UV) light, chemical oxidants and catalysts (e.g., ozone, hydrogen peroxide, titanium dioxide) to generate highly reactive radicals, such as hydroxyl radicals, which are strong oxidants and react rapidly and non-selectively with organic contaminants.

Rahman et al. (2014) summarized studies that have demonstrated that PFAS like PFOA will likely be resistant to oxidation, even by molecular ozone and hydroxyl radicals. Due to the low reactivity of PFOA with ozone and AOPs, chlorine–based oxidation processes will likely not oxidize PFOA under typical drinking water conditions. The resistance of PFOA to oxidation is due to the shielding effect of the fluorine atoms and the strength of the carbon-fluorine bonds (3M, 1999; ATSDR, 2009). These conclusions have been confirmed in surveys of full-scale treatment plants (Quinones and Snyder, 2009; Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013) described below.

In a survey of several drinking water utilities, Quinones and Snyder (2009) observed that PFOA was resistant to chlorination, chloramination and ozonation even in a combination with other treatment processes such as coagulation/flocculation, deep bed filtration and UV irradiation. Results from drinking water treatment plants in Japan reported similar concentrations of PFOA in samples of water treated with an ozonation process and in the raw water samples (Shivakoti et al., 2010; Takagi et al., 2011). Ozone doses in the range 0.37–0.85 mg/L and contact time as high as

120 minutes showed that the ozonation process was ineffective to degrade PFOA at four utilities (Takagi et al., 2011). Thompson et al. (2011) observed that an ozone dose of 5 mg/L with a contact time of 15 minutes in reclaimed water was not effective at reducing PFOA concentrations in the range of 7.1–12.4 ng/L.

A full scale treatment plant employing two UV reactors, each capable of treating 3 MG/D groundwater with a UV dose of 80 mJ/cm^2 and UV transmittance of 95%, were not capable of reducing an influent PFOA concentration in the range of 11–15 ng/L. Another full scale 5 MG/D treatment plant reported that a UV dose of 500 MJ/cm^2 in combination with a dose of 4 mg/L H_2O_2 was also ineffective at degrading 19 ng/L PFOA in surface water (Appleman et al., 2014). Oxidation/AOPs and UV irradiation appear ineffective for PFOA removal in drinking water. However, ozone or AOPs may be able to oxidize polyfluorinated precursor chemicals that may be present in raw water, resulting in the potential for increasing the concentration of PFOA and PFOS in the finished water (Rahman et al., 2014).

7.1.6 Aeration/air stripping

The removal of compounds using air stripping is based on the equilibrium partitioning of chemicals between air and water, which is affected by the contact surface area between the air and the water, as well as temperature, vapour pressure and the pH of the water.

Dickenson and Higgins (2013) evaluated 23 PFASs (including PFOA and PFOS) in raw and finished drinking water and at various steps along the treatment train. They found that aeration was ineffective at removing PFOA and PFOS (10% removal).

7.1.7 River bank filtration (soil aquifer treatment)

River bank filtration (RBF) is a drinking water treatment method where surface water flows through the subsurface sand and gravel layers of the bank or bed of a river to extraction wells and contaminants are removed through the processes of filtration, sorption, dilution and biodegradation.

A drinking water utility utilizing RBF with a hydraulic residence time of approximately 10 days observed approximately 30% removal for PFOA, variable removal of some PFASs, and increases in concentration for other PFASs (Appleman et al., 2014). The authors concluded that this variation was possibly due to the variability in the influent concentrations from wastewater effluents impacted the drinking water sources and/or due to breakdown of precursor compounds through the river bank. Dickenson and Higgins (2013) concluded that RBF was not likely to result in significant removal of PFASs.

7.1.8 Emerging technologies

Other potential treatment technologies for removal of PFOA and PFOS have promise, but are still being researched actively. They have not yet all been evaluated on drinking waters by laboratory, pilot, or full-scale studies, but have been mentioned in reviews of bench scale studies of some PFASs removal from drinking water and wastewater (Vecitis et al., 2009; Eschauzier et al., 2012).

7.1.8.1 Nanomaterials and nanotechnologies

Nanomaterials are being developed for drinking water treatment applications, including ion exchange, sorption and oxidation processes, and abiotic reduction (e.g., nanozerovalent iron) (Boyd et al., 2013). Different nanomaterials/nanotechnologies show promise for removal of PFOS including carbon nanotubes (CNTs), chitosan-based molecularly imprinted polymers (MIPs),

electrospun nanofibrous membranes (ENFMs), and titanium dioxide (TiO_2) assisted photocatalysis (Yu et al., 2008; Deng et al., 2012; Dai et al., 2013). CNTs are carbon molecules composed of carbon lattices that can take the form of tubes. Chitosan is a natural polysaccharide based on the shells of crustaceans. It may be prepared as a nanoparticle or electrospun in nanofibers (Sonia and Sharma, 2011; Zhao et al., 2011a; Boyd et al., 2013). Molecular imprinting is a technique where specific sites for target compounds are constructed on a polymer so that specific adsorbates are recognized in the sorption process. ENFMs are prepared by electrospinning nanofibers of polymer or polymer composite materials to create membranes of non-woven fibers with diameters ranging from several hundreds to tens of nanometers (Greiner and Wendorff, 2007; Dai et al., 2013; Boyd et al., 2013).

Deng et al. (2012) have demonstrated the effectiveness of CNTs for removal of perfluorinated contaminants, including PFOA and PFOS, from aquatic environments when the hydrophobic interactions were involved in the sorption of perfluorinated contaminants onto the CNTs. The sorption of the perfluorinated contaminants was increased with increasing carbon-fluorine chain length with the same functional group.

7.1.8.2 Photolysis and photochemical degradation

Although a full-scale UV treatment process was reported ineffective in removal of PFOA in drinking water, several laboratory-scale evaluations of synthetic waters, wastewaters and industrial waters have reported that UV-visible light, UV in the presence of persulfate, UV in the presence of TiO_2 and perchlorate, UV in the presence of iodide and UV irradiation using carbonate radical ions may degrade PFOA concentrations (Hori et al., 2004a, 2005; Chen and Zhang, 2006; Chen et al., 2007; Fujii et al., 2007; Giri et al., 2011, 2012, 2013; Dillert et al., 2007; Panchangam et al., 2009; Qu et al., 2010).

A laboratory-study reported 87% degradation and defluorination of an initial PFOA concentration of 25 mg/L under 185 nm UV light irradiation in the presence of persulfate. When compared to direct photolysis the photochemical reaction enhanced PFOA degradation. The study observed a formation of short-chain PFCAs (Chen and Zhang, 2006). Another laboratory-study reported on the effectiveness of sulfate radical anion ($SO_4^{\cdot-}$) to decomposed PFOA in a photochemical reaction. The authors reported that PFOA concentration of 1.35mmol was completely decomposed by the photochemical system using $SO_4^{\cdot-}$ and 4 hours of UV visible light irradiation. The study also reported on the formation of shorter-chain PFCAs in a stepwise manner (Hori et al., 2005). After UV-visible light irradiation was applied under 0.48 MPa of oxygen, 89.5% of an initial PFOA concentration of 1.35 mmol was decomposed and the formation of CO_2, F^- and short-chain PFCAs was observed. The authors also reported that heteropolyacids due to their high stability are attractive photocatalysts in the degradation reactions of PFCAs. In the presence of heteropolyacid, 7.44 µmol PFOA in aqueous solution were completely degraded after 24 hours of UV irradiation. The photocatalyst enhanced the PFOA degradation and suppressed the formation of the short-chain PFCAs (Hori et al., 2004a). Tang et al. (2012) studied the effectiveness of the UV–Fenton technique for PFOA removal in water and found almost complete degradation and defluorination of PFOA within several hours, while PFOA was hardly degraded by a conventional Fenton system alone.

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to municipally treated water. In cases where an individual household obtains

its drinking water from a private well, a private residential drinking water treatment device may be an option for reducing PFOA concentrations in drinking water.

Although there are no certified residential treatment devices for the reduction of PFOA from drinking water, available data suggests that residential activated carbon and reverse osmosis can achieve treated PFOA concentrations of 0.2 µg/L and below 0.05 µg/L, respectively. In addition, treatment devices using anion exchange may be effective for the reduction of PFOA.

The Minnesota Department of Health (MDH, 2008b) completed a study of the effectiveness of point-of-use (POU) water treatment devices for PFOA, PFOS and PFBA removal and demonstrated that RO and activated carbon filters were capable of reducing PFOA concentrations typically found in drinking water. Laboratory screening tests and field evaluation of devices installed in municipal water systems were undertaken. In the laboratory tests, the challenge waters had a PFOA concentration of 3.0 µg/L and the target goals for performance was 0.2 µg/L. The field testing involved monitoring and sampling of four activated carbon and seven RO point-of-use devices installed at two municipal wells. One of the wells had concentrations of 0.6 µg/L PFOA, 0.9 µg/L PFOS, and 1.4 µg/L PFBA, while only PFBA was present (1.5 µg/L) at the second well. All RO devices were equipped with an activated carbon pre-filter (before the RO membrane) and a post-treatment (after the RO membrane) activated carbon polishing filter. Results indicated that all activated carbon and RO devices were effective in removing PFOA to below the quantification limit of 0.2 µg/L and below the detection limit of 0.05 µg/L, respectively. Based on these results, activated carbon and RO are expected to be effective at reducing the level of PFOA in drinking water to levels below the MAC of 0.2 µg/L.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2015):

- CSA Group (www.csagroup.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- UL LLC (www.ul.com);
- Bureau de normalisation du Québec (www.bnq.qc.ca); and
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

Activated carbon filtration systems may be installed at the faucet (POU) or at the location where water enters the home [point-of-entry (POE)]. RO systems are intended for POU installation, as larger quantities of influent (incoming) water are needed to obtain the required volume of treated water, which is generally not practical for residential-scale point-of-entry systems. RO systems should only be installed at POU as the water they have treated may be corrosive to internal plumbing components. A consumer may need to pre-treat the influent water to reduce fouling and extend the service life of the membrane.

Ion exchange treatment technology using anion exchange resins may also be a feasible for PFOA removal in residential scale applications. Ion exchange treatment devices is typically

designed and constructed for residential use by drinking water treatment system providers or dealer. If an ion exchange system is used, the water may need to be filtered through a GAC filter to remove any chlorine or chloramine (if connected to a treated water supply) from the water before it reaches the resin.

Health Canada strongly recommends that chemicals used in treatment systems be certified to NSF/ANSI Standard 60 – Drinking Water Treatment Chemicals Health Effects (NSF/ANSI, 2015a) and that materials and components be certified to NSF/ANSI Standard 61 – Drinking Water System Components Health Effects (NSF/ANSI, 2016a) and NSF/ANSI Standard 372 – Drinking Water System Components Lead Content (NSF/ANSI, 2016b). These standards ensure that these materials meet health-based leaching and lead content requirements and are safe for use in potable water applications. Activated carbon filters are covered in NSF/ANSI Standard 53: Drinking Water Treatment Units-Health Effect (NSF/ANSI, 2015b) and reverse osmosis systems are covered in NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems (NSF/ANSI, 2015c).

Before a treatment device is installed, the water should be tested to determine general water chemistry and verify the presence and concentration of PFOA. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Devices can lose removal capacity through use and time and need to be maintained and/or replaced.

8.0 Kinetics and metabolism

PFOA is considered chemically unreactive, and it is not metabolized. The oral absorption of PFOA is rapid and complete (Kemper, 2003; Hundley et al., 2006; Lau et al., 2007). Once absorbed, PFOA is primarily restricted to plasma and extracellular fluid (Butenhoff et al., 2004a; Han et al., 2012) and excreted in urine.

8.1 Absorption

PFOA is rapidly and nearly completely absorbed in the GI tract. In rats, studies consistently estimated the oral absorption rates of PFOA at >93% after a single dose (0.1 to 25 mg/kg bw) by gavage (Johnson and Ober, 1979, 1999; Kemper, 2003; Cui et al., 2010). Hundley et al. (2006) derived similar absorption rates for mice, rats, hamsters and rabbits after a single oral bolus of PFOA at 10 mg/kg bw. The estimated absorbed fractions were generally higher in males (rats: 89%, mice: 82%, hamsters: 92%) than in females (rats: 76%, mice: 61%, hamsters: 75%) except for rabbits (88% in both sexes). Fasted rats exhibited PFOA plasma concentrations approximately 2–3 times higher after a single oral bolus at 10 mg/kg bw (Hinderliter et al., 2006).

No controlled study data regarding the oral absorption of PFOA in humans are available; however, studies of residents living in areas with contaminated drinking water (Emmett et al., 2006a; Wilhelm et al., 2008) provide evidence of elevated serum PFOA concentrations. Emmett et al. (2006a) correlated the number of glasses of tap water ingested per day with blood concentrations, indicating this was the primary exposure route for populations with elevated PFOA concentrations in drinking water.

Limited inhalation or dermal studies have reported PFOA kinetics; however, the physicochemical properties of the compound suggest that these routes of exposure are not important when PFOA is found in drinking water (see Section 5.7).

8.2 Distribution

PFOA is mainly present in serum/plasma (Johnson and Ober, 1999; Kudo et al., 2007). The volume of distribution, which is similar across species (approximately 170 mL/kg bw), suggests extracellular distribution (Butenhoff et al., 2004a; Han et al. 2012). PFOA is tightly bound to serum protein, which plays an important role in distribution in blood and to tissues (Han et al., 2005). Binding in blood is primarily to serum albumin, with >90% of PFOA in serum expected to be bound to albumin in rats and humans (Han et al., 2003). To a lesser extent, PFOA can also bind to plasma γ-globulin, α-globulin, α-2-macroglobulin, transferrin and β-lipoproteins (Kerstner-Wood et al., 2003; Butenhoff et al., 2012a). Protein binding also occurs in organs and tissues. Luebker and coworkers (2002) reported *in vitro* binding of PFOA to rat liver fatty acid binding protein (L-FABP). PFOA has also been shown to bind to rat kidney and urine α2μ-globulin; however, dissociation constants were low compared to other ligands known to induce hyaline droplet nephropathy (Han et al., 2004). Linear PFOA isoform preparations bound more tightly to human serum albumin compared to branched isoforms, although the binding affinities were similar to one another (within one order of magnitude) (Beesoon and Martin, 2015).

PFOA kinetics are non-linear at high doses, which is hypothesized to be due to the saturation of organic ion transporters (OATs) responsible for renal reabsorption at high doses (e.g., 20 mg/kg bw per day administered in capsules), resulting in a higher excretion rate at high doses than at low doses (e.g., 0.1 mg/kg bw per day) (Andersen et al., 2006). Serum levels did not increase proportionally with increasing dose, except at lower doses in some studies and steady-state was reached more rapidly than expected at high doses with classical kinetics (4–5 half-lives). However, at lower gavage doses closer to those relevant to human environmental exposures, kinetics are consistent with linear first order processes, and serum levels are proportional to administered dose (Loveless et al., 2006; Lou et al., 2009). This non-linearity can affect PFOA distribution; for example, after a single intravenous dose in male rats, a lower proportion of the dose was distributed to the liver (27%) at 17 mg/kg bw compared to 52% at 0.4 mg/kg bw (Kudo et al., 2007).

Few data have been gathered on the human tissues to which PFOA is typically distributed. However, the tissue distribution is well documented in experimental animals, including monkeys, rats, and mice. In monkeys, PFOA distribution to the liver has been documented following administration of oral capsules containing PFOA (Butenhoff et al., 2002; 2004a). PFOA levels in other organs were not investigated. In orally exposed rats, PFOA has been detected most frequently and at the highest levels in the liver (Ylinen et al., 1990; Kemper, 2003; Martin et al., 2007). Additional primary tissues of distribution include the testes, spleen, lung, kidney, brain, skin, muscle, bone gastrointestinal tract and adipose tissue (Ylinen et al., 1990; Kemper, 2003). In orally exposed mice, PFOA has been detected in the liver, kidney, and bile (Lou et al., 2009; Minata et al., 2010).

In humans, PFOA was detected in approximately one half of the analyzed liver samples (in 6 males and 6 females from Catalonia, Spain; aged 27–79 years), and was significantly higher in males than in females (Kärrman et al., 2010), but was below the limits of quantification in livers in cadavers with environmental exposure (Olsen et al., 2003a). Neither cerebrospinal fluid (Harada et al., 2007) nor thyroid (Pirali et al., 2009) have been observed to be relevant partitioning sites for PFOA.

In rats, PFOA concentrations were consistently higher in males than in females after single or repeated exposures (Ylinen et al., 1990; Kemper, 2003). The differences have been attributed to more rapid elimination of PFOA in females than males. In mice and non-human

primates, there do not appear to be sex differences in PFOA concentrations (Griffith and Long, 1980; Butenhoff et al., 2004a; Lou et al., 2009). Lou et al. (2009) reported similar serum, liver and kidney PFOA concentration time-courses in male and female CD-1 mice after a single oral gavage of 1 or 10 mg/kg bw; however, the 95% confidence intervals on the mean half-lives do not overlap, indicative of possible sex differences in mice. Sex differences in PFOA concentrations have also been noted in human biomonitoring studies (see Section 5.6). As previously described in Section 5.6, serum PFOA levels in humans appeared to be influenced by age and gender in CHMS. The effect was also observed in U.S. studies, such as the National Health and Nutrition Examination Survey (NHANES) 1999–2008 (Kato et al., 2011) and other reference populations (Harada et al., 2004; Hölzer et al., 2008; Ingelido et al. 2010). As age increases, PFOA concentration has been shown to decrease in males and increase in females (Kato et al. 2011). Plausible explanations are menstrual bleeding, especially in nulliparous women (Ingelido et al., 2010), pregnancy and lactation. Supporting this hypothesis is the observation of higher serum PFOA levels in primiparous women than multiparous women (Kim et al., 2011), as well as the significant decrease in serum PFOA levels with duration of lactation (2–7 weeks vs. 3–4 months after delivery) (von Ehrenstein, 2009; Monroy et al., 2008).

PFOA exposure can occur transplacentally and lactationally. Fetal transfer via the placenta has been demonstrated in rats (Hinderliter et al., 2005) and mice (Fenton et al., 2009). In humans, concentrations of PFOA in cord blood of newborns are similar to maternal blood concentrations (Tittlemier et al., 2004; Midasch et al., 2007; Monroy et al., 2008; Beesoon et al., 2011; Needham et al., 2011; Gützkow et al., 2012). Moreover, serum concentrations in young children have been noted to be higher than serum concentrations in their mothers in a reference (i.e., not PFOA-contaminated) area (Hölzer et al., 2008) and in an area with elevated environmental PFOA levels (Mondal et al., 2012); however, serum concentrations were similar between children and mothers in an area with elevated PFOA levels in drinking water (Hölzer et al., 2008). Lactational transfer of PFOA has been measured in various mammal species, including humans, rats, mice, and sheep (Hinderliter et al., 2005; Fenton et al., 2009; Kim et al., 2011; Needham et al., 2011). Concentrations of PFOA in milk are consistently lower than in maternal plasma (Hinderliter et al., 2005; Fenton et al., 2009; Liu et al., 2011); Milk PFOA levels were approximately 10% and 25% of maternal plasma levels in rats and mice, respectively. In humans, a review of milk and maternal serum concentrations found the maternal milk:serum ratios across several studies to be approximately 0.11–0.12 (Liu et al., 2011). PFOA levels in human milk decrease significantly throughout the lactation period (Thomsen et al., 2010), and with increasing number of infants breastfed (Tao et al., 2008; Kadar et al., 2011). In a community with PFOA-contaminated water, infants breastfed for ≥ 12 months had significantly higher serum PFOA concentrations than infants who were not breastfed (Mondal et al., 2014); however, the authors noted that the estimates may be imprecise as they are based on only 8 infants in the long-duration group. Similarly, a study of Faroese infants with serum PFOA data at birth and at 11, 18, and 60 months estimated an increase in serum PFOA concentrations of about 28% per month during the period of exclusive breastfeeding and of about 4% per month during periods of partial breastfeeding (Mogensen et al., 2015a). In this study, serum PFOA levels measured up to five years of age did not decline to serum PFOA levels at birth, which the authors attributed to ongoing dietary exposure to PFOA (in particular through traditional intake of pilot whale meat).

8.3 Metabolism

The available data indicate that PFOA is not metabolized. Studies conducted in rodents and non-human primates did not reveal quantitatively significant metabolism of PFOA, and

PFOA was not metabolized when incubated with microsomal fractions of human or rat intestine, kidney or liver homogenates (Kemper and Nabb, 2005; EFSA, 2008; ATSDR, 2009).

8.4 Excretion

Remarkable species-dependent differences in elimination half-life have been observed, with PFOA remaining in human bodies for a much longer duration than other species, including non-human primates, rats and mice (Post et al., 2012). Elimination half-lives from serum in humans are significantly longer than in non-human primates and rats. Species- and sex-related differences are primarily attributed to elimination kinetics where, at higher doses, the kinetics of PFOA in rodents and primates do not follow one-compartment or simple first-order models (Andersen et al., 2006). Half-life values for serum elimination of PFOA in humans were derived from data obtained in retired workers from a 3M Company factory in Alabama, U.S.A (arithmetic mean of PFOA serum half-life = 3.8 years; range = 1.5–9.1 years; 95% CI = 3.1–4.4 years; Olsen et al., 2007) and current workers in a fluorochemical plant in China (geometric mean of PFOA serum half-life = 4.1 years; range = 0.44–3663 years; no 95% CI reported; Fu et al., 2016). In populations exposed environmentally through the consumption of PFOA-contaminated drinking water, half-life values could be estimated using measured declines in serum or plasma PFOA levels after exposures ceased due to filtration of drinking water. The geometric average half-life in Germany was reported as 3.26 years (range = 1.03–14.67; no 95% CI reported; Brede et al., 2010), and the average value for Mid-Ohio Valley was 2.3 years (95% CI = 2.1–2.4 years; no range provided; Bartell et al., 2010). An additional cross-sectional study in the Mid-Ohio Valley (with estimated, rather than measured, initial serum concentrations) identified average half-life values of 2.9–10.1 years (with values varying depending on the average serum concentrations in the community and duration since cessation of exposure) (Seals et al., 2011). The arithmetic mean of the elimination half-life was estimated as 2.1 years (95% CI = 1.8–2.4 years; range = 0.19–5.2 years) in young females and 2.6 years (95% CI = 2.2–3.0 years; range = 0.06–14 years) in males and older females in healthy adult volunteers in China (Zhang et al., 2013). In a study of Faroese children followed from birth to 5 years, the biological half-life of the serum-PFOA concentration was estimated as 4.2 years (Mogensen et al., 2015a). The authors cautioned against drawing conclusions regarding differences in elimination kinetics between children and adults based on this data because the cohort is not representative of the general population and the half-lives were calculated assuming negligible subsequent exposures following peak exposure levels. The half-life of PFOA in animals varies depending on experimental protocols, but is on the order of days to weeks in rodents and monkeys (see Table 1).

Table 1: Serum half-life estimates in humans and experimental animals

Species	Dosing regime	Mean half-life (days)	Reference
Rat	Single oral dose of 0.1 mg/kg bw; followed for 22 days (M) or 5 days (F)	8.41 ± 1.56[a] (M) 0.13 ± 0.04[a] (F)	Kemper, 2003
	Single oral dose of 0.1 mg/kg bw; followed until PFOA < quantitation limits	11.55 ± 2.36[a] (M) 0.14 ± 0.05[a] (F)	
	Single oral dose of 1 mg/kg bw; followed for 22 days (M) or 5 days (F)	5.76 ± 1.33[a] (M) 0.14 ± 0.05[a] (F)	
	Single oral dose of 5 mg/kg bw; followed for 22 days (M) or 5 days (F)	7.26 ± 1.21[a] (M) 0.19 ± 0.03[a] (F)	
	Single oral dose of 25 mg/kg bw;	6.56 ± 1.60[a] (M)	

Species	Dosing regime	Mean half-life (days)	Reference
	followed for 22 days (M) or 5 days (F)	0.68 ± 0.41[a] (F)	
	Single i.v. dose of 1 mg/kg bw; followed for 22 days (M) or 5 days (F)	7.73 ± 0.815[a] (M) 0.12 ± 0.02[a] (F)	
Mouse	Single oral dose of 1 or 10 mg/kg bw; followed for up to 80 days	21.7 (19.5–24.1)[b] (M) 15.6 (14.7–16.5)[b] (F)	Lou et al., 2009
Monkey	Single i.v. dose of 10 mg/kg bw; followed for 123 days	20.9 ± 12.5 (M) 32.6 ± 8 (F)	Butenhoff et al., 2004b
	Daily oral dose of 10 mg/kg bw for 6 months; followed for up to 147 days post-dosing	19.5[c] (M)	
	Daily oral dose of 20 mg/kg bw for 6 months; followed for up to 147 days post-dosing	20.8[c] (M)	
Human	26 former workers with an average of 31 years of work and 2.6 years retired; external exposure data not provided	1387 (1132–1606)[b]	Olsen et al., 2007
	138 adults and children, 2 years after reduction of PFOA concentrations in drinking water; doses not provided (Arnsberg, Germany)	1190[c]	Brede et al., 2010
	200 adults, ~1–2 years after reduction of PFOA concentrations in drinking water; doses not provided (Mid-Ohio Valley)	840 (767–876)[b]	Bartell et al., 2010
	86 adults; external exposure data not provided	767 (657-876)[b] (F) 949 (803-1095)[b] (M & F)	Zhang et al., 2013
	81 children; prenatal exposure assessed from mother's serum-PFOA at pregnancy week 32; external exposure data not provided	1533[c] (M & F)	Mogensen et al., 2015a
	302 workers before and after PFOS was restricted in 2009; years of service not reported; external exposure data not provided	1497[d] (M & F) 1716[d] (M) 1132[d] (F)	Fu et al., 2016

[a] ± Standard deviation
[b] 95% confidence interval
[c] No standard deviation or confidence interval was provided by authors
[d] Geometric mean since authors did not provide arithmetic mean

Urinary excretion is the major route of elimination in rats (particularly females, which have much greater urinary elimination rates than males) (Vanden Heuvel et al., 1991; Kudo et al., 2001) and monkeys (Butenhoff et al., 2002, 2004a). The urinary excretion process involves glomerular filtration, secretion into the tubular fluid, and reabsorption from tubular fluid. Glomerular filtration of PFOA is limited by extensive binding of PFOA to plasma proteins. Renal

reabsorption of PFOA is thought to be driven by OAT proteins residing on membranes of proximal tubular cells (Yang et al., 2010; Han et al., 2012), and contribute to rat sex-related differences in renal clearance (Yang et al., 2009a). Unlike the rat, no gender differences in PFOA urinary elimination are apparent in the mouse (ATSDR 2009) or monkey (Butenhoff et al., 2004a). A dose-dependent (non-linear) upward trend for urinary excretion of PFOA was observed in male rats after dosing with capsules containing PFOA (Butenhoff et al., 2004b). Consistent with observations in animals given low doses, the relationship between external dose and internal dose (serum level) is linear in humans with environmental exposures to PFOA (Clewell, 2009); however, non-linear kinetics—as seen in animals at higher doses—might occur at higher human exposures. The relevance of urinary clearance in humans has been questioned, as renal clearance of PFOA was substantially lower than in animals (Harada et al., 2005). It is important to note that the non-linear toxicokinetics of PFOA have only been investigated in experimental animals following bolus oral exposures to PFOA, therefore, it is not clear if non-linear toxicokinetics are applicable to other modes of administration.

Biliary and fecal excretion also contributes to the elimination of PFOA, which may be subject to extensive enterohepatic recirculation (Vanden Heuvel et al., 1991; Kudo et al., 2001; Harada et al., 2007; Kudo et al., 2007). The relative importance of fecal excretion of PFOA depends on the urinary clearance. Fecal excretion is less important than urinary excretion in rats (Harada et al., 2007) and monkeys (Butenhoff et al., 2004a); however, data in rats indicate that the proportion of excretion occurring from this route becomes greater as doses and exposure durations increase (Cui et al., 2010). The relevance of this excretion route in humans is unclear. Harada et al. (2007) reported that the biliary excretion rate in four humans was significantly higher than serum clearance via urine and concluded that biliary excretion may represent a major excretion route in human; however, these data are not consistent with a case history that reported detection of PFOA in urine but not feces in a man with elevated serum PFOA levels (Genius et al., 2010).

In females, lactation can be a significant route of excretion, as shown in mice (Abbott et al. 2007) and in women (von Ehrenstein, 2009; Kim et al., 2011; Mondal et al., 2014; Mogensen et al., 2015a). Menstrual bleeding may be a significant route of excretion for women (Harada and Koizumi, 2009) and could potentially contribute to differences in serum levels measured between genders in humans.

8.5 Physiologically-based pharmacokinetic (PBPK) models

Several models with varying complexities have been developed to describe the kinetics of PFOA in both experimental animals and humans (Andersen et al., 2006; Tan et al., 2008; Loccisano et al., 2011, 2012a, 2012b, 2013). Due to the non-linear nature of PFOA pharmacokinetics, where faster clearance is seen with high bolus oral dosing, physiological models can provide an improved means of assessing cross-route and cross-species dosimetry for risk assessment.

The first model developed for PFOA was a biologically-motivated compartmental pharmacokinetic (PK) model for monkeys, which included saturable renal resorption of filtered PFOA (Andersen et al., 2006). Subsequent work to refine the model included the addition of a liver compartment and of time-dependent functions for protein binding and volume of distribution to fit high-dose monkey and rat oral and intravenous plasma, urine and feces kinetic data (Tan et al. 2008). PFOA PBPK models for adult rats (Loccisano et al., 2012a), monkeys (Loccisano et al., 2011) and humans (Loccisano et al., 2011) built upon the compartmental models. Further models for lactation and pregnancy were developed for rats (Loccisano et al., 2012b) and humans

(Loccisano et al., 2013). No models have been developed for mice, and no pregnancy and lactation models have been developed for monkeys. The basic structure of the PBPK model was the same for all three species, with only time-dependent changes in physiology included to describe pregnancy and lactation along with the time-dependency for plasma and tissue binding. The models included tissue compartments for gut (for oral/dietary dosing), skin (human and monkey model only; for dermal dosing), liver, fat, and kidney, with remaining body tissues grouped together (and not divided into richly and poorly perfused compartments). Biliary excretion and fecal elimination of the unabsorbed bolus oral dose or dietary exposure was added to the rat model; moreover, the rat version did not include a fat compartment (which became lumped with the rest of the body) or physiological gut, which was described as a one compartment non-physiological compartment. The PBPK model assumes only the free plasma fraction of PFOA is available for uptake into tissue, excretion or resorption. Elimination from plasma is described as glomerular filtration of the free fraction into a filtrate compartment. The filtered PFOA can either be eliminated in urine or resorbed into the kidney where it can return to systemic circulation. The models were relatively good at reproducing controlled dosing data for rats (dietary, oral gavage, and IV routes of exposure; Loccisano et al., 2012a), and monkeys (IV and oral gavage routes of exposure; Loccisano et al., 2011). Although no controlled dosing data were available for humans, biomonitoring data (for typically only a single timepoint) were within similar ranges as model simulations (using measured water concentrations for the biomonitored populations, along with assumptions on ingestion patterns; Loccisano et al., 2011).

The Loccisano models for humans (2011), monkeys (2011) and rats (2012a) were considered for use in the current assessment (see Section 10). Additionally, a mouse model that was scaled from the rat model was used, but it could not be validated. Further specifics of the models used for this assessment, including the values used for each of the physiological and chemical-specific parameters, are described in Campbell and Clewell (2013). Exposure was described as a constant intake of PFOA in humans (ingesting 1.5 L of water per day) and the model was allowed to reach steady state conditions prior to determining the predicted drinking water concentration consistent with the internal dose metric. To be conservative, the longest regularly reported half-life (3.8 years) was used, as this would result in the lowest predicted water concentration. The human was simulated as a 70 kg adult.

The Andersen et al. (2006) pharmacokinetic model was modified by Wambaugh and colleagues (2013) by adding a gut compartment for oral absorption and specifying an upper limit on tissue distribution. The authors used the model to translate dose regimes and available LOEL, NOEL, and benchmark dose (BMD) values from 9 *in vivo* studies of PFOA into internal dose metrics (area under the curve, average, and maximum serum concentrations). The data were modelled for cynomolgus monkeys, male and female Sprague-Dawley rats, and CD-1 and C57Bl/6 mice. A Bayesian approach was employed to model ranges of various physiological parameters. Wambaugh et al. (2013) identified relatively good concordance between predicted and measured (at study termination) serum concentrations, with few outliers, and identified that mean and maximum serum concentrations were most consistent among the various adverse endpoints. Dose metrics for points-of-departure (PODs) tended to be similar, indicating consistency between species and adverse outcomes. However, this model could not be fully validated based on existing human pharmacokinetic data.

Dermal and inhalation routes from contact with drinking water were not included in as potential routes of exposure in this effort, as their contribution to exposure is considered to be negligible (see Section 5.7).

8.6 Animal-to-human extrapolation

Although animal-to-human extrapolations are typically discussed after the selection of potential PODs, consideration has been given to this extrapolation earlier in the PFOA assessment, as the large variability between species can affect POD selection. The large differences in PFOA clearance between humans and other species must be accounted for when using animal studies as a basis for human risk assessments. The application of default approaches for animal-to-human extrapolation—such as the use of an interspecies uncertainty factor of 10 or allometric scaling—might not be sufficiently protective of humans, who receive longer internal exposures to target tissues. For this reason, chemical-specific approaches that can account for pharmacokinetic differences between species and nonlinear behavior of PFOA were considered for the risk assessment. These approaches include the application of chemical-specific adjustment factors (CSAFs) and PBPK modelling. A discussion and application of each of these approaches is outlined below, and further details can be found in a report prepared for Health Canada by Summit Toxicology (2015).

8.6.1 Derivation of CSAFs

A major advantage of the application of CSAFs over default uncertainty or allometric scaling factors is that the approach incorporates both species- and chemical-specific data. Despite this strength, the approach relies on single values representative of pharmacokinetics in each species, and does not necessarily account for non-linear pharmacokinetics.

IPCS guidelines on calculating CSAFs (IPCS, 2005) were applied to derive the toxicokinetic portion of the interspecies uncertainty factor (AK_{UF}). IPCS recommends that the default interspecies uncertainty factor of 10 be divided into values of 4.0 ($10^{0.6}$) for the toxicokinetic portion (AK_{UF}) and 2.5 ($10^{0.4}$) for the toxicodynamic component (AD_{UF}). The default AK_{UF} of 4.0 becomes replaced with any AK_{UF} values calculated based on chemical-specific data (IPCS, 2005). As data were not available to quantitatively evaluate toxicodynamic differences between species, no AD_{UF} was calculated.

To calculate the AK_{UF} (i.e., reflecting interspecies toxicokinetic differences), the following equation was used:

$$AK_{UF} = \frac{CL_{animal}}{CL_{human}}$$

where:

- AK_{UF} is the toxicokinetic component of the interspecies uncertainty factor; and
- CL is clearance in animals and humans (e.g., mL/kg bw per day).

In rats, a single oral dose of 0.1 mg/kg bw per day was provided to Sprague-Dawley rats (4/sex), who were followed for 22 days (males) or 5 days (females) (Kemper et al., 2003). Increased clearance and decreased half-life in female vs. male rats has been repeatedly demonstrated (see Section 5); females appear to have increased urinary excretion of PFOA over males, but the reason for this phenomenon is not clear. For this reason, AK_{UF} values are presented separately for each sex. Clearance rates for male and female rats were 23.1, and 777, respectively.

Clearance was not reported directly for monkeys, mice, or humans, and must be calculated based on species-specific half-life values using the following equation:

$$CL = \frac{Ln\ 2 \times V_d}{T_{½}}$$

where:

- CL is clearance in animals and humans (L/kg bw per day);
- ln 2 is the natural log of 2;
- V_d is the volume of distribution, which is the theoretical volume of blood in which the amount of a chemical would need to be uniformly distributed to produce the observed blood concentration; and
- $T_{½}$ is the half-life of a compound.

A half-life of 20.15 days was obtained from cynomolgus monkeys, which was averaged from monkeys provided a daily oral dose of 10 and 20 mg/kg bw for 6 months and followed for up to 147 days post-dosing (Butenhoff et al., 2004a). No volume of distribution was presented for monkeys in the chronic exposure study, but an average value of 190 mL/kg wbw as obtained from the single dose study that was presented in the same publication (Butenhoff et al., 2004a). Half-life values in mice were obtained from a study that provided a single oral dose of 1 or 10 mg/kg bw per day to CD-1 mice (3/sex/dose) that were followed for up to 80 days (Lou et al., 2009); the average value was 18.7 days. In humans, a half-life of 1387 days (3.8 years) was calculated from decreases in serum concentrations of 26 workers previously occupationally exposed to PFOA, with an average of 31 years of work and 2.6 years retired (Olsen et al., 2007). Despite the availability of half-life values for general populations, the occupationally-derived half-life was selected to be conservative, as it is the longest of half-life values estimated from longitudinal data (see Section 8.4). Volume of distribution values for PFOA are typically relatively consistent among species (Thompson et al., 2010); as no volumes of distribution were provided in the human and mouse studies, a value of 200 mL/kg bwwas used to represent a chemical that is mostly distributed extracellularly. Using the above equation, the resulting clearance values were 6.5 mL/kg bw per day in monkeys, 7.4 mL/kg bw per day in mice, and 0.1 mL/kg bw per day in humans. Using the human:animal ratios of clearance values described above, the calculated AK_{UF} values for PFOA for monkeys, mice, and average, male, and female rats were 65, 74, 231 and 7774, respectively.

Clearance was selected as the dose metric for the derivation of AK_{UF} values because data for this metric were readily available in most species, and could be calculated from half-life data in humans. Moreover, the use of clearance as a dose metric is a reasonable assumption for chemicals with long half-lives (i.e., in the order of days to years). Preliminary analyses have suggested that peak concentrations might be more predictive of PFOA toxicity for certain adverse endpoints (Haber et al., 2013); PFOA was not investigated in these analyses. Although this hypothesis was not further explored for the present analysis, using clearance is considered to be a more conservative alternative to using peak concentrations as the dose metric for AK_{UF} derivation. Finally, ratios of clearance levels are considered an appropriate basis for AK_{UF} derivation typically only if first-order kinetics are assumed to apply; however, as urinary clearance of PFOA is complex, this assumption might not be appropriate.

8.6.2 PBPK modelling

A typical approach for PBPK modelling is to use the model to calculate human-relevant PODs, which are derived by applying a human PBPK model to internal dose metrics (e.g.,

concentrations of PFOA in plasma) that were either calculated or measured in animals. With sufficiently validated models, this approach is considered to be the most robust approach for performing animal-to-human extrapolations. However, there is only medium confidence in human, monkey, and rat models, because different model codes were used for different species, and model fits to some datasets were not optimal. Moreover, the limited understanding of reasons for the observed sex differences in clearance in rats means there are weaknesses in how this could be addressed in the model. Finally, a major drawback in using the standard PBPK modelling approach is that human models have not been fully verified. Human data available for verification are limited to biomonitoring studies that allow for only rough estimates of exposure scenarios, and for which serum concentration measurements were typically only performed once (with a few populations with measurements at two timepoints) (see Section 5.6). Loccisano and colleagues did not develop PBPK models for mice, but Health Canada modelling approaches using mouse studies scaled the rat models using mouse data. As insufficient toxicokinetic data exist to verify whether the mouse model is appropriate, confidence in the mouse model is low. Therefore, there is insufficient confidence to use precise PBPK model results as points-of-departure for the risk assessments.

As an alternative approach to using the PBPK model for POD calculations, ratios of PBPK model-predicted dose metrics were used to calculate AK_{UF} values for relevant doses. This approach is thought to provide more robust estimates of the AK_{UF} than the traditional calculations described in Section 8.6.1, as it can address the non-linear kinetics of PFOA, identifying different values at steady state for different oral dose levels. In contrast, the AK_{UF} values calculated above are dependent on the specific doses and dose regimes used in the pharmacokinetic studies; uncertainties arise in the values obtained from these studies as the AK_{UF} values are calculated for animals administered single doses, which cannot account for non-linear kinetics, and the human data were not obtained from controlled dosing studies. Furthermore, clearance-based AK_{UF} values are ratios of low doses in humans to high doses in animals, and therefore exposures between the species are not of the same magnitude; using the PBPK model to derive the AK_{UF} allows for a more appropriate comparison of doses of the same magnitude.

The selected dose metric for the PBPK-derived AK_{UF} values was steady-state concentrations of PFOA. Steady-state concentration was selected as it is typically relevant for chemicals with long half-lives, and is a conservative assumption. Although alternative dose metrics—including peak concentrations (Haber et al., 2013)—might be more predictive of PFOA toxicity for certain adverse endpoints, additional work was not performed to further investigate the most appropriate dose metric. Plasma was selected as the relevant tissue for steady-state concentrations, as it is a metric that can act as a relevant proxy for a wide variety of organs, because blood flows to these different organs. Liver steady state concentrations were also incorporated into the assessment for comparison with plasma-based AK_{UF} values, as the liver has been identified as a primary organ for PFOA distribution in pharmacokinetic studies, and is also a potential target organ for toxicity. However, there is lower confidence in liver-based values than plasma values, as very little pharmacokinetic data exists to be able to perform verification of the PBPK model for liver concentrations. Liver concentrations could not be verified for humans, mice, and monkeys; for rats, minimal verification could be performed, but as data were available for only one to two timepoints in each study, the comparisons are not robust. Moreover, the use of plasma concentrations as a proxy for a variety of organs simplifies the application of AK_{UF} values in the assessment, which is already complex due to the use of AK_{UF} values that are species- and dose-specific.

Using the Loccisano PBPK models described in Section 8.5, steady-state plasma and liver concentrations were obtained at various doses in each of the species. The same doses were used for each of the species. For each dose run in the PBPK model, ratios of steady-state PFOA concentrations in humans vs. other species were calculated to obtain dose- and species-specific AK_{UF} values (Summit Toxicology, 2015). Steady-state concentrations and AK_{UF} values for plasma and liver at potentially relevant doses are listed in Table 2.

To select the appropriate AK_{UF} for each POD, the POD is rounded down to the nearest value in the oral dose column (i.e., values within the same order of magnitude are used). As discussed above, low confidence is placed on the mouse PBPK model. Until a PBPK model has been developed based on mouse data, the use of rat AK_{UF} values for mice is recommended (Summit Toxicology, 2015).

Table 2: PBPK dose metrics and PBPK-derived AK_{UF} values at relevant doses

Metric	Species	Oral dose (mg/kg bw per day)			
		0.001	0.01	0.1	1
Steady-state plasma PFOA predictions (µg/mL)	Human	8.74	86.1	706	1493
	Monkey	0.17	1.61	11.5	38.9
	Mouse	0.05[a]	0.47	4.74	47.4
	Rat	0.09	0.9	8.96	89.5
Steady-state liver PFOA predictions (µg/mL)	Human	19.2	189	1555	3289
	Monkey	0.37	3.58	25.5	88.3
	Mouse	NC	NC	NC	NC
	Rat	0.32	3.16	31.6	316
AK_{UF} derived based on plasma predictions	Monkey	52	53	62	38
	Mouse[b]	184	182	149	31
	Rat	97	96	79	17
AK_{UF} derived based on liver predictions	Monkey	52	53	61	37
	Mouse[b]	NC	NC	NC	NC
	Rat	61	60	49	10

[a]NC = could not be calculated due to limitations in the PBPK model
[b]AK_{UF} values for rats will be applied due to low confidence in the PBPK model

8.6.3 Recommended interspecies extrapolation approach

The recommended approach for interspecies extrapolation is the use of a PBPK model for the calculation of the AK_{UF} component of the CSAF, using steady-state plasma concentrations as the dose metric. The use of plasma concentrations ensures the relevance of the dose metric to adverse effects that occur in a variety of organs. Organ-specific dose metrics are typically preferred over blood-based values, whenever available; however, using the plasma metrics for this assessment provides consistency in the application of the AK_{UF} over a wide variety of adverse endpoints. AK_{UF} values were calculated for liver metrics for comparison with plasma values; the behaviour of PFOA in the liver was similar to that in the plasma, and AK_{UF} estimates were on the same order in both compartments. These results indicate that plasma values are appropriate proxies to be used for adverse hepatic effects. The liver-based values in rats were slightly lower than plasma-based values; however, greater confidence is placed in the plasma values because more data were available to verify this compartment of the PBPK model. The dose- and species-specific AK_{UF} values (for steady-state plasma concentrations) in Table 2 are applied in sections 10.1 and 10.2.

Although PBPK-derived AK_{UF} values were selected as the recommended approach for this assessment, several weaknesses have been identified. As described above, the AK_{UF} was plasma based rather than being organ specific. Steady state concentrations were also selected as the dose metric, as a conservative assumption relevant to the nature of the compound; detailed work was not performed to identify whether other dose metrics (e.g., peak concentrations) would be more appropriate for the various adverse endpoints. Steady state was also not reached in the human model at doses below 0.1 mg/kg bw per day. Furthermore, PBPK models have not been developed specifically for the mouse, and have been scaled instead from the rat, without further pharmacokinetic data for mice to be used for verification; the application of AK_{UF} values for rats is therefore recommended for use in mice in the absence of robust data in the species. AK_{UF} values for rats were derived based on male rats, which experience slower clearance of PFOA compared to female rats, in order to minimize the interspecies differences..

Despite these weaknesses, using the PBPK model to derive the AK_{UF} was thought to be equally or more robust when compared with other potential interspecies extrapolation approaches. The selected approach quantitatively incorporates pharmacokinetic differences among species; however, non-linear kinetics of PFOA are addressed, which cannot be done using the default AK_{UF}-derivation approach. Moreover, the PBPK-derived AK_{UF} values do not rely on individual pharmacokinetic studies that are often single-dose studies and not easily comparable among species. An ideal approach to address species differences would be to use blood concentrations of PFOA—either by using pharmacokinetic models to estimate the concentrations, as employed by Wambaugh et al. (2013), or using the values specifically measured in individual studies—as PODs for the assessment. However, the human PBPK models that would be used to extrapolate from this serum concentration cannot be fully verified based on existing human pharmacokinetic data, which decreases the level of comfort of using this approach to estimate precise PODs. The recommended approach was selected as a means of quantifying interspecies differences while addressing the non-linear kinetics of PFOA, without relying on precise PBPK-derived estimates of PODs.

9.0 Health effects

PFOA can be found as part of mixtures with other PFAS. Nonetheless, the vast majority of available studies on the toxicology of PFOA are carried out using the compounds individually. Information on the toxicology of mixtures is generally a data gap. However, the value of toxicity information that could be gained from mixture studies is limited to mixtures that do not significantly change in their composition, which is not the case for environmental mixtures of PFAS.

The summary of literature on health effects for PFOA is largely based on a comprehensive review conducted by a consultant (Sanexen Environmental Services Inc., 2013), and includes only the studies of direct relevance to the derivation of the health-based value. More specifically, this summary includes reports, reviews, and original papers published concerning PFOA in order to understand toxicity in humans exposed to PFOA via drinking water.

9.1 Effects in humans

9.1.1 Acute toxicity

No information related to acute or short-term epidemiological studies could be located.

9.1.2 Subchronic and chronic toxicity

Many quality epidemiological studies have been conducted. Large cohorts of workers and environmentally-exposed populations have been followed, with observations of significant relationships between exposure to PFOA and various health endpoints, such as haematological and clinical biomarkers (cholesterol, uric acid, serum liver enzymes), cancer (testicular, kidney), preeclampsia, immunological, endocrine (thyroid), renal functions, and fecundity (semen quality, birth weight) outcomes. Although all of these studies present limitations to some extent, including in terms of study design, bias and confounders, the human weight of evidence provides a strong argument in favor of detrimental health effects of the compound. This information should support the choice of a health endpoint; however, deriving a safe human exposure dose based on studies in humans remains a challenge because of the difficulties in characterizing a dose-response pattern with current studies. Their use in the present assessment is important to verify the relevance of animal to human extrapolation, and the monitoring of future studies will help in determining the accuracy of the observed associations.

Most environmental studies among PFAS-exposed populations were conducted in the Mid-Ohio Valley within the C8 Science Project. The C8 Science Panel was convened as a result of a class action settlement against DuPont, and is composed of independent epidemiologists jointly selected by lawyers for the community and DuPont. The C8 Health Project is the largest study of a population exposed to PFAS in drinking water, containing residents of Ohio and West Virginia communities surrounding the DuPont Washington Works plant. The health survey was conducted in 2005–2006 on approximately 69,000 individuals, including children and adults. The median PFOA serum concentrations in this population were 28.2 ng/mL, compared to 4.2 ng/mL in the general American population during the same period (Frisbee et al., 2009). Some longitudinal/prospective studies were also conducted among this population after a follow-up period. Some recent data in the project have not yet been published in peer reviewed literature; summaries of these studies—as well as panel conclusions and further information on the members of the panel—are available on the C8 Science Panel website (www.c8sciencepanel.org/panel.html).

9.1.2.1 Liver effects

Some level of association between PFOA exposure and alteration in liver enzymes has been observed, but no clear trend has been defined. A negative association for bilirubin and a positive association for aspartate transaminase (AST) and gamma glutamyl transpeptidase (GGT) have been reported in workers (Sakr et al., 2007a, 2007b). The clinical significance of results in the occupationally-exposed population is unclear, because the magnitudes of the changes were small and inconsistent (Steenland et al., 2010a). Moreover, the high number of endpoints analyzed also increases the likelihood of chance findings. Abnormal increases of liver enzymes (ALT and GGT) were reported in a cross-sectional study of adults aged 18 years or older in the general U.S. population, particularly in obese or in subjects with insulin resistance and/or metabolic syndromes (Lin et al., 2010). An association between serum PFOA levels and uric acid, ALT, GGT, and total bilirubin was reported in a cross-sectional survey in the general U.S. population recruited as part of NHANES (Gleason et al., 2015). Causal interpretation of general population results is limited by the study design, and multiple covariates were not included in the analysis.

9.1.2.2 Lipidemia

Increased exposure to PFOA has been associated with increases in serum cholesterol levels in several studies. A recent study including large cohorts of workers and environmentally-exposed residents found an increased risk of hypercholesterolemia with higher PFOA exposure compared to lower exposure (Winquist and Steenland, 2014). A small longitudinal study conducted in workers in Italy showed a positive association between PFOA and total cholesterol (Costa et al., 2009). A cross-sectional study and a longitudinal study were conducted among DuPont production workers. In the cross-sectional study, positive associations between PFOA and total cholesterol, LDL and VDLD were observed (Sakr et al., 2007a). In the longitudinal study, a negative association with bilirubin was observed, whereas positive associations between serum PFOA and total cholesterol were found after adjustment for cofounders (Sakr et al., 2007b).

Inconsistent results were found concerning the association between PFOA and cholesterol and lipoproteins in studies of fluorochemical production workers from U.S. and European 3M plants (Olsen and Zobel, 2007). No association between serum PFOA levels and plasma lipids (measured as triglycerides, HDL, LDL, and total cholesterol) was found as measured in a subsample of Canadians as part of the CHMS (Cycle 1 2007 – 2009) (Fisher et al., 2013). An increase in HDL level, a decreased total cholesterol/HDL ratio and no changes in total cholesterol and non-HDL cholesterol were observed in an occupational study (Olsen et al., 2012). Under the C8 Health Project, associations between serum PFOA and different blood components, such as an increase in cholesterol levels, were found in children and adults (Steenland et al., 2009, Frisbee et al., 2010, Kerger et al., 2011). Associations also occurred for lipoproteins (LDL, HDL), but were inconsistent between studies. A positive association with cholesterol was also found in the general U.S. population (Nelson et al., 2010), while another cross-sectional study conducted in the Mid-Ohio valley found no association (Emmett et al., 2006b). A longitudinal study conducted in 560 adults (2005–2006 with follow-up in 2010) indicated that the level of LDL decreased with the decreased serum PFOA level. A similar (but not statistically significant) pattern was found for total cholesterol; however, there were no changes for HDL or triglycerides (Fitz-Simon et al., 2013).

Overall, cross-sectional and longitudinal study data from the studies reviewed in the preceeding paragraphs indicate some level of association between serum PFOA and total cholesterol and/or LDL observed in different populations, although results were inconsistent in terms of exposure and effects observed. The strength of association was generally higher in the general population than in workers. This discrepancy could be due to the lack of lower range serum PFOA levels in occupationally exposed populations compared to the general population that is exposed to a wider range of PFOA levels (low to high). Considering the weight of evidence, the C8 Science Panel (2012a) concluded that there is a probable link between elevated cholesterolemia and PFOA. The clinical significance is uncertain, given the results inconsistencies, the unknown mechanism of action, the limits inherent to the study design, and the low magnitude of the changes. In particular, the conclusions and associations found from the cohort studies are limited by the risk of selection and misclassification bias, and uncontrolled variables, as some associations were lost when the participants were stratified by location (Costa et al., 2009; Winquist and Steenland, 2014).

9.1.2.3 Thyroid disruption

Inconsistent effects on thyroid hormone levels were observed in PFOA-exposed populations. An occupational study conducted among 552 employees in three plants found a negative association between PFOA and free thyroxine and a positive association between PFOA

and triiodothyronine, after adjusting for confounders (Olsen and Zobel, 2007). However, no adjustment for PFOS was performed, and the authors indicated there were no associations between PFOA and thyroid hormones because the results were inconsistent and within normal values. Moreover, no significant association of PFOA with T3, T4, or TSH was observed in two other occupational studies (Olsen et al., 1998, 2003b). Multiple cross-sectional studies (C8 Health Project and NHANES) have evaluated the relationship between environmental exposure to PFOA and thyroid functions. These studies have reported alterations in the levels of thyroxin, T3 uptake, serum albumin, hypothyroidism in children, thyroid disease in women (Chan et al., 2011; Knox et al., 2011b; Lopez-Espinosa et al., 2012). However, temporality cannot be established with the study design, and it is not possible to know the PFOA serum levels before the development of thyroid disease. A positive correlation between maternal serum PFOA levels and fetal TSH levels (but not T3 or T4 levels) was found after adjustment for covariates in a South Korean study (Kim et al., 2011).

9.1.2.4 Hypertension and cardiovascular outcomes

Cardiovascular outcomes were not consistently found to be associated with PFOA in cohort and cross-sectional studies (Sakr et al., 2007a; Costa et al., 2009; Steenland et al., 2010b). Elevated PFOA exposures were associated with higher cerebrovascular risk in an occupational cohort study (Lundin et al., 2009), and with cardiovascular, peripheral arterial disease, systolic blood pressure, and a marker of inflammation in cross-sectional studies of the general U.S. population (Shankar et al., 2012; Min et al., 2013). These results are equivocal and were not confirmed in other occupational cohort studies (Leonard et al., 2008; Sakr et al., 2009; Steenland and Woskie, 2012), nor in another cross-sectional study in the general population (Melzer et al., 2010). The C8 Science Panel concluded there is not a probable link between exposure to PFOA and diagnosed high blood pressure and coronary artery disease (including myocardial infarction, angina and coronary bypass surgery) (C8 Science Panel, 2012a).

9.1.2.5 Kidney effects

An association between adverse kidney effects and PFOA was observed; however, several factors limit the generalizability of the results to the general population. An increased risk of renal disease was found in a cohort mortality study conducted in 5,791 workers at a DuPont Chemical Plant (Steenland and Woskie, 2012). This level of evidence does not support a causal relationship between reduced kidney function and exposure to PFOA, particularly because altered kidney function could cause an increase in serum PFOA levels. Likewise, if PFOA induces adverse effects on the kidney, elevated PFOA levels may induce alterations of the kidney function. Moreover, only a small number of cases were observed in the occupational study (as attested by the large margin of error), and many workers were lost to follow-up, increasing the risk of selection bias, and was not supported by the results of an unpublished cohort study conducted in the same region (C8 Science Panel, 2012a).

9.1.2.6 Diabetes

The possible association between PFOA and diabetes was studied in mortality studies conducted among workers occupationally exposed to PFOA (Leonard et al., 2008, Lundin et al., 2009, Steenland and Woskie, 2012), and in two environmental studies regarding the prevalence of diabetes conducted within the C8 Health Project (MacNeil et al., 2009, C8 Science Panel, 2012b). The results from the occupational studies of employees of a 3M Company plant in Cottage Grove, MN, and of the DuPont polyfluorimer plant were inconsistent. Considering that diabetes is

usually not fatal (and is not necessarily indicated on death certificates) and that mortality may thus not be the best way to study diabetes (C8 Science Panel, 2012b), the findings based on diabetes prevalence within exposed residential populations may be more reliable. The data available from cross-sectional environmental studies conducted within the C8 Health Project (MacNeil et al., 2009; C8 Science Panel, 2012b) suggest that there is no link between PFOA and Type II diabetes. Additionally, no association between serum PFOA levels and metabolic function (calculated using fasting glucose and insulin levels) was found in a subsample of Canadians as part of Cycle 1of the CHMS (Fisher et al., 2013).

9.1.2.7 Immune suppression

Studies in environmentally-exposed populations have identified associations between PFOA levels and decreased antibodies against various illnesses, but the influence of PFOA exposure on clinical immunosuppression (i.e., incidence of illnesses) appears to be more tenuous. A study in children found an inverse relationship in immune response with PFAS exposure (Grandjean et al., 2012; Grandjean and Budtz-Jørgensen, 2013), with prenatal PFOA exposure negatively correlated with antidiphtheria antibody concentrations. A two-fold increase in the PFOA concentration in children in this population was associated with increased odds of not reaching antibody protective levels for tetanus and diphtheria after vaccination at 7 years old (Grandjean et al., 2012; Mogensen et al., 2015b) and 13 years old (Grandjean et al., 2017), although antibody levels had increased at 13 years compared to 7 years of age. The prospective nature, sample size, low risk of selection bias and defined objectives make the results relevant to the studied population; however, relevance to other populations is questionable, as increased exposure to the other potential immunosuppressants occurring in this region (Faroe Islands) was not accounted for in the study. Additionally, a portion of the 13-year old cohort had received booster vaccinations during emergency room visits, which could add variance to the study design (Grandjean et al., 2017). Increased PFOA exposure was also associated with decreased antibodies against rubella (in children from a prospective birth cohort of pregnant women from Norway, 2007–2008) (Granum et al., 2013) and influenza (for A/H3N2 only; in adults living in communities with PFOA-contaminated drinking water) (Looker et al., 2014). A higher risk of not attaining the recognized influenza A/H3N2 threshold was also observed (Looker et al., 2014). Cord blood IgE decreased with maternal PFOA in female infants in a prospective cohort study of pregnant women from 2002 to 2005 in Japan (Okada et al., 2012).

Hospitalizations for infections were not associated with prenatal exposure to PFOA in a Danish Cohort (1996–2002) (Fei et al., 2010a); however, positive associations between maternal PFOA and the incidence of colds and gastroenteritis were observed in the Norwegian birth cohort (Granum et al., 2013).

There is some level of consistency across studies since they generally observed an association between environmental PFAS exposure and immunomodulatory effects in children of different ethnicities. The diversity of the study settings and the prospective nature of the observational study designs lower the risks of spurious associations and enhance generalizability of the results. However, the dataset remains relatively small with only 5 studies, which were all observational, and the risk of residual confounding, bias and chance cannot be discounted. Although all studies investigated the effects on the immune system, the outcomes were not specific (measured different effects), no clear dose-response was observed, and most associations were weak. Conflicting results were common in the dataset, with variations observed between genders, specific microbial immunoglobulins, PFASs, infections, mother vs. child exposure, and child years, amongst other characteristics. These flaws impede concluding on a causative

mechanism, and the nature of the association remains unclear. Similarly, in a systematic and critical review of the epidemiological evidence on the association between various immune-related health outcomes and exposure to PFOA and PFOS, Chang et al. (2016) concluded that the available epidemiological evidence is insufficient to reach a conclusion about a causal relationship. The authors recommended further work to confirm these suggestive associations, including large, prospective studies with repeated exposure assessment in independent populations. On the other hand, the U.S. National Toxicology Program conducted a systematic review of the literature related to PFOA-induced immunotoxicity and concluded that PFOA is presumed to be an immune hazard to humans based on moderate level of evidence in humans and high level of evidence that PFOA suppressed the antibody response in experimental animals (see Section 9.2.2.3), and after considering biological plausibility (NTP, 2016).

9.1.2.8 Autoimmune disease

The C8 Science Panel (unpublished study) found an increased risk of inflammatory bowel disease with increased cumulative exposure to PFOA, which was driven by associations for ulcerative colitis. The C8 Science Panel concluded that there is a probable link between PFOA and ulcerative colitis (C8 Science Panel, 2012c). However, there is a risk of selection bias because the panel was able to include only a portion of the sample population—participants were only included if their medical charts could be accessed and if exposure estimates could be derived. These results are concerning and should be corroborated in future studies.

9.1.3 Carcinogenicity

Several occupational and environmental cohort studies have been developed for PFOA. The U.S. studies are considered to be the highest quality studies, because they were based on registries covering all residents in the study area, were conducted in districts with large and measured contrasts in PFOA concentrations in water, were linked to cancer registry data, had a large study population and were adjusted for major confounders.

A case-only study that investigated the relationship between cancer and exposure to PFOA through drinking water among Mid-Ohio residents living near the DuPont Teflon-manufacturing plant found that higher PFOA concentrations were associated with testicular and kidney cancers in some of the areas (Vieira et al., 2013). Amongst all cancer endpoints, the odds of testicular cancer were elevated only in one of the two areas with the highest concentration of PFOA in drinking water. There was no statistically significant increase in the odds of testicular cancer in the total exposed, in the other districts, or in any dose level categories (except for the highest dose category). Kidney cancer was increased significantly in one district and in the two highest levels of individual exposure. Associations were not significant for cancers of the breast, prostate, ovarian and non-Hodgkin lymphoma. Although this study shows some cancer associations with PFOA exposure, the meaning of the cancer results remain uncertain because no dose-response was observed, the variability of the risk estimates was high, the number of cases was low, there were multiple endpoints calculated with two modelling approaches (geographical and individual), and risk of exposure misclassification bias (the lack of residential history information to account for duration of exposure, latency, migration, and other issues regarding timing of exposure relative to cancer). The geographical analysis (testicular cancer findings in the Mid-Ohio study) shares the bias and risk of confounding inherent to ecological studies.

Cumulative exposure to PFOA (retrospective estimates of log serum concentration) was associated with an increased risk of self-reported testicular, kidney, and thyroid cancers in a large cohort (n = 32,254) of C8 Health Project participants and DuPont Teflon-manufacturing plant

workers above 20 years old (mean of 53 years old), after adjusting for smoking, alcohol consumption, sex, and education, and stratifying by age (Barry et al., 2013). Some cases were included in both the Barry et al. (2013) and in the Vieira et al. (2013) studies. The associations less likely to have occurred by chance alone (lowest p-values) were the ones between PFOA cumulative log serum concentration and testicular cancer (using the geographical and the water district individual approaches) and kidney cancer (using the residential analysis, individual approach) risks; while the associations with thyroid cancer and melanoma were considered to have occurred by chance based on poor statistical support. However, the associations were inconsistent between exposure quartiles and scenarios (e.g., residential, geographical), after follow-up (with very few, or no reported cases since 2005 regarding testicular cancer while background rates indicated that 5 cases were expected), and lost for testicular, kidney, and thyroid cancer risks, when compared with rates in the general U.S. population. Moreover, the 95% CI of the hazard ratios were large, the trends for testicular, kidney, and thyroid cancer risks were likely to have occurred by chance in at least one exposure scenario, Barry et al. (2013) mentioned the likelihood of exposure and outcome misclassifications, and the trends reported for testicular cancers were based on 6 cases only in the high exposure group (C8 Science Panel, 2012b; Barry et al., 2013).

In another occupational study conducted on workers in Minnesota, increased risk of prostate cancer mortality was observed; however, uncertainty persists because of the low number of cases, leading to poor precision in the risk estimates (Lundin et al., 2009). No statistically significant excess death from kidney, liver, pancreas, testicular, thyroid or breast cancer was found in another occupational study in West Virginia (Leonard et al., 2008) nor in the six-year follow-up of this cohort, except for excess of mortality by kidney cancer (Steenland and Woskie, 2012). Caution in the interpretation of these results is required, because the results were based on a small number of cases, and there was a considerable risk of selection bias.

No increase in the incidence of prostate, bladder, pancreas or liver cancer was found in a prospective cohort study conducted in the general population of Denmark, although the PFOA plasma concentrations [plasma concentration in men with cancer: 6.8 ng/mL (5–95% percentiles: 3.1–14.0); women with cancer: 6.0 ng/mL (5–95% percentiles: 2.6–11.0)] tended to be lower than in the U.S. cohorts [mean of 76.5 ng/mL (SD = 208) in male serum concentration and 42.3 ng/mL (SD = 118) in women, in a community exposed population reported by Frisbee et al. (2009); and, as high as a mean of 2,210 ng/mL (SD = 6.4) in the serum of PFOA manufacture employees, as reported in Olsen and Zobel (2007)] (Eriksen et al., 2009). Also, no evidence of a relationship for PFOA and breast cancer was found in a small-case control study in Greenlandic Inuit (Bonefeld-Jorgensen et al., 2011).

The C8 Science Panel (2012b) provides an assessment of the probable link between PFOA exposure and cancer. The "probable link" defined by the Science Panel means that "given the available scientific evidence, it is more likely than not that among class members a connection exists between PFOA exposure and a particular human disease." Testicular and kidney cancers were the particular types of cancer on which the association was based. However, a causal relationship cannot be determined because there were inconsistencies in the dataset, and the cancer risks were found to be equivocal across studies (lack of coherence). Moreover, the interpretation of the observed increased risk in testicular and kidney cancers is limited by the risk of residual confounding (because not all covariates and exposures to other contaminants were included in the model), the small case numbers, the uncertainties in exposure characterization (roughly estimated based on residency within a certain area), and the high number of outcomes included in the models, increasing the likelihood of chance findings. Similarly, a systematic and

critical review of epidemiological studies on the association between cancer risk in humans and exposure to PFOA and PFOS concluded that the epidemiological evidence does not support a causal association between cancer in humans and exposure to PFOA and PFOS (Chang et al., 2014). Based on these considerations, it would be premature to base a guideline on a cancer risk in epidemiology studies, without a stronger understanding of the potential causality between PFOA and the observed cancers. It is suggested to continue monitoring the epidemiological evidence to understand better the relationship between PFOA and cancer risk.

9.1.4 Developmental and reproductive toxicity

9.1.4.1 Developmental toxicity

Based on data available for gestational age, birth weight and length, head and abdomen or chest circumference, developmental milestones, miscarriage, and birth defects, previous reviews of developmental epidemiology studies concluded that developmental effects are not expected in humans (Olsen et al., 2009). Although increases in the risk of some of these outcomes occurred in individual studies, there was a lack of consistency across studies. Newer environmental studies have shown a positive association between prenatal exposure to PFOA and obesity in female offspring at age of 20 years (Halldorsson et al., 2012), and a negative association between maternal serum PFOA and birth weight and related anthropometric parameters at birth (Apelberg et al., 2007; Fei et al., 2007; 2008b; Andersen et al., 2010; Maisonet et al., 2012; Whitworth et al., 2012a).

The obesogenic properties of PFOA and other PFAS were investigated in a prospective cohort study with long-term follow-up (20 years) among pregnant women recruited within the Danish National Birth Cohort (1988–1989) and their offspring (Halldorsson et al., 2012). At 20 years of age, the female offspring from mothers with elevated serum concentration of PFOA were more likely to be overweight and to have a high waist circumference, after adjusting for mother's education, BMI, smoking, age, and infant birth weight. This large longitudinal study also showed alteration in serum biomarkers with an increase in maternal PFOA (increase in serum insulin and leptin and decrease in serum adiponectin in female offspring), suggesting biological plausibility. However, important confounders, such as physical activity and diet, were not included in the analysis, which is likely to result in spurious associations. The authors also indicated that loss to follow-up was the main limitation of the study. In a trans-Canada cohort study, no association was found between first-trimester maternal plasma PFOA concentrations and cord blood concentrations of leptin and adiponectin using data on 1705 mother-infant pairs recruited as part of the Maternal Infant Research on Environmental Chemicals (MIREC) Study (Ashley-Martin et al., 2017). However, the study authors cautioned against generalizing these findings to other Canadian populations because on average the study participants were older, more educated, had higher incomes, and were less likely to smoke than other women giving birth in Canada. More studies with better adjustments and follow-up in different populations would be needed to confirm the observed associations.

The data currently available regarding an association between PFOA and reduced birth weight are not consistent. Positive associations were reported among the general population in some studies, whereas no association was reported in other studies in the general population and in communities highly exposed to PFOA through drinking water. Longitudinal studies conducted in Danish and British general populations have found inverse associations between plasma PFOA levels and birth weight (Fei et al., 2007; Andersen et al., 2010; Maisonet et al., 2012). Similarly, PFOA exposure (measured as maternal PFOA plasma concentration) was inversely associated with birth weight in the MIREC Study (Ashley-Martin et al., 2017). A small unpublished study

based on birth certificates for C8 Health Project Community Cohort follow-up participants found some level of association between serum PFOA and term low birth weight; however, results were inconsistent and significance was not provided for all results. These studies represent concerning findings; however, the validity of the results still need to be confirmed, because these studies presented risk of selection bias, recall bias, chance findings, uncontrolled covariates, and absence of dose–response pattern. Moreover, no significant association between serum PFOA levels or PFOA water concentrations and low birth weight was found in cross-sectional studies or highly exposed communities (Nolan et al., 2009; Stein et al., 2009; Savitz et al., 2012a; 2012b). The C8 Science panel concluded that there is no probable link between PFOA and low birth weight (C8 Science Panel, 2011). Similarly, a systematic review of the epidemiology data conducted by Bach et al. (2015) concluded that the existing data are insufficient to confirm or reject an association between PFAS exposure and fetal growth. However, application of a novel systematic review methodology (called the Navigation Guide methodology), to determine whether developmental exposure to PFOA affects fetal growth in humans, concluded that there is sufficient evidence that developmental exposure to PFOA reduces fetal growth (Johnson et al., 2014). Additionally, considering that PFOA was found to be obesogen in mice (Hines et al., 2009) and humans (Halldorsson et al., 2012), and that *in utero* exposure to low doses of obesogens are known to reduce weight at birth (and induce obesity later in life; Holtcamp, 2012), a link between PFOA and low birth weight cannot be ruled out and close monitoring of new studies is recommended.

Investigation of different fetal growth indicators in association with PFOA exposure gave equivocal results. PFOA levels in maternal blood from the Danish National Birth Cohort (1996–2002) demonstrated negative associations with abdominal circumference (with a dose–response relationship) and birth length, after adjustment for multiple relevant cofounders (Fei et al., 2008b). These associations were obtained from large databases, and errors in exposure and outcome measurements and coding is possible. There is also a risk of residual confounding, as stated by the authors. Small negative associations were observed with head circumference, ponderal index and birth weight in a cross-sectional study of the general population (n = 293 singleton births) in Maryland (Apelberg et al., 2007). These must be considered with caution due to the limits inherent to the study design. Also, no associations between maternal serum PFOA levels and birth weight were observed in other general population studies in Canada (Hamm et al., 2010) or Japan (Washino et al., 2009).

There was no conclusive evidence of attention deficit/hyperactivity disorder (ADHD), learning disorder, motor developmental milestones, or behavioral or motor coordination problems based on results of cross-sectional studies conducted within the C8 Health Project and in the general population with exposure to PFOA (Fei et al., 2008a; Hoffman et al., 2010; Fei and Olsen, 2011; Stein and Savitz, 2011).

9.1.4.2 Puberty and sex hormone disruption

Serum PFOA levels were associated with delayed puberty in girls (reduced odds for the 2nd, 3rd, and 4th quartiles vs. the lowest quartile: delay of 142, 163 and 130 days for menarche and delay of 155, 158 or 183 days for combined high estradiol or menarche) in a cross-sectional study within the C8 Health Project (Lopez-Espinosa et al., 2011). Serum PFOA levels were inversely associated with testosterone in boys aged 6–9 years from the same cross-sectional study but were not associated with any sex hormones in girls of the same age group (Lopez-Espinosa et al., 2016). Further investigations are needed to establish the nature of the relationship, and identify the mechanisms behind these associations. No association was found between PFOA and serum

estradiol levels in perimenopausal or menopausal age groups of women (n = 25,957) from the C8 Health Project (Knox et al., 2011a).

9.1.4.3 Reproductive toxicity

No clear pattern of pregnancy-induced hypertension was observed in cohort studies on residents of the Mid-Ohio Valley within the C8 Health project and a cross-sectional study based on Washington County (Savitz et al., 2012b; Nolan et al., 2010; C8 Science Panel, 2011). Conversely, an unpublished prospective study presented by the C8 Science Panel (2011) addressed pregnancies among participants enrolled in the C8 Health Project. The four highest quintiles had higher odds of pregnancy-induced hypertension; however, there was no clear dose–response pattern. Based on this dataset, it would be premature to conclude a link exists between PFOA and pregnancy-induced hypertension.

Overall, no definitive association between PFOA and preeclampsia has been established. No increased occurrence of preeclampsia was observed in a study conducted among Mid-Ohio Valley residents (pregnant in 2000–2006) exposed to PFOA-contaminated drinking water (Stein et al., 2009). In a second study, risk of preeclampsia was examined among C8 Health Project participants from 1990–2005 (Savitz et al., 2012a). Self-reported preeclampsia was weakly associated with estimated serum PFOA at the time of pregnancy, and there was no dose–response pattern. The association was strengthened when restricted to pregnancies occurring after 1999.

An association between PFOA exposure and a reduction in fecundity has been observed; however, the studies were not robust and the results are inconclusive. A reduction of fecundity (increased time to pregnancy and irregular menstrual periods) was found to be associated with the plasma PFOA levels in 1,240 parous/nulliparous women; however, the information for multiple confounders was omitted from the analysis (e.g., sperm quality, occurrences of intercourses; Fei et al., 2009). Relative increases in the odds of subfecundity (time to pregnancy greater than 12 months) were reported in a case–control study on parous women enrolled in the Norwegian Mother and Child Cohort Study (with no increased odds of subfecundity in nulliparous women) (Whitworth et al., 2012b). Time to pregnancy and fecundity were not associated with serum PFOA levels in nulliparous women in a longitudinal cohort study in Denmark (Vestergaard et al., 2012). The lack of adjustment for confounders and of consistency in the results generates doubt on the link between lower fecundity and PFOA.

Three epidemiological studies reported associations of maternal serum PFOA with decreased duration of breast-feeding. A prospective cohort study recruited 1,400 pregnant women (randomly out of 43,045) within the Danish National Birth Cohort (DNBC, 1988–1989) and measured PFOA concentration in their plasma (Fei et al., 2010b). Duration of breastfeeding was reported 6 and 18 months after birth by phone interviews. The risk of breastfeeding for a shorter period was higher with increasing plasma PFOA. For example, the risk (adjusted hazard ratio) of shorter breastfeeding duration (weeks) for women with plasma PFOA > 7.0 ng/mL was 1.4 (95% CI 1.2–1.7) times higher than for those with plasma PFOA < 3.9 ng/mL, after adjusting for maternal age at delivery, pre-pregnancy BMI, maternal socioeconomic status, alcohol consumption and smoking (the trend for an increase in risk with increasing four-quartile comparison was also significant). Also, the odds (adjusted odds ratio) of weaning before 6 months of age was 1.23 (95% CI: 1.1–1.3) times higher for each 1 ng/mL increase in plasma PFOA when restricting the model to multiparous women (not significant in primiparous women), after statistical adjustments. A similar association was observed with weaning before 3 months of age. However, more studies would be needed to support these results, since PFOA plasma concentration was measured only one time, only 18% of eligible women participated in the

DNBC study, there is a risk of outcome recall bias (mothers might not report accurately the date of weaning), and the authors did not rule out the possibility that reverse causation could explain the association (especially since not observed in primiparous women, and considering that women that have breastfed longer can be more likely to breastfed longer their next infants, and that PFOA is excreted in breast-milk, lowering the plasma concentration). In a longitudinal cohort study of 468 pregnant women, recruited as part of the prospective pregnancy and birth cohort called Health Outcomes and Measures of the Environment (HOME) Study in the Cincinnati, Ohio area, Romano et al. (2016) measured serum PFOA, PFOS, perfluorononanoic acid (PFNA) and PFHxS concentrations. The duration of breastfeeding was reported in telephone interviews every three months until breastfeeding was discontinued. An association between higher maternal PFOA serum concentration and shorter duration of any breastfeeding (defined as the duration of breastfeeding notwithstanding supplementation with formula, liquids, or solid food) was observed, even after controlling for previous breastfeeding. The women in the cohort had higher average PFOA serum concentrations compared to pregnant women in NHANES. Notably, no association was found between PFOA exposure and exclusive breastfeeding; the authors suggested that other factors are likely responsible for the low rates of exclusive breastfeeding in this cohort. In a larger study of 1130 mother-child dyads from two birth cohorts recruited in the Faroe Islands, Timmermann et al. (2016) measured maternal serum PFOA, PFOS, PFHxS, PFNA, and perfluorodecanoic acid (PFDA) concentrations. The duration of breastfeeding, defined as the sum of exclusive and mixed breastfeeding, was reported either in an interview at offspring age 5 years or 18 months. An association between higher maternal serum PFOA and duration of both total and exclusive breastfeeding was observed; however, although the authors adjusted for the influence of other environmental chemicals (i.e., p,p'-DDE and polychlorinated biphenyls) they did not collect sufficient information to control previous breastfeeding. Neither study measured PFOA in drinking water.

The studies on the associations between PFOA exposure and sperm quality or hormone levels are sparse, inconsistent, and need to be corroborated in larger studies to better inform the possibility of a relationship. In a cross-sectional study conducted in 256 men from Durham, NC, a positive correlation was found between plasmatic PFOA and serum luteinizing hormone levels. No association between PFOA and semen quality measurements was found (Raymer et al., 2012). A positive association between PFOA and semen motility was identified in a group of men from one country, but not in the two other countries studied (Greenland, Poland and Ukraine). The author indicated the positive result might be attributable to chance findings (Toft et al., 2012). A prospective study has suggested that *in utero* exposure to PFAS may affect adult human male semen quality and reproductive hormone levels; however, there are concerns about the selection of participants (Vested et al., 2013).

Considering the weight of evidence, it is not possible to rule out possible adverse effects of PFOA on development and reproduction. Large cohort studies of offspring of mothers with high serum PFOA have reported an increased risk of lower abdominal circumference, length and weight at birth, as well as being overweight and having a high waist circumference 20 years after birth. These results are supported by effects on serum biomarkers (insulin, leptin, and adiponectin). Moreover, some evidence of reproductive toxicity has been observed, although to a lower extent. Higher level of exposure to PFOA has been associated with an increased risk of pregnancy-induced hypertension, preeclampsia, shorter duration of breastfeeding, altered sperm quality and reduced fecundity in longitudinal studies. However, the dataset for each individual outcome remains relatively small and definitive conclusions on the relationship between reproduction and developmental outcomes and exposure to PFOA are mainly limited by a lack of

consistencies in the results and the possibility of confounding. These limitations do not allow determining the nature of the association for the moment.

9.2 Effects on experimental animals

The vast majority of animal studies stated that exposure to PFOA was through its ammonium salt (APFO). Studies that did not state the specific salt used in their study were assumed to have used the ammonium salt, as this was the only compound used in studies that stated the PFOA salt. No studies stated whether the administered dose referred to the APFO compound, or specifically to the PFOA ion, separate from the ammonium salt. The summaries described herein use the concentrations and doses stated by authors. This approach is also used for quantitative assessments; however, as the PFOA ion contributes to 96% of the molar weight of APFO and is released from the compound upon exposure, only minor quantitative differences would result from using APFO and PFOA doses interchangeably.

9.2.1 Acute toxicity

The acute toxicity studies for PFOA or APFO indicate oral LD_{50} values of >500 and 680 mg/kg bw for male Sprague-Dawley and CD rats, respectively (Glaza, 1997), 250–500 mg/kg bw and 430 mg/kg bw for female Sprague-Dawley and CD rats, respectively (Dean and Jessup, 1978; Glaza, 1997), and <1,000 mg/kg for Sherman-Wistar rats of both sexes (Gabriel, 1976).

No mortality was reported in Sprague-Dawley rats of both sexes following inhalation exposure to PFOA at 18,600 mg/m^3 for 1 hour (Rusch, 1979).

The dermal LD_{50} in rabbits was determined to be >2,000 mg/kg bw or 4,300 mg/kg bw (Glaza, 1995; Kennedy, 1985). Higher values were obtained in rats, with a LD50 at 7,000 mg/kg bw in males and at 7,500 mg/kg bw in females (Kennedy, 1985).

Acute developmental neurobehaviour studies are discussed in Section 9.2.5.5.

9.2.2 Short-term exposure

Studies documenting the toxicity of PFOA after short-term oral exposure identified three main targets, namely reproductive and developmental effects (summarized in Section 9.2.5), hepatic effects, and serum lipid effects. Delayed mammary gland development appears to be the most sensitive target, with a LOAEL of 0.001 mg/kg bw per day (serum PFOA: 74.8 ng/mL; no NOAEL) in mice (White et al., 2011) (see Section 9.2.5.1). The lowest LOAELs for hepatic effects were 0.15 mg/kg bw per day in adult mice (Kennedy, 1987; NOAEL of 0.05 mg/kg bw per day). Serum lipid effects were observed at ≥0.3 mg/kg bw per day in rats (Loveless et al., 2006, 2008). This section will focus primarily on these key effects observed at the lowest levels, and will only briefly discuss other types of changes observed in animals.

9.2.2.1 Hepatic effects

The hepatic effects observed at the lowest levels in short-term studies were hepatocellular hypertrophy in male rats and mice (Perkins et al., 2004; Loveless et al., 2008) and increased liver weight in rats (Kennedy, 1987) and mice (Loveless et al., 2006). These studies will be described in greater detail, and other hepatic effects observed at higher levels will be discussed only briefly.

The lowest LOAEL for liver weight was in pups exposed *in utero* to 0.1 mg/kg bw per day on gestational days (GD) 1–17; further details on this study are provided in Section 9.2.5.4. In adults, the studies that observed liver weight increases at the lowest levels were Loveless et al. (2006; LOAEL of 0.3 mg/kg bw per day) and Kennedy (1987; LOAEL of 0.15 mg/kg bw per day and NOAEL of 0.05 mg/kg bw per day). These studies are described below.

A LOAEL of 0.3 mg/kg bw per day (no NOAEL) was identified in male CD-1 mice (n=10/dose) after oral exposure to PFOA (0, 0.3, 1, 3, 10 or 30 mg/kg bw per day) for 14 days (Loveless et al, 2006). Different preparations of PFOA were used (branched, linear, or combined branched/linear APFO). The LOAEL refers to increased relative liver weight in mice treated with linear and with branched APFO (most studies expose animals to a mixture that is predominantly linear APFO). Liver weights were also increased in rats, but only at ≥1 mg/kg bw per day. Absolute liver weights were significantly increased in at least one APFO form at ≥1 mg/kg bw per day in both species. In both rats and mice, the overall liver weight responses to linear and branched forms of PFOA were similar. The same researchers performed a 29-day study with linear APFO, and found no increases in liver weight at 0.3 mg/kg bw per day—absolute liver weight was increased in both species at ≥1 mg/kg bw per day, and relative liver weight was increased at ≥1 mg/kg bw per day in mice and ≥10 mg/kg bw per day in rats (Loveless et al., 2008). The latter study contained a high-dose (i.e., 30 mg/kg bw per day) recovery group (with exposure cessation at test days 23 in rats and 24 in mice), with liver weight increases still present at termination of the study in both species.

In the study with the lowest LOAEL for the endpoint (Kennedy, 1987), male and female CD rats were exposed to APFO at 0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 30 ppm in food (using Health Canada default assumptions of 1 ppm in food = 0.05 mg/kg bw per day in rats [Health Canada, 1994], the approximate doses were 0.0005, 0.0015, 0.005, 0.015, 0.05, 0.15, 0.5, and 1.5 mg/kg bw per day) for 21 days. Increased absolute and relative liver weight was observed at ≥0.15 mg/kg bw per day in both males and females, with a NOAEL of 0.05 mg/kg bw per day. The same study also exposed rats for 14 weeks, and observed increases at the highest dose in the study (30 ppm in food, equivalent to 1.5 mg/kg bw per day).

A wide variety of short-term studies observed increases in liver weight in adult animals at higher doses. These effects were observed in rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Staples et al., 1984; Kennedy et al., 1986; Biegel et al, 2001; Perkins et al., 2004; Cui et al., 2009), in mice (Metrick and Marias, 1977; Liu et al., 1996; Yang et al., 2001, 2002; Lau et al., 2006; Abbott et al., 2007; Wolf et al., 2007; DeWitt et al., 2008; Son et al., 2008; Qazi et al., 2010; Yahia et al., 2010) and in monkeys (Thomford, 2001a; Butenhoff et al., 2002). Increases in liver weight appear to be generally reversible, as they were no longer observed after the exposure period in most studies with a recovery period (Palazzolo, 1993; Thomford, 2001a; Butenhoff et al., 2002; Perkins et al., 2004). In contrast, in a study of mice exposed for 10 days, the effect was still observed 10 days after ceasing exposure (Yang et al., 2001). Increases in liver weight were also observed in mice exposed *in utero* or peripubertally to PFOA; descriptions of these results can be found in Section 9.2.5.4.

The study that observed hepatocellular hypertrophy at the lowest levels exposed male Sprague-Dawley rats (n=10 per group) and male CD-1 mice (n=19–20 per group) to 0, 0.3, 1, 10, or 30 mg/kg bw per day of PFOA by for 29 days (Loveless et al., 2008). Incidence and severity of hypertrophy increased with dose, with effects of greater severity in mice. In the high-dose recovery group, hypertrophy persisted at the end of the study, despite cessation of exposure on study days 23 (rat) or 24 (mouse).

The most robust study with an observed NOAEL for increased liver weight and hepatocellular hypertrophy exposed male Crl:CD rats (n=55 per dose) to 0, 0.06, 0.64, 1.94, and 6.5 mg/kg bw per day in food (Perkins et al., 2004). Two control groups were included in the study—one set of controls pair-fed with the high dose group, and one *ad libitum* feeding group. The rats were divided into sacrifice groups exposed for a duration of 4, 7, or 13 weeks (n=15 per dose per duration), and each dose (and the *ad libitum* controls) had a recovery group that was

observed for 8 additional weeks after cessation of exposure at week 13 (n=10 per dose). Significant dose-related increases in incidence and severity of hypertrophy were observed (Table 3). Most rats exposed to ≥0.64 mg/kg bw per day had minimal-to-slight hypertrophy, which was most severe in the high-dose group exposed for 13 weeks; effects did not persist in recovery groups. Hypertrophy was not accompanied by degenerative lesions in the liver. Relative liver weight was increased at ≥0.64 mg/kg bw per day in the 4-week group and at ≥1.94 mg/kg bw per day at the longer durations; the effect did not persist in the recovery groups. Thus, a NOAEL of 0.06 mg/kg bw per day for lack of hepatocellular hypertrophy is derived.

Table 3: Incidence and severity of hepatocellular hypertrophy in Perkins et al. (2004)

Dose (mg/kg bw per day)	Duration of exposure (wk)	Grade of hypertrophy			
		None	Minimal	Slight	Moderate
Ad libitum control	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	10	0	0	0
Pair-fed control	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	N/A	N/A	N/A	N/A
0.06	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	10	0	0	0
0.64	4	3	12	0	0
	7	3	12	0	0
	13	2	13	0	0
	13 (recovery)	10	0	0	0
1.94	4	0	7	8	0
	7	0	14	1	0
	13	1	12	2	0
	13 (recovery)	10	0	0	0
6.5	4	0	5	9	0
	7	0	6	9	0
	13	0	3	12	0
	13 (recovery)	10	0	0	0

Higher dose studies also identified hepatocellular hypertrophy in mice (Yahia et al., 2010) and rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Cui et al., 2009).

Other histological effects observed in the liver at higher doses in short-term studies include single cell and focal necrosis in mice (Loveless et al., 2008; Yahia et al., 2010) and rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Loveless et al., 2008; Cui et al., 2009); increased mitosis in mice (Yahia et al., 2010); mild calcification in mice (Yahia et al., 2010); cytoplasmic enlargement of hepatocytes in rats (Metrick and Marias, 1977); and cytoplasmic

vacuolation in rats (Cui et al., 2009). Histological effects were also observed in livers of rats exposed to PFOA for 2 years; these effects are described in Section 9.2.3.

Changes in serum levels of markers of liver damage were observed in mice at higher levels than the LOAELs for increased liver weight and hepatocellular hypertrophy. These effects included increased ALT (Son et al., 2008; Yahia et al., 2010), increased AST (Son et al., 2008; Yahia et al., 2010), increased GGT (Yahia et al., 2010), and increased ALP (Yahia et al., 2010; Qazi et al., 2010). Increased ALP was also observed in rats (Kennedy et al., 1986).

Dietary fat content has been proposed to contribute to the increased risk for PFOA-induced hepatotoxicity (Tan et al., 2013). Male Balb/c mice on a regular diet or a high fat diet were dosed with 0, 5, 10 or 20 mg/kg bw per day PFOA for 40 days. High fat diet alone did not cause any liver damage; however, high fat diet exaggerated PFOA-induced hepatotoxicity, including increased plasma AST and ALT levels, more severe hepatocellular hypertrophy, lipid droplet accumulation and necrosis and inflammatory cell inflammation. These results were supported by gene expression and metabolomics analysis that showed that a combination of high fat diet and PFOA significantly perturbed hepatic metabolism with activation of PPARα and hepatic inflammation.

9.2.2.2 Serum lipid effects

Alterations in serum lipid parameters were some of the effects observed at the lowest PFOA exposure levels in adult animals in short-term studies. The effects include changes in HDL, total cholesterol and triglycerides. Total cholesterol and HDL were decreased in most studies of mice (Loveless et al., 2006, 2008; Qazi et al., 2010) and rats (Loveless et al., 2006, 2008), but total cholesterol (along with phospholipid and free fatty acid) was increased in one high-dose study in mice (Yahia et al., 2010). Triglycerides were observed in mice to be increased in certain studies (Loveless et al., 2006; Yahia et al., 2010) and decreased in another (Loveless et al., 2008). They were decreased in both rat studies (Loveless et al., 2006, 2008).

The studies in which serum lipid changes were observed at the lowest levels were both performed by Loveless et al. (2006, 2008), which are described in greater detail in Section 9.2.2.1. The lowest LOAELs were in rats, with values of 0.3 mg/kg bw per day for decreases in cholesterol and triglycerides (Loveless et al., 2006, 2008) and 0.3 mg/kg bw per day for decreases in HDL (Loveless et al., 2008; in the 2006 study by Loveless et al. the LOAEL was 3 mg/kg bw per day). Most of the effects were only observed at higher levels in mice—in Loveless et al. (2008), the LOAELs were 1 mg/kg bw per day for decreased HDL and 10 mg/kg bw per day for decreased total cholesterol and triglycerides, and most of the LOAELs in Loveless et al. (2006) were 3 mg/kg bw per day. An exception was for triglyceride increases specifically in the linear/branched APFO-exposed mice, as effects were observed at ≥0.3 mg/kg bw per day.

The effects on cholesterol and HDL did not appear to be persistent upon cessation of exposure; total cholesterol and HDL levels returned close to control levels when exposure to 30 mg/kg bw per day dose was ceased at days 23 (rat) or 24 (mouse) in the 29-day study (Loveless et al., 2008). Triglyceride levels in mice continued to rise following cessation of exposure but triglyceride levels in rats did not change following cessation of exposure relative to the rats with continuous exposure; in both species triglyceride levels following cessation of exposure were significantly lower than controls.

Loveless et al. (2006) investigated different forms of PFOA (branched, linear, or combined branched/linear). The linear form (the form most commonly appearing in PFOA mixtures used in studies) appeared to have the lowest LOAELs in rats for all lipid endpoints. In

mice, the PFOA form did not appear to have any effect on HDL or cholesterol, but the linear/branched mixture appeared to be the only form that had any effect on triglycerides.

Additional studies saw increases in triglyceride, total cholesterol, and free fatty acid at 10 mg/kg bw per day in ICR mouse dams (Yahia et al., 2010) and reduction in total serum cholesterol in male C57BL/6 mice (Qazi et al., 2010).

Dietary fat content has been proposed to contribute to the observed differences in effects of PFOA on serum lipids in rodents versus humans (Tan et al., 2013; Rebholz et al., 2016). Consistent with the studies above, Tan et al. (2013) reported decreases in both serum cholesterol and triglycerides in a dose-related fashion in mice on the regular fat content diet, whereas serum cholesterol and triglycerides were unaffected by PFOA in mice on a high fat diet. Also, male and female C57BL/6 and male BALB/c mice fed a high fat diet containing 3.5 ppm PFOA (equivalent to 0.56 mg/kg bw per day) had significant increased plasma cholesterol (Rebholz et al., 2016). The response in C57BL/6 mice was more exaggerated compared to BALB/c mice, which the authors explained as strain-specific effects.

9.2.2.3 Other effects

Other effects besides hepatic and serum lipid effects in short-term studies of adult animals occurred at PFOA exposure levels of ≥1 mg/kg bw per day. The studies are described briefly below.

At ≥1 mg/kg bw per day, increased kidney weight was observed in several studies of mice (Yahia et al., 2010) and rats (Goldenthal et al., 1978; Butenhoff et al., 2004b; Cui et al., 2009). In many of the studies, the increases were only in relative, but not absolute, kidney weight. The effects were also often accompanied by histological effects (Butenhoff et al., 2004b; Cui et al., 2009; Yahia et al., 2010).

Changes in weight of neurologically-relevant organs occurred at ≥3 mg/kg bw per day in monkeys. These observations were an increased group mean weight of the pituitary gland and decreased absolute brain weight (Goldenthal et al., 1978). The only other neurological effect noted in adult animals exposed for a short-term duration was reduced activity and lethargy in rats (Cui et al 2009).

Indications of immunosuppression occurred at ≥0.49 mg/kg bw per day in mice. More specifically, Son et al. (2009) reported decreased numbers of splenic lymphocyte populations ($CD4^- CD8^+$, $CD4^+ CD8^+$) in ICR mice dosed with ≥0.49 mg/kg bw per day PFOA in drinking water for 21 days. No NOAEL was identified. Additionally, PFOA exposure has been shown to induce decreased immunoglobulin levels, changes in cellularity and subtypes of immune cells, and changes in cytokine expression (Yang et al., 2001, 2002; DeWitt et al., 2008; Loveless et al., 2008; Son et al., 2008, 2009; Qazi et al., 2009, 2010). Splenic and thymic atrophy were also observed in mice (Yang et al., 2001, 2002; Loveless et al., 2008; Son et al., 2009; Qazi et al., 2009), and histological changes were observed in these organs in rats (Cui et al., 2009; Qazi et al., 2009; Son et al., 2009). Studies in mice also indicated a possibility for hypersensitivity due to exposures to PFOA, with a dose-related increase of serum histamine levels at ≥1 mg/kg bw per day (Singh et al., 2012) and increased IgE after challenge with OVA in mice exposed dermally to ≥18.75 mg/kg bw per day (Fairley et al., 2007). The U.S. NTP (2016) concluded that there is high confidence that exposure to PFOA is associated with antibody response suppression in animals based on consistent suppression of the primary antibody response in mice.

Effects on other organs were observed at ≥10 mg/kg bw per day. These effects included hypertrophy and vacuolation of the zona glomerusa of the adrenal gland in rats (Butenhoff et al., 2004b); pulmonary congestion, thickening of epithelial walls, cell infiltration and vasodilation in

rats (Cui et al., 2009); pulmonary edema in rats (Kennedy et al., 1986); and decreased heart weight in monkeys (Goldenthal et al., 1978).

Two studies reported changes in thyroid hormone levels. Butenhoff et al. (2002) reported decreased free and total T3 and T4 in monkeys exposed for 6 months. Decreases in total and free T4 were observed at most timepoints, including termination, for monkeys exposed to 10 or 20–30 mg/kg bw per day; at termination (and not earlier timepoints), a significant decrease was also observed for total (but not free) T4 at the 3 mg/kg bw per day dose. Decreased total and free T3 was observed at most timepoints (including termination) in monkeys exposed to 20–30 mg/kg bw per day; decrease in total (not free) T3 was also observed at two mid-study timepoints, but not at termination, in low-dose monkeys. The effects were accompanied by significant increases in TSH at study termination in monkeys exposed to 3 or 10 mg/kg bw per day (no effect at high dose). The 4-week range-finding study for the Butenhoff monkey study (Thomford, 2001b) did not note any effects on TSH, or in total or free T3 or T4. Martin et al. (2007) measured thyroid hormone (total and free T4, and total T3) levels in male Sprague-Dawley rats one day following daily administration of 20 mg/kg bw per day PFOA or vehicle control by oral gavage for one, three, or five days. Levels of free and total T4 and total T3 were significantly reduced at all three time points, although the magnitude of decreases was smaller for T3 compared to T4.

Decreased bodyweight or bodyweight gain was observed in many different studies. The effects were observed at LOAELs of 3 mg/kg bw per day in rats (Metrick and Marias, 1977; Goldenthal et al., 1978; Staples et al 1984; Kennedy et al., 1986; Butenhoff et al., 2004b; Cui et al., 2010), 3 mg/kg bw per day in mice (Christopher and Marias, 1977; Lau et al., 2006; Wolf et al., 2007; Asakawa et al., 2008; Son et al., 2008; White et al., 2009; Yahia et al., 2010; Suh et al., 2011), and 30 mg/kg bw per day in monkeys (Goldenthal et al., 1978). This effect was accompanied by a decrease in food consumption at ≥5 mg/kg bw per day in rats (Metrick and Marias, 1977; Butenhoff et al., 2004b; Cui et al., 2009) and at 20.7 mg/kg bw per day in mice (Asakawa et al., 2008).

Clinical signs observed in studies included soft stools, diarrhea, and frothy emesis in monkeys (Goldenthal et al., 1978) and roughed fur, muscle weakness, and cyanosis in mice (Christopher and Marias, 1977).

Few studies reported increased mortality in animals. The endpoint was observed at high levels in studies of rats (Metrick and Marias, 1977; Staples et al., 1984; Butenhoff et al., 2004b), mice (Christopher and Marias, 1977), and monkeys (Goldenthal et al., 1978b; Thomford, 2001a; Butenhoff et al., 2002).

9.2.3 Long-term exposure and carcinogenicity

Two chronic toxicity studies in laboratory animals were identified for the oral route. No inhalation or dermal study was located. As was observed in long-term carcinogenicity studies, the liver was the most sensitive target organ in the chronic studies (LOAEL = 1.3 mg/kg bw per day in male rats for increased serum liver parameters) (3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b). Other effects observed in rats after chronic exposure to PFOA include an increased incidence of hyperplasia and tumors in various tissues (mammary gland in females, Leydig cells, pancreas and liver in males) and alteration of serum hormone levels (3M, 1983; Sibinski, 1987; Biegel et al., 2001).

Only one study included more than one dose – this study was conducted by 3M Company and the results were presented as part of laboratory reports (3M, 1983; Sibinski, 1987) and a peer-reviewed publication (Butenhoff et al., 2012b). A LOAEL of 1.3 mg/kg bw per day (no NOAEL) in male rats was identified for liver toxicity. Sprague-Dawley rats (50/sex/group) were given

APFO at 0, 30 or 300 ppm in the diet for 2 years (0, 1.3 or 14.2 mg/kg bw per day for males; 0, 1.6 or 16.1 mg/kg bw per day for females). The LOAEL of 30 ppm was based on significant increases in serum liver parameters in males (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and albumin at many timepoints, which were still elevated—although not significantly at the low dose—at termination) and a dose-related increase of chronic sialadentitis in the salivary gland of males. Hepatocellular hypertrophy was also elevated in both male treatment groups, with significance only being reached at the high dose (incidence was 0% in controls, 12% at the low dose, and 80% at the high dose). Other effects in males include a dose-dependent increased incidence of Leydig cell adenomas, statistically significant at 300 ppm (14.2 mg/kg bw per day). In female rats, the first data analysis indicated a dose-dependent increase in mammary fibroadenomas, statistically significant at ≥30 ppm; however, a more recent analysis was conducted by a pathology working group using current diagnostic criteria, which concluded that PFOA treatment did not result in proliferative lesions in the mammary tissues (Hardisty et al., 2010; Butenhoff et al., 2012b). Non-neoplastic changes in the liver (hepatocellular hypertrophy, portal mononuclear cell infiltrate or cystoid degeneration at the high dose) and the lungs (alveolar macrophages and hemorrhage at the high dose) were observed, and proliferative acinar cell lesions were observed in the pancreas of rats at the high dose. PFOA did not increase the incidence of neoplastic or non-neoplastic lesions in the other organs (thyroid, pituitary, adrenal gland, kidney, uterus).

A follow-up study was performed in male CD rats given APFO in the diet (0 or 300 ppm) for 2 years (average daily dose of 13.6 mg/kg bw per day) (Biegel et al., 2001). Two controls groups were used; the first was an *ad libitum* fed (AL) group, and the second was a pair-fed (PF) group in which the food intake was controlled to match the food intake of the PFOA exposed group. Rats were evaluated at 1 and 3 months and at every 3 months for hormone status, cell proliferation in liver, testis and pancreas and hepatic peroxisome proliferation. Treatment with PFOA increased the relative liver weight at all time points (except at 24 months) compared to both controls. Hepatic β-oxidation activity was significantly elevated at all times, but cell proliferation was not increased in the liver. Pancreatic acinar cell proliferation was increased at 15, 18, and 21 months. Serum estradiol was increased during the first year of the study, serum LH at 6 and 18 months, and serum FSH at 6 months; changes in serum testosterone did not show any consistent pattern. There was a significant increase in tumours in treated animals when compared with one or both of the control groups for Leydig cell adenomas, hepatic adenomas, acinar cell adenomas and combined pancreatic adenomas and carcinomas. An increased incidence of hyperplasia was also observed in Leydig cells and acinar cells (Biegel et al., 2001).

Although the LOAEL for liver endpoints was higher in chronic studies than in shorter-term studies, the comparisons are difficult to make, as the lowest dose used in the chronic study (1.3 mg/kg bw per day) is higher than the lowest LOAELs for liver effects in the shorter-term studies (i.e., 0.1–0.3 mg/kg bw per day). However, some endpoints observed at these low doses in shorter duration studies, most notably hepatocellular hypertrophy in male rats (Loveless et al., 2008) were not observed at the lowest doses used in the chronic studies (i.e., the chronic NOAEL for this endpoint is 1.3 mg/kg bw per day).

9.2.4 Genotoxicity

The genotoxicity database indicates that PFOA compounds are not mutagenic, and generally not genotoxic (U.S. EPA, 2005; UK HPA, 2009; Environment Canada and Health Canada, 2012).

9.2.4.1 In vitro *findings*

Testing of PFOA (or its ammonium or sodium salts) produced no evidence of genotoxic activity in several Ames bacterial mutation assays and in three *in vitro* chromosomal aberration tests (two in hamster cells and one in human cells) (Environment Canada and Health Canada, 2012). More recently, PFOA (tested up to 1,000 µM) had no mutagenic activity in the *umu* test (Oda et al., 2007) and in the Ames test, with or without S9 metabolic activation (Fernandez Freire et al., 2008). PFOA did not increase oxidative DNA damage (as measured in a comet assay) in rat testicular cells exposed to 100 and 300 µM for 24 hours (Lindeman et al., 2012). In human hepatoma HepG2 cells, PFOA (up to 400 µM for 24 h) did not induce ROS generation, DNA single strand breaks or micronucleus (Florentin et al., 2011). In another study using human HepG2 cells, PFOA induced slight ROS generation (0.4-2,000 µM) without generating detectable DNA damage (200 µM) (Eriksen et al., 2010).

In contrast, positive results were obtained in one chromosome damage test in hamster cells and one micronucleus assay in human cells *in vitro*, and PFOA caused oxidative DNA damage in human hepatoma cells in culture (Environment Canada and Health Canada, 2012). PFOA (200 µM) led to mutagenicity induction in human-hamster hybrid (A_L) cells and mitochondria-dependent ROS was shown to play an important role in this process (Zhao et al., 2011b).

9.2.4.2 In vivo *findings*

Testing of PFOA (or its ammonium or sodium salts) for genotoxic potential produced no evidence of activity in three *in vivo* bone marrow micronucleus tests in mice (up to 5,000 mg/kg bw per day). PFOA caused oxidative DNA damage in the liver of rats treated through the oral route (200 ppm in diet for 2 weeks) or the intraperitoneal route (100 mg/kg bw, once) (Environment Canada and Health Canada, 2012).

9.2.5 Reproductive and developmental toxicity

The reproductive and developmental database for PFOA is robust. Two multi-generational studies have been conducted in rats (Butenhoff et al., 2004b/York et al., 2010; White et al., 2011), and reproductive and developmental parameters have been investigated in many one-generation studies in rats, mice, and monkeys. Furthermore, early life or peripubertal exposures were performed in mice (Johansson et al., 2008, 2009; Yang et al., 2009b; Zhao et al., 2010; Dixon et al., 2012).

The most sensitive effects identified are delayed mammary gland development in the offspring of mice (Macon et al., 2011; White et al., 2011), obesity in the female offspring of mice at adulthood (Hines et al., 2009), uterine effects in immature female mice (Dixon et al., 2012), liver weight changes in pups (Abbott et al., 2007; Macon et al., 2011; Onishchenko et al., 2011) and altered neurobehaviour (Johansson et al., 2008, 2009; Onishchenko et al., 2011). These effects were all observed at exposure levels of ≤0.3 mg/kg bw per day, and will be discussed in greater detail. Other reproductive and development effects occurred at higher doses, and will only be described briefly in this section.

9.2.5.1 Mammary gland effects

Changes in mammary gland development (MGD) have only been studied in mice. Delayed MGD was consistent in 1-generation (White et al., 2007, 2009; Wolf et al., 2007; Macon et al., 2011), 2-generation (White et al., 2011), and peripubertal (Yang et al., 2009; Zhao et al., 2010) studies, and has been observed to be significantly different than controls at every dose level studied (≥0.001 mg/kg bw per day) in maternal and F1 generations (both as offspring and dams).

The studies primarily identified delayed MGD development (noted to be as long as 10 days in a study that exposed mice to 5 mg/kg bw per day [White et al., 2007]) and lower MGD scores[1] at many different time points. The specific mammary gland structures that were affected included ducts (reduced and delayed ductal elongation and branching), terminal ducts (decrease in number of stimulated TDs), terminal end buds (delayed time of appearance, excess of and decrease in number of TEBs), and longitudinal epithelium (reduced and delayed growth). One study also noted higher densities of darkly staining foci, along with other histological changes, at 18 months (White et al., 2009).

Three studies investigated MGD at ≤1 mg/kg bw per day (Macon et al., 2011; White et al., 2011; Tucker et al., 2015) and will be more thoroughly described below because the LOAELs from these studies are the lowest of any endpoint, including those observed in subchronic and chronic studies. The other studies observing these effects will be summarized more concisely.

A two-generation study (White et al., 2011) found that exposure of mice to low levels of PFOA in drinking water (5 µg/L) delayed mammary gland development in both P0 and F1 dams and F1 and F2 offspring, which persisted until adulthood (at least PND 63). Parental (P0) female CD-1 mice (n = 7–12 per group) were placed into different treatment groups, receiving:

- daily doses of PFOA by gavage (0, 1 or 5 mg/kg bw per day: control, G1 and G5 groups, respectively) on GD 1–17,
- PFOA in drinking water only (5 µg/L, DW group) on GD7–17, or
- PFOA by both gavage (1 mg/kg bw per day on GD1–17) and drinking water (5 µg/L on GD7–17) (G1+DW group).

On PND 1, F1 litters were pooled randomly and redistributed to dams of their respective groups (n=12–13 neonates per litter). F1 female offspring from G1 and G5 groups were not exposed after birth while F1 female offspring from DW and G1+DW groups were exposed via drinking water throughout the rest of the study (n=2–10 F1 dams per group). F1 female offspring were mated with unexposed males to produce the F2 generation. F2 female offspring from DW and G1+DW groups were exposed through drinking water up to the end of the study. Necropsies were performed on F1 and F2 females at PND 42 and PND 63, and on F1 dams and F2 female offspring at PND 10 and PND 22 (White et al., 2011).

In the P0 (i.e., directly-exposed dams), a significant increase of MGD score was observed in all the treated groups on PND 22, even at the lowest dose (5 µg/L in drinking water on GD 7–17). These elevated scores reflect a delay in the normal weaning-induced mammary involution (on PND 22, the structure of the mammary gland in the treated P0 was similar to the structure normally observed at the lactation peak at PND 10). The authors only provided information on the amount of daily ingestion of PFOA in P0 dams consuming 5 µg/L drinking water (approximately 0.05 µg per day during gestation and 0.1 µg per day during lactation [PND 1–22]). Average daily doses are estimated to be approximately 0.001 mg/kg bw per day during gestation and 0.004 mg/kg bw per day during lactation (based on mean approximate weights of 62 g during gestation and 25 g during lactation; the average maternal weight gain during gestation was 25 g, and the initial body weight of dams was not reported by the authors but is assumed to be approximately

[1] MGD is scored on a 1–4 subjective, age-appropriate developmental scale based on the number of primary ducts and large secondary ducts, lateral side branching, appearance of budding from the ductal tree, and longitudinal outgrowth of the epithelia. For female offspring, a score of 4 refers to excellent development/structure and a score of 1 to poor development/structure. For dams, a value of 4 represents well-differentiated, functionally lactating tissue characterized by extensive epithelium, reduced adiposity, and presence of secretory alveoli, consistent with the peak of lactation (PND10). A value of 1 represents little or diminishing presence of lobuloalveoli and extensive involution and regression of the tissue, with the presence of apoptotic bodies, increasing adiposity, and regressing alveoli, as anticipated at weaning (PND22).

25 g for this strain of mice). The maternal LOAEL was therefore considered to be 0.001 mg/kg bw per day.

F1 pups from all treatment groups exhibited reduced MGD scores (reduced ductal elongation and branching, delays in timing of TEB appearance) until at least 9 weeks of age (PND 63, i.e., the last time point). In F1 dams (i.e., adult F1 pups), all of the PFOA-treated groups exhibited reduced MGD scores on PND 10; low score value persisted on PND 22 in the G1+DW, whereas in the G5 group, the score became higher than the control on PND 22 (i.e., normal involution was delayed). In the F2 females, MGD scores at PND 10 and PND 22 did not differ significantly from control; however, this result may be biased due to unusually low scores in the control group. At later times, significantly reduced scores were obtained in all treated groups (PND 42 for DW, G1+DW and G5, PND 63 for G1) and were characterized by an excess of terminal end buds (TEBs) (White et al., 2011).

In summary, White et al. (2011) demonstrated that ingested PFOA alters the development of mammary glands in both dams and offspring of CD-1 mice after exposure to low, human-relevant doses of PFOA (as low as 5 µg/L in drinking water) leading to human-relevant PFOA serum concentrations in pups and dams (range of approximately 20–90 ng/mL). The corresponding dose (LOAEL) was estimated at a maternal exposure of approximately 0.001 and 0.004 mg/kg bw per day during gestation and lactation, respectively. Effects in this study occurred independently of body weight changes, and the only adverse maternal effects observed at these levels were the mammary gland changes.

Macon et al. (2011) performed two separate studies of MGD in CD-1 mice—a late-gestation study and whole-gestation study. In the late-gestation study, dams (n=13 per group) were exposed to PFOA (0, 0.01, 0.1, and 1.0 mg/kg bw per day) by oral gavage on GD 10–17. The whole-gestation study exposed dams (n=13 per group) by gavage to PFOA at 0, 0.3, 1.0 or 3.0 mg/kg bw per day on GD 1–17.

Results of the late gestation study indicate significantly reduced MGD scores (in all treated groups, with a dose-dependent relationship) at PND 21. Other effects observed in the mammary gland at PND 14 (at 0.1 and 1.0 mg/kg bw per day, respectively) included reduced longitudinal epithelial growth by 14.4% and 37.3% compared to control (reduction by 27.4% and 56.5% compared to PND 1) and a statistically significant reduction of TEBs. In the whole-gestation study, the effects observed at all doses were dose-dependent and included reduced MGD scores in female offspring, which persisted until adulthood (PND 84). The LOAELs for the late and whole gestation studies were 0.01 and 0.3 mg/kg bw per day, respectively. No decreases in pup body weight were observed in these studies; therefore, MGD delays did not arise from decreased body weight.

Tucker et al. (2015) studied MGD in both CD-1 and C57Bl/6 female mouse pups that were exposed *in utero* to PFOA. Dams were exposed to PFOA via gavage at concentrations of 0, 0.01, 0.1, 0.3, and 1 mg/kg bw per day on GD 1–17. Significant dose-related trends in decreases in MGD scores were observed in pups of both strains. In CD-1 mice, the decreases were significant at ≥0.1 mg/kg bw per day when measured at PND21, which then decreased to ≥0.01 mg/kg bw per day at PND35 and PND56. The LOAEL for C57Bl/6 was slightly higher, with significant decreases at ≥0.3 mg/kg bw per day at PND21 and PND61. The authors also noted that average serum PFOA levels were lower in C57Bl/6 mice than in CD-1 mice.

Although the LOAEL for MGD scores was lower in CD-1 than C57Bl/6 mice, the results from this study are not sufficient to conclude that strain sensitivity occurs for the endpoint. Fewer pups were born in all C57Bl/6 groups, which resulted in a smaller sample size for the strain. This was particularly notable in the 0.01 and 0.1 mg/kg bw per day groups, which contained 8–22

CD-1 mice, but only 2–5 C57Bl/6 mice. As average MGD scores were similar between the strains at all doses, the lower sample size might have prevented statistical significance from being reached at these lower doses for C57Bl/6 mice. Moreover, the timing of MGD scoring was different for the strains at later timepoints (CD-1 mice were studied at PND 21, 35, and 56, whereas C57Bl/6 mice were only studied at PND 21 and 61), which might also affect results; MGD scores in control C57Bl/6 mice at PND 61 were lower than in control CD-1 mice at PND 35 and 56.

Tucker et al. (2015) also investigated other sexual maturity effects. No treatment-related effects on estradiol or progesterone levels, or on timing of vaginal opening or first estrus, were observed in either strain.

Several other higher-dose studies have noted delays in MGD at many different time points in female CD-1 mice (dams and offspring) exposed to gavage doses of ≥3 mg/kg bw per day (White et al., 2007, 2009; Wolf et al., 2007). These delays in MGD development are supported by data indicating reduced placental mRNA expression for genes in prolactin family (at ≥2 mg/kg bw per day; Suh et al., 2011), and a delay in lactotransferrin expression at 5 mg/kg bw per day (White et al., 2007).

A peripubertal study in mice (dosing beginning at 21 days of age) noted strain differences, with significant MGD delays at ≥5 mg/kg bw per day in Balb/c, but only at 10 mg/kg bw per day in C57Bl/6 (no inhibition occurred in either strain at 1 mg/kg bw per day; rather, stimulation was observed at this dose in C57Bl/6 mice) (Yang et al., 2009b). An additional peripubertal study (Zhao et al., 2010) noted effects at the only dose in the study, 5 mg/kg bw per day.

Although mammary gland delays can sometimes be associated with decreased body weight, two studies specifically stated that the effects were observed in absence of bodyweight disparities (White et al., 2007, 2009). One study also noted that the effect was not entirely due to underdeveloped offspring and insufficient stimulation by suckling, as the alteration of the functional mammary gland differentiation occurred prior to parturition and lactation (i.e., prior to stimulation of the gland by offspring) (White et al., 2007; 5 mg/kg bw per day).

Other effects related to sexual maturity were accelerated puberty (≥1 mg/ kg bw per day in M mice & 20 mg/kg bw per day in F mice; Lau et al., 2006), delayed sexual maturation (preputial separation & vaginal patency in rats; only at 30 mg/kg bw per day; Butenhoff et al., 2004b), and increased age of vaginal opening (at ≥5 mg/kg bw per day in C57BL/6 mice, but not Balb/c mice; Yang et al., 2009b).

9.2.5.2 Uterine effects

Histological changes in the uterus have been observed in CD-1 mice exposed to low doses of PFOA (Dixon et al., 2012). In immature mice exposed PND 18–20 to 0.01 mg/kg bw per day of PFOA by gavage, endometrial edema, hyperplasia of endometrial mucosa and glands, edema, and hypertrophy and hyperplasia of myometrium were induced. No histological effects were observed at the two higher doses in the study (0.1 and 1 mg/kg bw per day). The study also saw a dose-related increase of mucification (significant at the high dose only) in the cervix and vagina.

Differential effects were observed in uterine weight in mice. Increases in uterine weight in the Dixon et al. (2012) study were only observed in the lowest (0.01 mg/kg bw per day) group. The only other study reporting changes in uterine weight was a 4-week gavage study that exposed peripubertal Balb/c and C57BL/6 mice to 0, 1, 5, or 10 mg/kg bw per day (Yang et al., 2009b). In Balb/c mice, uterine weight was decreased at all doses (≥1 mg/kg bw per day), whereas in C57BL/6 mice, uterine weight was increased at 1 mg/kg bw per day, with a dose-dependent decrease at higher doses, which became significant only at 10 mg/kg bw per day.

9.2.5.3 Obesity in adulthood

Obesity in adulthood was noted to occur in a non-monotonic dose-response fashion in mice, in the only study that investigated this effect (Hines et al., 2009). Dose-dependent effects on body weight, appetite control (increased leptin and insulin blood concentration) and fat distribution were observed at adulthood in female CD-1 mice exposed *in utero* to PFOA. Pregnant mice (n=7–22 per dose group) were exposed daily by gavage on GD 1–17 (PFOA doses of 0, 0.01, 0.1, 0.3, 1, 3 and/or 5 mg/kg bw per day); offspring were weaned at 3 weeks and then female offspring were selected and received a standard diet for the rest of study.

At low doses (0.01, 0.1 and 0.3 mg/kg bw per day), data indicate an excessive weight gain in mice aged 20–29 weeks that coincided with increased blood levels of leptin and insulin (by approximately 2.5-fold) at 21–33 weeks of age (Hines et al. 2009). At higher doses, tissue weights at 18 months of age revealed a decreased relative weight of abdominal white fat at 1 and 5 mg/kg bw per day (no data at 3 mg/kg bw per day), and an increased relative weight of interscapular brown fat at 1 and 3 mg/kg bw per day (no effect at 5 mg/kg bw per day); overall bodyweight was decreased at the higher tested dose (5 mg/kg bw per day). No effects on bodyweight were observed at 1 or 3 mg/kg bw per day.

Similar experiments conducted in ovariectomized siblings of the exposed offspring (ovariectomy performed at PND 21/22) indicated no effect on body weight and abdominal fat weight, but an increased relative weight of interscapular brown fat at 1 mg/kg bw per day (no effect at 5 mg/kg bw per day). Although the latter data were difficult to interpret, the authors concluded that the ovaries appeared to play an important role in the overweight effect in mid-life and proposed that potential dysregulation of PPAR and its signaling through ovarian hormones may be responsible for the low-dose effects observed (Hines et al., 2009). It should be noted that exposure of 8 week-old mice to the same doses for the same period (17 days) did not lead to any effect on the same endpoints (see Section 9.2.2.1), suggesting the timing of dosing was critical for latent effects (Hines et al., 2009).

9.2.5.4 Developmental hepatic effects

As described in Section 9.2.2.1, hepatic effects are the most sensitive non-developmental effect resulting from short-term exposure to PFOA. Likewise, increases in liver weight were also observed after *in utero* or peripubertal exposure to PFOA.

The lowest maternal exposure dose at which increases in liver weight were observed in pups exposed prenatally to PFOA was 0.1 mg/kg bw per day (Abbott et al., 2007). In this study, 129S1/SvImJ mice (n=5–22 dams/dose) were exposed by gavage to 0, 0.1, 0.3, 0.6, 1, 3, 5, 10, and 20 mg/kg bw per day on GD 1–17. Increased relative liver weight in pups was observed in all doses, and was worsened at higher doses. In another study, Quist et al. (2015) reported significant increases in liver:body weight ratios at 0.3 and 1.0 mg/kg bw per day on postnatal day 21 in female offspring from pregnant CD-1 mice administered PFOA (0, 0.01, 0.1, 0.3, and 1 mg/kg bw per day) by oral gavage on GD 1-17; however, this was a transient effect as it was no longer observed at postnatal day 91. One other study observed slight but significant effects at <1 mg/kg bw per day; the study had only 1 dose group, 0.3 mg/kg bw per day (Onishchenko et al., 2011). The effect was observed at ≥1 mg/kg bw per day in other studies in mice exposed *in utero* (Wolf et al., 2007; White et al., 2009, 2011;Macon et al., 2011) or peripubertally (Yang et al., 2009b).

Filgo et al. (2015) exposed pregnant CD-1 mice, 129/SV mice, and PPARα-null mice (on 129/SV background) to PFOA by oral gavage throughout gestation. Doses administered differed depending on the mouse strain but ranged from 0.01 to 5.0 mg/kg bw per day. Livers from female

offspring (exposed in utero and during lactation) were examined histologically at 18 months of age. In CD-1 pups, there was a significant increase in centrilobular hepatocyte hypertrophy and Ito cell hypertrophy at 5 mg/kg bw per day, as well as hepatocellular adenomas at 0.3 mg/kg bw per day only. Quist et al. (2015) similarly reported hepatocellular hypertrophy in pups exposed by the same regime at postnatal day 91 with an increase in severity compared to controls at ≥0.01 mg/kg bw per day. Transmission electron microscopy of the liver slides showed cell damage and changes to mitochondrial morphology and numbers, which are not generally associated with PPARα-mediated effects. Filgo et al. (2015) reported a significant reduction in diffuse fatty change in 129/SV pups at 1 mg/kg bw per day, as well as a significant increase in bile duct hyperplasia at 3 mg/kg bw per day and significant decrease in Ito cell hypertrophy at ≥1 mg/kg bw per day in PPARα-null pup. Quist et al. (2015) reported no change in serum liver enzymes at postnatal days 21 and 91 in pups from dams fed control fat diets or high fat diets throughout lactation but did report a significant decrease in total cholesterol at ≥0.3 mg/kg bw per day in pups from dams fed high fat diet during lactation.

9.2.5.5 Neurodevelopmental effects

Neurobehavioural effects were observed in mice exposed *in utero* or shortly after birth, at the lowest doses applied in two studies—0.3 mg/kg bw per day (Onishchenko et al., 2011) and 0.58 mg/kg bw per day (Johansson et al., 2008). The effects manifested as changes in activity levels in mice.

Dietary exposure of C57BL/6/Bkl mice (n=6 dams/group) to 0 or 0.3 mg/kg (the only treatment group) of PFOA from GD 1 throughout pregnancy was found to induce gender-specific changes in offspring exploratory behaviour (first hour spent in a new environment), with an increased exploring activity in males and a decreased activity in females (Onishchenko et al., 2011). Prenatal exposure to PFOA also decreased the total number of inactive periods during the light phase in both males and females as well as in the dark phase of the circadian cycle in males. Motor coordination was slightly altered in females only. No effects were noted on locomotor activity, anxiety behaviour (elevated plus maze test), and immobility in the forced swimming test or muscle strength.

A LOAEL of 0.58 mg/kg for neurodevelopmental effects was identified in NMRI male mice administered a single gavage dose of PFOA (0.58 or 8.70 mg/kg) at the age of 10 days (Johansson et al., 2008). Mice were tested for spontaneous behavior and habituation at the age of 2 and 4 months, and the susceptibility of their cholinergic system was explored in a nicotine-induced spontaneous behaviour test at the age of 4 month (Johansson et al., 2008). Data indicate time-dependent and dose-related effects on the behaviour (deranged spontaneous behaviour, lack of habituation and increased susceptibility of the cholinergic system) reflecting the advance of a brain dysfunction process induced at the time of brain growth spurt in the neonatal mouse. At both doses, the exposed mice exhibited an altered spontaneous behaviour and a hypoactive response to nicotine. Any of the three variables of the behavioural test (locomotion, rearing and total activity) were altered, indicating hypoactivity during the first 20 minutes and hyperactivity in the last 20 min period (40–60 min after start of the test), and the effects worsened with age. These effects were supported by significantly increased levels of proteins that are important for normal brain development (CaMKII, GAP-43, and synaptophysin in the hippocampus, synaptophysin and tau in the cerebral cortex, and tau in the hippocampus) in mice under the same neonatal exposure conditions (Johansson et al., 2009).

9.2.5.5 Other effects

Reproductive and developmental effects other than those described earlier in this section were observed at higher doses; 0.6 mg/kg bw per day was the lowest LOAEL for delayed eye opening (Abbott et al., 2007), and all other effects were observed at ≥1 mg/kg bw per day.

The additional reproductive effects in mouse included a reduced number of implants (White et al., 2011), increased resorption, dead fetuses, post-implantation loss, or prenatal loss (White et al., 2007; Suh et al., 2011; White et al., 2011;) including increases in full-litter resorption or loss (Lau et al., 2006; Wolf et al., 2007; White et al., 2009), decreased placental weight (Suh et al., 2011), increased time to parturition (Lau et al., 2006), reduced number of live fetuses (White et al., 2011), increase in number of stillborn pups (Yahia et al., 2010), decreased survival of pups (Lau et al., 2006; Wolf et al., 2007; White et al., 2009; 2011; Yahia et al., 2010) and histopathological changes in mouse placenta (Suh et al., 2011).

The additional developmental effects in mouse offspring included delayed eye opening at in 1-generation studies (Lau et al., 2006; Abbott et al., 2007; Wolf et al., 2007; White et al., 2009), skeletal effects in one-generational studies [one study observed altered ossification (enlarged fontanel, reduced ossification of sternebrae and calvaria; Lau et al., 2006), another found delayed ossification of phalanges, increased cleft sternum, and delayed eruption of incisor occurred; Yahia et al., 2010], decreased relative spleen weight, without a clear dose–response relationship (Hines et al., 2009), reduced fetal or pup weight (Staples et al., 1984; Lau et al., 2006; Abbott et al., 2007; White et al., 2007; 2009; Wolf et al., 2007; Yahia et al., 2010; Suh et al., 2011), and increased fetal weight (Yahia et al., 2010).

The only effects noted in a 2-generation study of rats included delayed growth (at ≥10 mg/kg bw per day in M and 30 mg/kg bw per day in F) and increased post-weaning mortality (in F only, at 30 mg/kg bw per day), with no effects on the F2 generation (Butenhoff et al., 2004b; York, 2002).

9.3 Mode of action

Mode of action analysis was considered for effects occurring at the lowest PFOA levels (i.e., Leydig cell tumours, hepatocellular hypertrophy, and changes in serum lipids in rats, and liver weight increases, hepatocellular hypertrophy, obesity, developmental delays, and delayed mammary gland development in mice). Only a preliminary evaluation of data could be performed for most of the MOAs; a MOA analysis using recent guidance (Meek et al., 2014) could only be performed for peroxisome proliferation effects on liver endpoints. Based on the MOA analysis, no endpoints were considered to be irrelevant to humans, and the results suggest that the TDI approach is the most appropriate method for cancer risk assessment. Results of the MOA evaluations are summarized in this section.

9.3.1 Direct-acting mutagenicity

Direct-acting mutagenicity and DNA reactivity was considered as a potential MOA for the development of Leydig cell tumours in rats. As discussed in Section 9.2.4, evidence predominantly indicates that PFOA is not mutagenic, with or without metabolic activation. PFOA was negative for genotoxicity in a wide variety of *in vitro* and *in vivo* assays. Positive results were obtained only in one chromosome damage test in hamster cells, one micronucleus assay in human cells, and mutagenicity was observed in human-hamster hybrid (A_L) cells, but mitochondria-dependent ROS was shown to play an important role in this process. The pattern of PFOA-induced tumours also did not follow that of typical mutagens. For example, mutagens are typically expected to cause tumours in many different organs, but PFOA only affected testicular

Leydig cells, liver, and pancreas (i.e., organs associated with the PPARα tumour triad) in one study (Biegel et al., 2011), and only Leydig cells in another study at similar doses (Butenhoff et al., 2012b). Furthermore, mutagens often produce a high incidence of tumours, which occur at early timepoints and at low doses. In PFOA-exposed animals, the tumours were only observed after lifetime duration to high doses in PFOA studies, and at low incidences (10–14%).

Further support for non-mutagenic activity of PFOA is provided by a study that suggests that PFOA acts as a tumour promoter. Liver tumours—primarily hepatocarcinomas—were observed in rats that underwent initiation protocols (i.e., were exposed to the mutagen diethylnitrosamine) and were exposed to feed containing 0.015% PFOA (equivalent to 7.5 mg/kg bw per day using the Health Canada [1994] assumption that 1 ppm in food is equivalent to 0.05 mg/kg bw per day in rats) on weeks 5–28 of the study (Abdellatif et al., 1990). Hepatic tumours were observed in 33% of animals (vs. 0% in controls that were initiated but not exposed to tumour promoters); therefore, effects were observed earlier (after 6 months of PFOA exposure and 7 months after initiation) and at a higher incidence than higher dose studies of rats exposed only to PFOA.

The weight of evidence for non-mutagenic MOAs of tumours (as discussed later in this section) is stronger than for direct-acting mutagenicity, which suggests that low-dose linear extrapolation is not appropriate for PFOA-induced tumours. No further MOA analysis is required for direct-acting mutagenicity, unless contradictory data are published.

9.3.2 Peroxisome proliferation

Peroxisome proliferation was considered as a potential MOA for hepatocellular hypertrophy in rats and mice, serum lipid changes and hepatocellular tumours in rats, and liver weight increase and obesity in mice. Some data exist for hepatic PPAR activity in rats and mice; therefore, this is the primary focus of the analysis. Because few studies directly measured PPAR impact on other outcomes, these could not be fully assessed; however, studies in PPAR-null mice indicate a decreased sensitivity to reproductive and developmental endpoints (including litter loss, delayed eye opening, and decreased body weight in pups [Abbott et al., 2007]) but not mammary gland development delays (Zhao et al., 2010). The evolved Bradford-Hill criteria were applied to evaluate the weight of evidence for the MOA of peroxisome proliferation for liver endpoints, which is summarized below.

Three main key events in the peroxisome proliferation MOA are considered to lead to liver histological effects and hepatocellular tumours. These key events are 1) the activation of hepatic PPARα receptors, which leads to 2) altered cell growth pathways that inhibit apoptosis and/or promote cell replication, eventually leading to 3) hepatocyte proliferation (Corton et al., 2014).

9.3.2.1 Key event 1 – PPARα activation

An absence of hepatic palmitoyl CoA oxidation was observed in rats exposed to 0.3 mg/kg bw per day of PFOA for 14 days (Loveless et al., 2006). The lowest dose at which the hepatic oxidation was observed in rats was 0.64 mg/kg bw per day after 4 weeks of exposure (Perkins et al., 2004), with the effect regularly occurring at higher doses (at ≥1 mg/kg bw per day for 14 days [Loveless et al., 2006], ≥1.94 mg/kg bw per day for ≥4 weeks [Perkins et al., 2004], ≥2 mg/kg bw per day for 14 days [Liu et al., 1996], 7.5 mg/kg bw per day for 23 weeks [Abdellatif et al., 1990], 13.6 mg/kg bw per day for ≥1 month [Biegel et al., 2011], and approximately 20 mg/kg bw per day for ≤28 days [Elcombe et al., 2010]). In mice, hepatic palmitoyl CoA oxidation was observed at lower PFOA doses than rats, with the effect measured at ≥0.3 mg/kg bw per day after 14 days

of exposure (Loveless et al., 2006) and higher doses in other studies (Yang et al., 2002; Minata et al., 2010; Nakagawa et al., 2012); moreover, increased expression of PPAR-related genes was observed in wild-type mice, but not humanized PPAR or PPAR-null mice, exposed for 2 weeks to ≥0.1 mg/kg bw per day (Nakamura et al., 2009). In rats exposed to 13.6 mg/kg bw per day of PFOA for 2 years, no increase in palmitoyl CoA oxidation was observed in Leydig cells (Biegel et al., 2011); however, the same study did not measure an increase in the effect in a model peroxisome proliferator (Wyeth-14,643 [WY]).

9.3.2.2 Key event 2 – altered cell growth

No studies of markers of altered cell growth pathways could be found.

9.3.2.3 Key event 3 – cell proliferation

An absence of hepatocyte proliferation was noted in rats exposed to 13.6 mg/kg bw per day for 1–24 months, when it was observed in positive controls (i.e., WY-exposed mice) at the same time periods (Biegel et al., 2001), but the effect was observed in rats exposed to approximately 20 mg/kg bw per day for 2–29 days (Elcombe et al., 2010). A dose-related increase in labelling index was observed in both wild-type and PPAR-null mice exposed for 7 days, with significance reached at 10 mg/kg bw per day (but not 1 or 3 mg/kg bw per day) in both strains (Wolf et al., 2008).

Cell proliferation was measured in pancreatic acinar cells, but not Leydig cells, in rats exposed to 13.6 mg/kg bw per day for 2 years (Biegel et al., 2011).

9.3.2.4 Assessment of Bradford-Hill considerations

Biological concordance — PPAR activation, leading to increased replication in hepatocytes and increased hepatic tumours, is a well-recognized MOA. Increases were observed in testicular (Leydig cell), pancreatic, and hepatocellular tumours in rats (Biegel et al., 2011), which is a recognized tumour triad for the peroxisome proliferation MOA (Corton et al., 2014); pancreatic acinar cell proliferation and hyperplasia were also observed to be increased in rats (Biegel et al., 2011). However, inconsistencies in this observation arise as the tumour triad was not observed at a similar dose in another two-year study in rats (Butenhoff et al., 2012b). Studies of peroxisome proliferation and tumour development in these cells in mice (which are more sensitive to peroxisome proliferation than rats) would potentially provide more useful information for the MOA analysis.

Essentiality of key event — Studies of PPAR-null mice (Yang et al., 2002; Abbott et al., 2007; Wolf et al., 2008; Nakagawa et al., 2012) provided information to evaluate the essentiality of the key events for hepatic effects; no studies of PPAR-null rats exposed to PFOA could be found. In the Abbott et al. (2007) study, PPAR-null mice had decreased sensitivity to liver weight effects, which lends some support to the MOA for this adverse outcome; however, liver weight effects still occur (albeit at higher doses) in PPAR-null mice, and hepatomegaly is induced to the same extent in wild-type and PPAR-null mice in other studies (Yang et al., 2002; Wolf et al., 2008; Nakagawa et al., 2012). Similarly, Filgo et al. (2015) observed significant increases and significant trends in the development of neoplastic and non-neoplastic hepatic lesions in the female offspring from PPARα-null mice. The increase hepatocyte proliferation (as measured by increase in labelling index) was also similar between wild-type and PPAR-null mice (Wolf et al., 2008). Moreover, despite an absence of increased expression of PPAR-related genes in PPAR-null and humanized PPAR mice, increases in liver weight were similar among these strains and wild-type mice (i.e., mice with increased PPAR expression) (Nakagawa et al., 2012). Despite these quantitative similarities between strains for non-cancer liver effects, qualitative differences

were observed—including differences in microscopic appearance and ultrastructure of hepatic cells (Wolf et al., 2008; Minata et al., 2010). Further studies that expose PPAR-null mice at lower doses and investigate other adverse outcomes, as well as studies of PPAR-null rats, would help to better evaluate the MOA.

Temporal and dose–response concordance — Some dose–response concordance was observed for the MOA, as PPAR activation precedes hepatocyte proliferation in rats; however, hepatocyte proliferation was absent at tumour-relevant doses in rats (Biegel et al., 2001), and occurred only at higher levels than those resulting in hepatocellular hypertrophy and increased liver weight (Elcombe et al., 2010). The sole study of hepatocyte proliferation in mice indicates its occurrence only at doses above those at which increases in hypertrophy and liver weight were observed (Wolf et al., 2008). Moreover, the absence of data on altered cell growth pathways precludes the evaluation of whether this key event is triggered by PPAR activation and is a precursor for hepatocyte proliferation.

The first key event (PPAR activation) does not appear to precede the adverse hepatic outcomes in rats. Both increased liver weight and hepatocellular hypertrophy were observed either at or below doses where an absence of PPAR activation was observed.

Consistency (across species, strains, organs, and test systems) — PPAR activation begins at lower doses in mice than rats and monkeys, as is expected, based on knowledge of PPAR biology (Corton et al., 2014). However, in monkeys, PPAR activation is not consistent, is not accompanied by cell proliferation, and occurs only at higher doses than adverse liver effects.

Analogous compounds — The tumour triad observed in male rats, along with an increase in serum estradiol, was observed similarly in both PFOA and a model peroxisome proliferator, WY. However, hepatic effect in PFOS-exposed rats appears to occur in absence of peroxisome proliferation, and the tumour triad was not observed in PFOS-exposed rats.

Some evidence in rats and mice supports the occurrence of peroxisome proliferation as a mode of action for hepatocellular hypertrophy. The characteristic tumour triad of peroxisome proliferators (cancers of the testes, pancreas, and liver) was observed in rats, and the doses at which hepatocellular tumours are observed are higher than earlier key events in the peroxisome proliferation MOA. However, increases in liver weight and hepatocellular hypertrophy appear to occur at lower doses than PPAR activation in rats; therefore, although PPAR activation does occur in rats, it does not appear to be the sole driver for these two effects. Studies of PPAR-null mice indicate that peroxisome proliferation might play a role in observed hepatocellular hypertrophy and liver weight increases, but despite qualitative (i.e., appearance) differences between the strains, the quantitative similarities in the changes in PPAR-null vs. wild type mice indicate that other MOAs play a large role in the development of the effects. Because the peroxisome proliferation MOA does not seem to be the sole MOA involved, human relevance of PFOA-induced non-carcinogenic hepatic effects cannot be ruled out. Conversely, a detailed MOA analysis has concluded that the weight of evidence for the peroxisome proliferation MOA for PFOA-induced liver tumours was strong. The relevance of these tumours to humans is limited, as PPARα activation by PFOA is weaker in humans than in rats. Moreover, PPARα activation by various compounds in does not appear to result in hepatocellular proliferation and tumours (Corton et al., 2012; Klaunig et al., 2012).

9.3.3 Sex hormone disruption

Sex hormone disruption is a potential MOA that should be considered for mammary gland development delays in mice, obesity in prenatally exposed mice, and Leydig cell tumours in rats. Insufficient data exist to be able to perform a quantitative analysis of sex hormone disruption;

however, a few different observations that could be relevant to the sex hormone MOA have been reported, including the muting of uterine effects when PFOA was co-administered with estradiol (Dixon et al., 2012), an enhancement of the effects of 17β-estradiol in a variety of *in vitro* assays, but with an absence of direct estrogenic activity (Sonthithai et al., 2016), the reversal of mammary gland development delays with the supplementation of physiological levels of estradiol or progesterone (Zhao et al., 2012), an increase in serum estradiol concentrations in male rats exposed for 1–12 months (Biegel et al., 2001), changes in estradiol genesis (decrease at lower doses and increase at higher doses) in an *in vitro* steroidogenesis assay (Rosenmai et al., 2013), an absence of PFOA binding to or activating human estradiol receptors *in vitro* (Ishibashi et al., 2007), and decreases in cholesterol levels, which might disrupt testosterone synthesis (Li et al., 2011). If more in-depth studies on the effect of PFOA on sex hormone disruption are performed, this potential MOA could be further investigated.

9.3.4 Other MOAs

Insufficient data exist to allow for the assessment of other potential MOAs considered in the MOA analysis. Some data—particularly in regards to PPAR activation/peroxisome proliferation—exist for other endpoints that were not included in the MOA analysis (i.e., effects that were observed only at higher PFOA exposure levels).

9.4 Additivity

The application of an additive approach for PFAS was considered using the World Health Organization /International Programme on Chemical Safety (WHO/IPCS) framework for risk assessment of combined exposure to multiple chemicals (Meek et al., 2011). This section focuses on the evaluation of additivity for PFOS and PFOA, which are the predominant PFAS detected in Canadian water samples.

Considerations relevant to the additivity analysis are addressed within four over-arching questions (Meek et al., 2011):

1. The ~~What is the~~ nature of exposure~~?~~
2. The likelihood of ~~Is~~ co-exposure ~~likely~~, taking into account the context~~?~~
3. The ~~Is there a~~ likelihood of co-exposure within a relevant time-frame~~?~~
4. The ~~What is the~~ rationale for considering compounds in an assessment group~~?~~

Additionally, evidence demonstrating the toxic effects of mixture exposure can be used as supporting information in an additivity analysis (Meek et al., 2011). Based on analysis of these considerations, the application of an additive approach for PFOS and PFOA in drinking water is the most appropriate method for the protection of human health. The results are summarized below.

The ~~What is the~~ nature of exposure~~?~~

PFOS and PFOA are highly fluorinated synthetic organic chemicals that consist of a straight-chain hydrocarbon backbone with a carbon chain length of eight. Structurally, they differ only in their terminal functional groups (i.e., PFOS has a sulfonic acid moiety and PFOA has a single carboxylate moiety). This class of chemicals has numerous uses, including stain/water resistant coatings and in fire-fighting foams, which is of particular concern for water (see section 4.1). Their elevated water solubility and the negligible volatility of ionized species suggest that PFOS and PFOA will partition primarily to the aquatic environment, supporting their occurrence in water. Additionally, they are persistent compounds that do not undergo biodegradation and are

thus stable in water. Many studies have confirmed the presence of PFAS in drinking water sources and tap water (see Sections 4.1, 5.1, and 5.1.1).

The likelihood of ~~Is~~ co-exposure ~~likely~~, taking into account the context?~~

~~Yes.~~ Routine monitoring programmes to test drinking water for PFOS and PFOA have not been implemented; however, available studies have reported co-exposure in Canadian drinking water sources and tap water (see Section 5.1.1). As discussed in Section 5.1.1, PFOS and PFOA are the predominant PFAS detected in Canadian water samples.

The ~~Is there a~~ likelihood of co-exposure within a relevant time-frame?

~~Yes.~~ Co-exposure to PFOS and PFOA is likely – through ingestion of contaminated food and water, inhalation of dust, and use of consumer products. PFOS and PFOA are persistent compounds that do not undergo biodegradation, thus they compartmentalize into similar media, making the temporal aspects of external co-exposure likely. Additionally, they do not undergo biotransformation and have relatively long half-lives in humans (i.e., 3.9-6.9 years for PFOS and 2.5-4.4 years for PFOA (Olsen et al., 2007; Brede et al., 2010; Bartell et al., 2010)), thus their toxicokinetics make internal co-exposure likely. Additionally, biomonitoring data indicate co-occurrence of PFOS and PFOA in human serum in Canadian studies, as well as International studies.

The ~~What is the~~ rationale for considering compounds in an assessment group?

Grouping of PFOS and PFOA is appropriate at the level of structure, application/use (as described above), and toxicology. The human health and toxicological effects, and modes/mechanisms of action induced by PFOS and PFOA are discussed below.

Human health and/or toxicological effects are similar. The available information on PFOS and PFOA toxicokinetics indicates a high degree of similarity (reviewed in section 8 of both documents). Oral uptake of PFOS and PFOA results in rapid and almost complete resorption (>90%) within 24 hours in male rats (Gibson and Johnson, 1979). PFOS and PFOA are weakly lipophilic, very water soluble, and bind preferentially to proteins, such as serum albumin. However, differences in their tissue distribution have been reported - whereas PFOA is mainly present in the serum/plasma (Johnson and Ober, 1999; Han et al., 2003; Kudo et al., 2007), PFOS is primarily distributed to the liver (Beskin et al., 2009; De Silva et al., 2009). Both PFOS and PFOA are highly resistant to biotransformation and are not metabolized in mammals, which accounts for their relatively long half-lives. Additionally, because of their resistance to biotransformation, the toxicity of the parent compound and not that of a metabolite is of concern for both PFOS and PFOA.

As reviewed in section 9.1 of this document and the PFOS document, studies in humans (including the general population and workers) have demonstrated similarities in health outcomes associated with elevated levels of serum PFOS and PFOA, including liver effects, immune suppression, lipidemia, thyroid effects, kidney effects, cancer, and some reproductive and developmental toxicities (i.e., reduced fecundity, reduced birth weight, changes in the onset of puberty). However, elevated serum PFOS is additionally associated with delays in developmental milestones, thyroid hormone levels, and immune system effects in offspring, while elevated serum PFOA is associated with decreased duration of breastfeeding.

Similarities and dissimilarities in health outcomes in experimental animals have also been demonstrated. Studies in experimental animals have demonstrated similarities in adverse effects of treatment with PFOS and PFOA on the liver (including increased liver weight, hepatocellular hypertrophy, changes in serum enzymes), immune system effects, serum lipids, thyroid effects, neurotoxicity, reduced body weight, and tumor formation (i.e., liver), and the induction of reproductive and developmental toxicities (including neurobehaviour, liver weight changes and histopathology, reduced survival/viability of pups, and increased mortality in pups). Additionally, neither PFOS nor PFOA are considered to be direct-acting genotoxic chemicals. However, discordant results are observed in some outcomes following treatment with PFOS and PFOA. For example, chronic administration of PFOA causes hepatocellular adenomas and Leydig cell adenomas in rats; yet while an increase in the incidence of hepatocellular adenomas is observed

following chronic administration of PFOS, no significant dose-responsive changes in the incidence of Leydig cell tumours were found. Furthermore, the most sensitive developmental effects observed following exposures to PFOA (i.e., delayed mammary gland development in the offspring of mice, uterine effects in immature female mice, and obesity in female offspring in mice at adulthood) are not observed following exposure to PFOS. Collectively, although some toxic effects appear to be compound-specific, there is a large degree of concordance in adverse toxicological effects induced by PFOS and PFOA in experimental animals.

There is similarity in their modes of action. The modes of action for PFOS and PFOA are not fully understood and it is likely that multiple pathways are involved in their toxic effects. The largest body of evidence points to PPARα ligand-dependent activation by PFOS and PFOA as a key initiating event in the development of liver toxicities (described in section 9.3 of each document). However, although some toxicity by PFOS and PFOA is attributable to PPARα activation, PPARα-independence has also been proposed. For example, PFOS-induced hypertrophy and lipid vacuolization occurred in the absence of peroxisome proliferation or increase in palmitoyl-CoA-oxidase activity in monkeys (Seacat et al., 2002) and transmission electron microscopy of liver sections with hepatocellular hypertrophy and hepatic inflammation observed in pups exposed to PFOA *in utero* revealed cellular damage and mitochondrial abnormalities with no evidence of peroxisome proliferation (Quist et al., 2015). Additionally, PFOS and PFOA have been shown to alter fatty acid metabolism, lipid transport, cholesterol synthesis, proteasomal activation and proteolysis, cell communication, and inflammation processes in experimental animals. Thus, although the mode of action for PFOS and PFOA-induced toxicities has yet to be elucidated, the similarity in the mechanisms activated by each compound is sufficient to suggest similar modes of action are at play.

In addition to the evaluation of data for additivity using the WHO/IPCS framework (Meek et al., 2011), evidence demonstrating the toxic effects of combined exposures were evaluated to strengthen support for the use of an additive approach for PFOS and PFOA. Only one *in vivo* mammalian study was found. Tatum et al. (2010) reported in a conference proceeding that a binary mixture of PFOS and PFOA (6 mg/kg bw per day and 4 mg/kg bw per day, respectively) behaves additively by dose addition (also known as concentration addition) on reproductive and developmental toxicity endpoints (i.e., maternal weight gain, pup body weight, maternal and neonatal liver weight) in CD-1 mice exposed to the mixture and to PFOS and PFOA individually by oral gavage on gestational days 1-17. The authors additionally reported less than additive behaviour for neonatal mortality (i.e., the mixture of PFOS and PFOA caused less neonatal mortality compared to PFOS and PFOA alone).

This finding is in general agreement with *in vitro* studies on the combined action of PFOS and PFOA (and other PFAS). In studies of binary mixtures of PFOS and PFOA, additivity has been observed at the level of apoptotic potential in mouse HEPG2 liver cells (Hu and Hu, 2009), mortality in zebrafish embyros (Ding et al., 2013), and PPARα activation in Cos-1 cells (Wolf et al., 2014). The additive effects reported by Wolf et al. (2014) and Ding et al. (2013) were observed at low exposure concentrations but deviations from additivity were observed at higher doses. Similarly, deviations from additivity showing less than additive effects (i.e., the mixture response is less than would be expected under conditions of additivity) have been observed at the level of PPARα activation in Cos-1 cells (Carr et al., 2013) and toxicity in cyanobacteria (Rodeo-Palomares et al., 2012) in studies of binary mixtures of PFOS and PFOA, as well as on cellular viability in human liver HL-7702 cells exposed to a simple mixture of 11 PFAS, including PFOS and PFOA. Greater than additive effects on cellular viability have also been reported in human liver HL-7702 cells (Hu et al., 2014) and in rare minnow hepatocytes (Wei et al., 2009) in studies

of binary mixtures of PFOS and PFOA, and in human U2OS bone osteosarcoma cells exposed to a simple mixture of five PFAS, including PFOS and PFOA (Wilson et al., 2016). Wilson et al. (2016) further investigated glucocorticoid receptor transactivation but the mixture responses were too weak to report, as were the estrogen receptor and androgen receptor activities in human MVLN breast cancer cells and hamster CHO-K1 ovary cells, respectively, exposed to a mixture of seven PFAS including PFOS and PFOA (Kjeldsen and Bonefeld-Jorgensen, 2013). Gene expression changes measured following exposure to PFOS and PFOA alone or in a binary mixture demonstrated that mechanisms activated following exposure to mixtures and individual chemicals are complex and can differ depending on the treatment (Wei et al., 2009). The differences reported among studies are largely attributable to the biological model, the concentrations used, and the particular composition/complexity of the mixtures.

The absence of *in vivo* studies investigating the additivity of PFAS was identified as a major data gap. However, based on the evaluation of the exposure and toxicological data for PFOS and PFOA in consideration of the WHO / IPCS framework for the risk assessment of combined exposures (Meek et al., 2011), an additive approach for PFOS and PFOA is the most appropriate in the interest of human health protection.

10.0 Classification and assessment

PFOA and its salts have been classified as possibly carcinogenic to humans (Group 2B) by IARC, based on limited epidemiological evidence demonstrating associations between PFOA and testicular and renal cancers, and on limited evidence in experimental animals (Benbrahim-Tallaa et al., 2014). When evaluated under the *Canadian Environmental Protection Act*, PFOA, its salts and its precursors met the criteria for persistence and immediate or long-term harmful effect on the environment or its biological diversity, but were not deemed to be bioaccumulative, nor entering the environment under conditions that constitute or may constitute a danger in Canada to human life or health (Environment Canada and Health Canada, 2012).

The benchmark dose (BMD) approach was used wherever possible to calculate potential PODs, because it is derived on the basis of data from the entire dose-response curve for the critical effect rather than from the single dose group at the NOAEL (IPCS, 1994). A lower confidence limit of the benchmark dose (BMDL) has been suggested as an appropriate replacement of the NOAEL (Crump, 1984). More specifically, a suitable BMDL is defined as a lower 95% confidence limit estimate of dose corresponding to a 1–10% level of risk over background levels. Definition of the BMD as a lower confidence limit accounts for the statistical power and quality of the data (IPCS, 1994). Benchmark dose values representing a 10% increase in adverse effect over background rates (BMD_{10}) and their lower 95% confidence limits ($BMDL_{10}$) were calculated using the U.S. EPA Benchmark Dose Software (BMDS Version 2.6.0.86; U.S. EPA, 2015).

Large pharmacokinetic differences exist between animals and humans, with lower clearance (i.e., higher half-life values) in humans than in rats, mice, and monkeys. These differences result in higher target tissue doses in humans when exposed to the same external doses as animals. Default approaches for interspecies extrapolation (e.g., interspecies uncertainty factor of 10, allometric scaling) are therefore not considered to be sufficiently protective of humans. As described in Section 8.6, AK_{UF} values (i.e., the component of the CSAF reflecting interspecies toxicokinetic differences) were calculated with a PBPK model to address pharmacokinetic differences between animals and humans. As different AK_{UF} values were calculated for various doses, the values can also address non-linearity in pharmacokinetics. Weaknesses still exist with

this approach, as outlined in detail in Section 8.6, including the use of the steady-state plasma concentration as a dose metric, rather than selecting organ-based values or exploring whether other dose metrics (e.g., peak concentrations) are more appropriate. However, despite the weaknesses, the approach was determined to be the best of the available options. This approach was selected over the use of serum concentrations as points-of-departure (PODs), because human PBPK models were determined to not be sufficiently robust for precise estimates of human exposure levels corresponding to serum-based PODs.

10.1 Cancer risk assessment

Epidemiological evidence has shown an association between exposure to PFOA and increased risk of incidence of testicular and kidney cancers (see Section 9.1.3). The associations were observed in large-scale epidemiology studies in a community with elevated PFOA concentrations in water (C8 project). However, causality and a point-of-departure cannot be determined from these studies due to the lack of consistency between studies (no association found in some prospective studies in Denmark and the U.S.). Limitations were also observed in the studies that found a positive association, including the risk of residual confounding (because not all covariates and exposures to other contaminants were included in the model), the small case numbers, the uncertainties in exposure characterization (rough estimates based on residency within a certain area), and the high number of outcomes included in the models, increasing the likelihood of chance findings.

Two chronic duration studies identified testicular Leydig cell adenomas in male Crl:CD BR (CD) rats exposed to PFOA for 2 years. The first study observed these adenomas at 13.6 mg/kg bw per day (the only dose tested in the study; Biegel et al., 2001); the other study observed a dose-related increase in incidence of adenomas, with significance achieved at the high dose (14.2 mg/kg bw per day; 3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b). The Leydig cell adenomas were accompanied by hyperplasia of Leydig cells and proliferation and adenomas of pancreatic acinar cells in the Biegel et al. (2001) study. Dose-dependent increases in mammary fibroadenomas was observed in female rats in the Butenhoff et al. (2012b) study, but were not considered proliferative lesions using current diagnostic criteria.

Although the mode of action for PFOA-induced tumours has not yet been elucidated, the weight of evidence more strongly suggests that PFOA is a non-mutagenic compound (see Sections 9.2.4 and 9.3). For this reason, the tolerable daily intake (TDI) approach is the most appropriate method for deriving a health-based value (HBV) for cancer.

The selected key study for the cancer risk assessment is Butenhoff et al. (2012b), as it is the only chronic study with more than one dose level. Incidence of Leydig cell tumours was 0, 2, and 7, in rats exposed to 0, 1.3, and 14.2 mg/kg bw per day, respectively. As significance was only observed at the high dose, the NOAEL and LOAEL for Leydig cell tumours in this study are 1.3 and 14.2 mg/kg bw per day, respectively. The use of benchmark dose modelling is not typically recommended for studies containing only two dose groups (U.S. EPA, 2012b); however, the approach was performed for comparison with the NOAEL. Three models (Log Logistic, Log Probit, and Multistage) had the best fit (all models had the lowest Akaike information criterion [AIC] among all considered models). The $BMDL_{10}$ values for these three models ranged from 1.06 to 1.26 mg/kg bw per day, and were therefore similar to the NOAEL of 1.3 mg/kg bw per day, which is used as the POD for the analysis.

To reflect the large interspecies differences in pharmacokinetics, the human-equivalent point-of-departure (POD_{HEQ}) can be calculated by dividing the NOAEL by the AK_{UF}, as follows:

$$POD_{HEQ} = \frac{1.3 \text{ mg/kg bw per day}}{17}$$

$$= 0.076 \text{ mg/kg bw per day}$$

where:

- 1.3 mg/kg bw per day is the NOAEL for Leydig cell tumours in male rats (Butenhoff et al., 2012b); and
- 17 is the dose-specific AK_{UF} for rats in the 1 mg/kg bw per day range (as described in Section 8.6.2).

Using the calculated POD_{HEQ}, the cancer TDI was calculated as follows:

$$TDI = \frac{0.076 \text{ mg/kg bw per day}}{25}$$

$$= 0.003 \text{ mg/kg bw per day}$$

where:

- 0.076 mg/kg bw per day is the POD_{HEQ} associated with the NOAEL for Leydig cell tumours in male rats (Butenhoff et al., 2012b); and
- 25 is the composite uncertainty factor, as described below.

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (×2.5) and intraspecies uncertainty factor (×10). A value of 2.5 is used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. A default value of 10 was applied for the intraspecies uncertainty factor. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOA excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. Average half-life values calculated from longitudinal data for different populations previously exposed to PFOA were similar (averages for each population ranged from 2.3–3.8 years; Olsen et al., 2007; Bartell et al., 2010; Brede et al., 2010); however, studies providing ranges indicated that there was approximately a 10-fold difference between the lowest and highest estimates of half-life. If further studies of PFOA consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed.

Using this TDI, the HBV for drinking water can be calculated as follows:

$$HBV = \frac{0.003 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= 0.028 \text{ mg/L}$$

$$\approx \quad 0.03 \text{ mg/L } (30 \text{ µg/L})$$

where:

- 0.003 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7).

10.2 Non-cancer risk assessment

Although epidemiological evidence has shown an association between the exposure to PFOA and multiple health outcomes, such as dysfunctions of the immunological system and alterations in birth weight and lipid levels (see Section 9.1.3), a POD cannot be derived from these studies due to limitations, including in terms of study design, bias and confounders.

The lowest LOAELs for PFOA were for reproductive and developmental effects in mice, with effects observed at levels as low as 0.001–0.01 mg/kg bw per day for delayed mammary gland development (Macon et al., 2011; White et al., 2011; Tucker et al., 2015), at 0.01 mg/kg bw per day for estrogenic effects in the uterus (Dixon et al., 2012) and weight changes in adult females exposed prenatally (Hines et al., 2009), and at 0.6 mg/kg bw per day for delayed eye opening (Abbott et al., 2007). These endpoints were not used as the basis of the risk assessment for several reasons. Estrogenic effects in the uterus (endometrial edema, hyperplasia of endometrial mucosa and glands, hypertrophy and hyperplasia of myometrium, and increase in weight in the uterotrophic assay) were excluded from the assessment because they did not occur in a dose–related manner—significant increases were observed in mice exposed only to 0.01 mg/kg bw per day, and not at higher levels (0.1 or 1 mg/kg bw per day; Dixon et al., 2012). A non-monotonic response was also observed for body weight changes in adult female mice exposed *in utero*, with increased body weight at 0.01–0.3 mg/kg bw per day (not 1 mg/kg bw per day) and in serum leptin and insulin at 0.01 and 0.1 mg/kg bw per day (not 0.3 or 1 mg/kg bw per day; Hines et al., 2009). Moreover, slight changes (although significant) in mammary gland development and bodyweight are indicative of treatment-related changes, but not necessarily adversity—there was no evidence of insufficient milk intake or inability to thrive in pups of dams with MGD changes, and weight changes were low (measured at <10%). The observation of delayed eye opening at ≥0.6 mg/kg bw per day in mice (Abbott et al., 2007) was not corroborated in other studies, as the effect had a LOAEL of 3 mg/kg bw per day (NOAEL=1 mg/kg bw per day; Lau et al., 2006), and was not observed at 3 mg/kg bw per day in another study (Albrecht et al., 2013). Mammary gland development effects might also be affected by strain sensitivity—the majority of the low-dose effects have only been observed in CD-1 mice exposed *in utero*, and other strains were typically only studied at higher doses and in peripubertal mice. A recent *in utero* study comparing MGD in both CD-1 and C57Bl/6 mice at doses of 0.01–1 mg/kg bw per day potentially provided support for low dose effects in a second strain of mice, albeit at slightly higher doses (LOAEL = 0.01 vs. 0.3 mg/kg bw per day in CD-1 and C57Bl/6 mice, respectively); however, a small sample size at low doses for C57Bl/6 mice (as few as two pups) might have

precluded the observation of significant changes at similar doses to CD-1 mice. Finally, species sensitivity might be occurring for these effects, as one- and two-generation studies in rats identified similar effects only at much higher doses, if at all; the NOAELs for body weight changes and delayed sexual maturation in pups were around 3 mg/kg bw per day (Staples et al., 1984; Butenhoff et al., 2004b) and 10 mg/kg bw per day (Butenhoff et al., 2004b), respectively, and no effects on lactation index were observed up to 30 mg/kg bw per day (Butenhoff et al., 2004b). Further support for the potential for species sensitivity is provided in studies using PPARα-knockout mice, which were less sensitive to body weight changes and eye opening (Abbott et al., 2007) and MGD delays (Zhao et al., 2012). PPAR activation is more sensitive in mice than in other species, including rats and humans (Corton et al., 2014); note that this study is specific to the mode of action of liver tumours and its conclusions are not necessarily applicable to other effects. Although the data from the studies described above provide indication of some reproductive and developmental effects at low doses, the data are not currently considered to be an appropriate basis for quantitative risk assessment; however, if further studies demonstrate consistency of these effects in other species or their relevance to humans, the endpoint could become a more appropriate basis for the PFOA evaluation.

Few epidemiological studies have investigated the developmental effects described above, which limits the ability to conclude on the relevance of these effects in humans. The human observations related to weight gain in adulthood after developmental PFOA exposures were increased odds of women being overweight and having increased biomarkers of adiposity at 20 years of age after *in utero* exposures (with maternal serum levels of 5.8 ng/mL, as compared with levels of 2.3 ng/mL) (Halldorsson et al., 2012). Estrogenic observations were limited to delayed puberty in girls, and slight associations between PFOA concentration and shorter duration of breastfeeding. As previously discussed, care should be taken before concluding on health effects based on these epidemiological studies. The nature of the observed associations between PFOA exposure and the developmental outcomes need to be investigated further because of the lack of consistency across studies, the non-specificity of the outcomes, the misunderstanding of the mechanism of action, the borderline significance and lack of strength and dose-response of many results, and the presence of various limitations inherent to the study design, such as the possibility of residual confounding, biases due to errors in outcome measurements, and chance.

Hepatic effects were observed at slightly higher levels than reproductive effects, but observations of changes were still made at PFOA doses of ≤0.3 mg/kg bw per day. Increased relative liver weight was observed at ≥0.1 mg/kg bw per day in prenatally-exposed mouse pups (Abbott et al., 2007; Macon et al., 2011) and at ≥0.15 mg/kg bw per day in adult mice (Kennedy, 1987; Loveless et al., 2006, 2008). Dose-related increases in incidence and severity of hepatocellular hypertrophy were observed at ≥0.3 mg/kg bw per day in rats (Perkins et al., 2004; Loveless et al., 2008) and mice (Loveless et al., 2008) exposed subchronically to PFOA. Although increases in hepatocellular hypertrophy and liver weight were observed at slightly lower levels in other studies, Perkins et al. (2004) was selected as a key study that was representative of the database for the endpoint. Hepatocellular hypertrophy was observed in male rats in the Perkins study at ≥0.64 mg/kg bw per day, which is on the same order of magnitude as the studies demonstrating LOAELs of 0.1–0.3 mg/kg bw per day. A major advantage presented by the Perkins study is that a NOAEL was observed (0.06 mg/kg bw per day), whereas the LOAELs in the majority of other low dose studies were the lowest administered doses. A similar NOAEL of 0.05 mg/kg bw per day can be obtained from Kennedy et al. (1987) when Health Canada (1994) assumptions for food intake and bodyweight in rats (Health Canada, 1994) are used, but the authors did not provide actual values of measured doses. A further advantage of the Perkins study

over the other low-dose studies is that the study duration was longer, with exposure durations of up to 13 weeks; moreover, in addition to *ad libitum* controls, the study provided pair-fed controls to ensure that effects did not result from food consumption quantities. Finally, PPAR-α activity was measured in the Perkins study, and was only increased at ≥1.94 mg/kg bw per day; because this suggests that hepatocellular hypertrophy was not resulting from peroxisome proliferation, human relevance of this endpoint cannot be excluded. A NOAEL of 0.06 mg/kg bw per day is also supported by the most conservative NOAEL for hepatic biochemical effects, which was estimated at 0.055 mg/kg bw per day in male rats demonstrating increased alkaline phosphatase levels in conjunction with increased liver weight (Kennedy et al., 1986), using default assumptions for bodyweight and inhalation rates (Health Canada, 1994), and linearly scaling from periodic to continuous exposure. The NOAEL is also approximately 10-fold lower than the NOAEL and 30-fold lower than the LOAEL for hepatic necrosis (0.56 and 1.72 mg/kg bw per day, respectively) observed in rats exposed for 90 days (Goldenthal et al., 1978a).

Although increased liver weight and hepatocellular hypertrophy can sometimes be considered effects that are adaptive rather than adverse in their own right, evidence of other histological effects in the liver at higher concentrations provide an indication of their progression upon continued exposure (ECETOC, 2002; Hall et al., 2012). An adverse histological effect (portal mononuclear cell infiltrate) was observed in livers of male rats at the same dose where significant increases in hepatocellular hypertrophy were observed (14.2 mg/kg bw per day of PFOA for 2 years; Butenhoff et al., 2012b). Although this dose is much higher than the lowest points of departure for increased liver weight and hepatocellular hypertrophy observed in subchronic studies, the latter effects are proposed as critical effects for this assessment, as they might be sensitive indicators of the potential for the progression of adverse histological effects. Additional histological effects observed in rats in studies of shorter duration included necrosis at ≥1.72 mg/kg bw per day (Goldenthal et al., 1978a; Loveless et al., 2008), cytoplasmic vacuolation at ≥5 mg/kg bw per day (Cui et al., 2009), and fatty change, angiectasis, congestion, and acidophil lesion at 20 mg/kg bw per day (Cui et al., 2009). Therefore, increased liver weight and hepatocellular hypertrophy are considered in the dose–response assessment—despite their potential to be adaptive, rather than adverse, effects—as a means of preventing the more serious histological effects observed in other studies or at higher doses. The use of conservative endpoints for liver effects is also somewhat supported by epidemiology studies, in which some associations between PFOA exposure and increases in liver enzymes (including AST, ALT, and GGT) were observed; however, the associations between serum PFOA levels and liver effects cannot be used to draw definitive conclusions in humans because of limitations. These limitations include the lack of consistency and specificity of the outcomes, the weakness of the effects, and the study designs presenting many limitations (e.g., do not allow for verification of temporality). Serum levels at which these effects were observed in humans were on the order of 1,000 ng/mL in occupational studies and <10 ng/mL in environmental studies, which were lower than serum concentrations associated with the NOAEL and LOAEL for the 13-week Perkins study (7,100 and 41,000 ng/mL, respectively).

Changes in serum lipid levels were also observed around the levels at which hepatic effects occur. The lowest dose at which serum lipid changes were observed was 0.3 mg/kg bw per day in rats exposed for 14 days (decreased total cholesterol; Loveless et al., 2006) or 29 days (decreased total and HDL cholesterol; Loveless et al., 2008). Typical observed changes were decreases in total cholesterol, HDL, and triglycerides. These effects are important for consideration during the assessment of PFOA risks, as epidemiology studies generally demonstrated positive associations between PFOA and serum cholesterol levels. Inconsistencies

in effect were observed not only in between the two databases, but also within both the toxicology (see Section 9.2.2.2) and epidemiology (see Section 9.1.2.2) databases. Clear dose–response relationships also tended to be absent in the animal studies. Due to these weaknesses, quantitative assessments were not performed for serum lipid effects; however, based on the present database, a TDI based on liver effects is assumed to be sufficiently protective of lipid changes.

Benchmark doses (BMD_{10}) and their 95% lower confidence limits ($BMDL_{10}$) were calculated for hepatocellular hypertrophy for male rats (Perkins et al., 2004). The analysis was performed using the U.S. EPA's BMDS (version 2.6.0.1) and BMD models were selected based on visual inspection of the curve, goodness of fit p-value ≥0.1, and BMD/BMDL ratios <10. Eight models were selected according to these criteria. The logprobit model provided the best fit (i.e., lowest Akaike information criterion). Estimated BMD values were BMD_{10} of 0.13 mg/kg bw per day and $BMDL_{10}$ of 0.05 mg/kg bw per day.

To reflect the large interspecies differences in pharmacokinetics, a human-equivalent point-of-departure (POD_{HEQ}) was calculated for hepatocellular hypertrophy as follows:

$$POD_{HEQ} = \frac{0.05 \text{ mg/kg bw per day}}{96}$$

$$= 0.000625 \text{ mg/kg bw per day}$$

where:

- 0.05 mg/kg bw per day is the $BMDL_{10}$ for hepatocellular hypertrophy in rats from Perkins et al. (2004), which was selected to represent the hepatocellular hypertrophy and liver weight increase database; and
- 96 is the dose-specific AK_{UF} for rats in the 0.01 mg/kg bw per day range (as described in Section 8.6.2).

Using the calculated POD_{HEQ}, the non-cancer TDI was calculated as follows:

$$TDI = \frac{0.000521 \text{ mg/kg bw per day}}{25}$$

$$= 0.000021 \text{ mg/kg bw per day}$$

where:

- 0.000521 mg/kg bw per day is the POD_{HEQ} calculated for hepatocellular hypertrophy in rats, as described above; and
- 25 is the composite uncertainty factor, as described below.

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (×2.5) and intraspecies uncertainty factor (×10). An interspecies uncertainty factor of 2.5 was used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. Likewise, a default value of 10 was applied for the intraspecies UF. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur

between species, insufficient data on the mechanism of PFOA excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. Average half-life values calculated from longitudinal data for different populations previously exposed to PFOA were similar (averages for each population ranged from 2.3–3.8 years; Olsen et al., 2007; Bartell et al., 2010; Brede et al., 2010); however, studies providing ranges indicated that there was approximately a 10-fold difference between the lowest and highest estimates of half-life. If further studies of PFOA consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed. No uncertainty factor was used for subchronic-to-chronic extrapolation, as liver effects were investigated in a chronic study (Butenhoff et al., 2012b), and increasing duration of exposure did not appear to worsen the effects in the key study (Perkins et al., 2004).

Using this TDI, the HBV for drinking water can be calculated as follows:

$$\text{HBV} = \frac{0.000021 \times 70\ \text{kg} \times 0.2}{1.5\ \text{L/day}}$$

$$= 0.00019\ \text{mg/L}$$

$$\approx 0.0002\ \text{mg/L}\ (0.2\ \mu\text{/L})$$

where:

- 0.000019 mg/kg bw per day is the TDI derived above,;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7).

10.3 Comparison of cancer and non-cancer risk assessment

The HBV for the non-cancer assessment, which was 0.0002 mg/L for hepatocellular hypertrophy in rats, is more conservative than the HBV for Leydig cell tumours of 0.03 mg/L. The HBV of 0.0002 mg/L that was derived for non-cancer effects is therefore considered to be sufficiently protective of the carcinogenic effects of PFOA.

10.4 Application of additive approach

In keeping with a precautionary approach, the currently available data support the implementation of an additive approach for PFOS and PFOA when evaluating situations where PFOS and PFOA co-occur in drinking water. Given that PFOS and PFOA are the predominant PFAS detected in Canadian water samples and the lack of toxicological data on PFAS besides PFOS and PFOA, the additive approach was not extended to other PFAS. Of the existing additivity approaches for risk assessment (i.e, hazard index, point of departure index, combined

margin of exposure index, toxic unit summation, and relative potency factors/toxic equivalency factors; Meek et al., 2011; SCHER, 2012), the hazard index approach was deemed to be the best choice for PFOS and PFOA that is health protective. The hazard index is the sum of the hazard quotients (i.e., the ratios between exposure and the reference value) for each component to be evaluated (SCHER, 2012). When the hazard index is less than 1, the combined risk is considered acceptable; values greater than 1 indicate potential health concern. This approach is the preferred approach for chemicals with high quality toxicology data (e.g., dose-response data, health hazard information), reflecting the scientific knowledge and toxicity associated with each chemical, and it is transparent and easy to apply (Meek et al., 2011; SCHER, 2012), although it is likely to overestimate risk (Boobis, 2009; Meek et al., 2011). Additionally, the value of this approach has been demonstrated for the combined risk assessment of PFOS and PFOA (Ludwicki et al., 2015) and for 17 perfluoroalkylated substances (Borg et al., 2013). Borg et al. (2013) noted that their assessment of 17 perfluoroalkylated congeners should be looked upon as conservative, given that the use of the hazard index approach is likely to overestimate risk (Boobis, 2009; Meek et al., 2011) and that the majority of congeners lack toxicological data, requiring the use of read-across extrapolations to the closest congeners with longer carbon chain lengths (assuming that potency is proportional to carbon chain length). Similarly, Ludwicki et al. (2015) cited the lack of toxicological data on other congeners besides PFOS and PFOA as a reason for not including them in any cumulative risk assessments of perfluoroalkylated substances. The differences between PFOS and PFOA described above (in section 9.4), in particular the lack of evidence demonstrating that a single receptor is required to mediate the toxicities of PFOS and PFOA and the ability of PFOS and PFOA to induce a multitude of toxicities, preclude the use of a scaling system analogous to the toxicity equivalence factor system used for polychlorinated biphenyls and polycyclic aromatic hydrocarbons (Scialli et al., 2007; Peters and Gonzalez, 2011). Therefore, in employing the additive approach for PFOS and PFOA, the addition of the observed concentration to MAC ratios for PFOS and PFOA should be kept below the value of 1. This approach can be expressed as:

$$\frac{\text{PFOA concentration}}{\text{MAC}_{\text{PFOA}}} + \frac{\text{PFOS concentration}}{\text{MAC}_{\text{PFOS}}} < 1$$

Or

$$\frac{\text{PFOA concentration in } \mu g/L}{0.2\ \mu g/L} + \frac{\text{PFOS concentration in } \mu g/L}{0.6\ \mu g/L} < 1$$

10.5 International considerations

The U.S. EPA (2016) has established a lifetime health advisory (LHA) of 0.07 µg/L (0.000 07 mg/L) for PFOA. This LHA was derived from a LOAEL of 1.0 mg/kg bw per day for reduced ossification and accelerated puberty (in males) in pups following maternal exposure to PFOA on GD 1–17 by oral gavage (Lau et al., 2006). A reference dose (RfD) of 0.000 02 mg/kg bw per day (0.02 µg/kg bw per day) was derived by applying pharmacokinetic modeling to serum PFOA concentrations to calculate a human equivalent dose (HED) (equivalent to an uncertainty factor of 189 from the LOAEL to the HED to account for interspecies differences in toxicokinetics). An additional uncertainty factor of 300 (10 for intraspecies differences, 3 for interspecies toxicodynamic differences, and 10 for use of LOAEL) was applied to the HED (U.S.

EPA, 2016). From the RfD, a health advisory of 0.07 µg/L was calculated assuming a drinking water exposure level of 0.054 L/kg bw per day (the 90th percentile drinking water intake for lactating women; a 3.78 L/day equivalent is calculated assuming 70 kg body weight). Additionally, when PFOA co-occurs with PFOS at the same time and location in a drinking water source, the U.S. EPA recommends comparing the sum of the concentrations of PFOS and PFOA to the LHA of 0.07 µg/L.

The Australia Department of Health (2017) has established a health-based drinking water quality value of 0.56 µg/L (0.000 56 mg/L) for PFOA based on a TDI calculated by Food Standards Australia and New Zealand (FSANZ, 2017). This drinking water quality value was derived from a NOAEL of 1 mg/kg bw per dayfor decreased body weight gain occurring at doses ≥ 3 mg/kg bw per day in mouse pups following maternal exposure to PFOA on GD 1-17 by oral gavage (Lau et al., 2006). A TDI of 0.000 16 mg/kg bw per day (1.6 µg/kg bw per day) was derived by applying pharmacokinetic modeling to serum PFOA concentrations to calculate a HED (equivalent to an uncertainty factor of 204 from the NOAEL to the HED to account for interspecies toxicokinetic differences). An additional uncertainty factor of 30 (10 for intraspecies differences and 3 for interspecies toxicodynamic differences) was applied to the HED. From the TDI, a drinking water quality value of 0.56 µg/L was calculated using a body weight of 70 kg, water consumption of 2 L/day, and an allocation factor of 0.1.

A drinking water guideline of 10 µg/L (0.01 mg/L) was derived by the UK Health Protection Agency (UK HPA, 2007, 2009) based on a TDI of 3,000 ng/kg bw per day (3 µg/kg bw per day) previously derived by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (UK COT, 2006). This TDI was based on a POD of 0.3 mg/kg bw per day, corresponding to the lowest $BMDL_{10}$ for increased liver weights in rats exposed for 13 weeks (data from Palazzolo, 1993 and Perkins et al., 2004); this value was similar to the $BMDL_{10}$ (0.31 mg/kg bw per day) for hepatic necrosis in F0 and F1 male rats (data from Butenhoff et al., 2004b). An uncertainty factor of 100 (for intra- and inter-species variation) was applied. The drinking water guideline (10 µg/L) was derived from the TDI using an allocation factor of 50%, a body weight of 5 kg and a water ingestion rate of 0.75 L per day for bottle-fed infants (UK HPA, 2007).

In their scientific opinion document on contaminants in the food chain, the CONTAM panel under the European Food Safety Authority derived a TDI of 1,500 ng/kg bw per day (1.5 µg/kg bw per day) based on a $BMDL_{10}$ of 0.3 mg/kg bw per day in rats (EFSA, 2008). This value refers to the lowest $BMDL_{10}$ identified for effects on the liver (Palazzolo, 1993; Butenhoff et al., 2004b; Perkins et al., 2004) among those (0.3–0.7 mg/kg bw per day) derived from a number of studies in mice (Lau et al., 2006) and male rats (Sibinski, 1987; Palazzolo, 1993; Butenhoff et al., 2004b; Perkins et al., 2004). The $BMDL_{10}$ was divided by an uncertainty factor of 200 (10 for interspecies differences, 10 for intraspecies differences and 2 to compensate for uncertainties relating to the internal dose kinetics).

11.0 Rationale

PFOA is an anthropogenic compound used in the manufacture of stain/water-resistant coatings for various consumer products. Environmental concentrations, and therefore potential exposure levels, may be higher in areas near facilities using high amounts of PFOA and near locations with extinguished fires if PFOA-containing fire-fighting foams were used. Canadians can be exposed to PFOA in food, consumer products, dust, and drinking water. The major sources

of PFOA are expected to be food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Based on its physico-chemical properties, exposure to PFOA via inhalation and dermal routes during showering or bathing is expected to be negligible.

Chronic exposure to PFOA has been associated with both cancer and non-cancer effects in animals and humans. HBVs for both endpoints have been calculated, with the non-cancer effects resulting in a lower, more conservative value.

Epidemiological studies have shown associations between exposure to PFOA and multiple non-cancer health outcomes, such as dysfunctions of the immunological system and alterations in birth weight and lipid levels. However, these studies cannot be used to derive the non-cancer HBV for PFOA due to limitations in terms of design, bias, confounding, and possibility of chance findings. In animals, non-cancer effects observed at the lowest levels of exposure include reproductive and developmental effects, liver effects and changes in serum lipid levels. For various reasons described in section 10.2, the most appropriate endpoint to derive a HBV for PFOA is hepatocellular hypertrophy (liver effects) in rats, occurring at the same levels as the changes in serum lipid levels. Using a TDI approach, a HBV of 0.0002 mg/L (0.2 µg/L) has been calculated for the non-cancer effects of PFOA based on liver effects in rats. This HBV is considered to be sufficiently protective of both cancer and non-cancer effects of PFOA.

A MAC of 0.0002 mg/L (0.2 µg/L) is established for PFOA in drinking water. This MAC for PFOA can be measured by available analytical methods and is achievable by municipal and residential treatment technologies.

However, when detected in drinking water, PFOA is often found with other PFAS, including PFOS. There is currently insufficient science to develop guidelines for PFAS other than PFOS and PFOA. Given the similarity of the health effects used to establish the MACs for PFOS and PFOA, and the extensive characterization of their toxicity and toxicokinetics, as well as the limited information on the risks and uncertainties of other PFAS, current science only supports the use of an additive approach for PFOS and PFOA. Although current science does not justify the use of this approach for other PFAS, it does support additivity for PFOA and PFOS, based on the similarity of the health effects used to establish their respective MACs, and the extensive characterization of their toxicity and toxicokinetics. Thus, when PFOS and PFOA are found together in drinking water, the best approach to protect human health is to consider both chemicals together, by ensuring that the sum of the ratios of the observed concentration to the MAC for PFOA and PFOS does not exceed 1. As part of its ongoing guideline review process, Health Canada will continue to monitor new research and recommend any change to the guideline that is deemed necessary.

12.0 References

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Appendix A: Reported full-scale drinking water treatment plant PFOA removal data

Developed from table 3 in Rahman et al. (2014)

Water Source	Treatment Train[2]	Influent concentration[3] (ng/L)	Effluent concentration[3] (ng/L)	% Removal of PFOA	Reference
Groundwater	DBF, UV, Cl_2	10	9.4	6	Quinones and Snyder, 2009
Surface water	O_3, COA/FLOC, DBF, Cl_2	1.4	1.4	0	Quinones and Snyder, 2009
Surface water	PAC, CHLM, DBF	1.7	1.9	-12	Quinones and Snyder, 2009
Surface water	Cl_2, COA/FLOC, DBF, UV	22	22	0	Quinones and Snyder, 2009
Planned potable indirect reuse facility	MF/RO, UV/H_2O_2, SAT	41	ND	100	Quinones and Snyder, 2009
Planned potable indirect reuse facility	Cl_2, DL, SAT	29	57	-97	Quinones and Snyder, 2009
River water	RSF, O_3, GAC, Cl_2	1.0 (summer)	0.93 (summer)	7	Takagi et al., 2008
River water	RSF, O_3, GAC, Cl_2	0.87 (summer) 3.2 (winter)	2.8 (summer) 1.6 (winter)	-222 (summer) 50 (winter)	Takagi et al., 2008
River water	RSF, O_3, GAC, Cl_2				Takagi et al., 2008
Lake water	RSF, GAC, Cl_2	4.6 (summer) 4.5 (winter)	0.16 (summer) <0.1 (winter)	97 (summer) >98 (winter)	Takagi et al., 2008
River, lake, subsoil and groundwater (7 plants)	RSF, Cl_2	0.56 – 22 (sum) 0.54 – 4.2 (win)	0.45 – 22 (sum) 0.37 – 4.5 (win)	20 – 0 (summer) 31 to -7 (winter)	Takagi et al., 2008
River water	Membranes, Cl_2	0.37 (summer) 0.26 (winter)	0.29 (summer) 0.20 (winter)	22 (summer) 23 (winter)	Takagi et al., 2008
Lake water	SSF, Cl_2	2.7 (summer) 1.8 (winter)	2.3 (summer) 1.9 (winter)	15 (summer) -6 (winter)	Takagi et al., 2008
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.3 (summer) 3.3 (winter)	3.7 (summer) 1.3 (winter)	-185 (summer) 60 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.6 (summer) 3.3 (winter)	2.3 (summer) 1.7 (winter)	44 (summer) 48 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.2 (summer) 2.8 (winter)	1.6 (summer) 1.9 (winter)	-33 (summer) 32 (winter)	Takagi et al., 2011
River water	SED, O_3, GAC, Cl2, SF	1.4 (summer) 3.3 (winter)	2.2 (summer) 2.0 (winter)	-57 (summer) 39 (winter)	Takagi et al., 2011
Lake water	COA/FLOC/SED, SF, GAC (reactivated), Cl_2	4.4 (summer) 4.1 (winter)	<0.5 (summer) <0.5 (winter)	>89 (summer) >88 (winter)	Takagi et al., 2011
Ground water	UF, Cl_2	16	16	0	Atkinson et al., 2008
Ground water	GAC (not in operation), super chlorination and dechlorination	135	130	3	Atkinson et al., 2008

Water Source	Treatment Train[2]	Influent concentration[3] (ng/L)	Effluent concentration[3] (ng/L)	% Removal of PFOA	Reference
Ground water	GAC (2 parallel GAC trains each having 6 beds; contactors are mature and act as biological contactors; not been regenerated for some years), Cl_2	42	45	-7	Atkinson et al., 2008
Ground and surface water (60:40)	SSF, O_3, GAC (6 beds-no regeneration for several years), Cl_2using NaOCl	20.6	25	-21	Atkinson et al., 2008
Ground water	Cl_2 using NaOCl				Atkinson et al., 2008
River water	COA/FLOC/SED, O3, GAC, RSF	5.3 (Aug) 5.8 (Oct)	9.4 (Aug) 6.4 (Oct)	-77 (Aug) -10 (Oct)	Shivakoti et al., 2010)
River water	COA/FLOC/SED, O3, GAC, RSF	5.8 (Aug) 8.8 (Oc)	3.9 (Aug) 4.2 (Oct)	33 (Aug) 53 (Oct)	Shivakoti et al., 2010)
Treated wastewater	De-nitrification, pre-O_3, OA/FLOC/SED, DAF, O_3, GAC (acts as biological contactor), O_3	2,2 (Oct) 3.7 (Nov) 3.6 (Nov)	<LOR (0.3) (Oct) 0.6 (Nov) 0.7 (Nov)	100 (Oct) 84 (Nov) 81 (Nov)	Thompson et al., 2011b
River water	COA/FLOC/SED, RSF, Cl_2	5.02	0.73	85	Kunacheva et al., 2010)
Treated wastewater	Clarifier/lamellar settler ($FeCl_3$&$(NH_4)_2SO_4$, NaOCl addition), UF, RO, UV+H_2O_2, stabilization/disinfection (addition of lime, CO_2, NaOCl)	38 39 23	<LOR (0.5) ND <LOR (0.2)	100 100 100	Thompson et al., 2011
River water	COA/FLOC, RSF, O_3, GAC, SSF	8.2	<0.23	<97	Eschauzer et al., 2012
River water	Cl_2, COA/FLOC, RSF, O_3, GAC	116	33	69	Flores et al., 2013
River water	Cl_2, COA/FLOC, RSF, O_3, GAC, UF, RO	86	13	86	Flores et al., 2013

[1] COA/FLOC/SED = coagulation/flocculation sedimentation; DAF = dissolved air flotation; DL=dilution; GAC = granular activated carbon; O_3 =ozonation; RSF = rapid sand filtration; SSF = slow sand filtration; SF = sand filtration; NaOCl = sodium hyochlorite; Cl_2 = chlorine; RO = reverse osmosis; UF = ultrafiltration; IX = ion exchange; UV/H_2O_2 = ultraviolet irradiation/hydrogen peroxide; SAT = soil aquifer treatment; CHLM = chloramines;
[2]LOR = limit of reporting; ND = not detected

Appendix B: List of acronyms

AFFF	aqueous film-forming foam
ALT	alanine transaminase
APFO	ammonium perfluorooctanoate
BMD	benchmark dose
BMDL	lower confidence limit on the benchmark dose
$BMDL_{10}$	lower 95% confidence limit on the benchmark dose for a 10% response
BV	bed volume
CAS	Chemical Abstracts Service
CI	confidence interval
CSAF	chemical specific adjustment factor
DI	direct injection
DL	detection limit
EBCT	empty bed contact time
EPA	Environmental Protection Agency (U.S.)
ESI	electrospray ionization
GAC	granular activated carbon
GD	gestational day
GM	geometric mean
HBV	health-based value
HED	human equivalent dose
HPLC	high performance liquid chromatography
ISO	International Standard Association
IT	ion-trap
LC	liquid chromatograph
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantitation
LLE	liquid-liquid extraction
MAC	maximum acceptable concentration
MDL	method detection limit
MGD	mammary gland development
MG/D	million gallons per day
MOA	mode of action
MRL	minimum reporting level
MS/MS	tandem mass spectrometry
NF	nanofiltration
NHANES	National Health and Nutrition Excamination Survey (U.S.)
NOAEL	no-observed-adverse-effect level
NOM	natural organic matter
PAC	powdered activated carbon
PBPK	Physiologically-based pharmacokinetic
PEFT	polytetrafluoroethylene
PFA	perfluoroalkyl

PFAA	perfluorinated alkyl acid
PFAS	perfluoroalkyl substance
PFCA	long-chain perfluorocarboxylic acids
PFDA	perfluorodecanoic acid
PFHxS	perfluorohexanesulfonate
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PND	postnatal day
POD	point of departure
POD_{HEQ}	human-equivalent points-of-departure
PTFE	polytetrafluoroethylene
RBF	river bank filtration
RO	reverse osmosis
SPE	solid phase extraction
TDI	tolerable daily intake
TDS	total diet study
UCMR3	third Unregulated Contaminant Monitoring Rule (U.S.)
WAX	weak anion exchange

Fishwick, David HLTH:EX

From: Anne Vezina <anne.vezina@hc-sc.gc.ca>
Sent: May 10, 2017 12:22 PM
To: angelina.polegato@novascotia.ca; Caroline.Robert@mddelcc.gouv.qc.ca; Fishwick, David HLTH:EX; donald.reid@gov.ab.ca; Peter_Workman@gov.nt.ca; ghsomers@gov.pe.ca; hkhan@gov.nl.ca; Kevin.Gould@gnb.ca; Kim.Philip@gov.mb.ca; pat.brooks@gov.yk.ca; sam.ferris@wsask.ca; Satish.Deshpande@ontario.ca; MLeBlanc-Havard@GOV.NU.CA
Cc: John Cooper; Michele Giddings; Stephanie McFadyen; Richard Carrier; France Lemieux; Veronique Morisset; Tanya Boucher; Wendy Enright
Subject: Power point presentations from CDW meeting
Attachments: Cdw2017-05 (presentations) final.pdf

CDW folks,

Thank you all for your participation in another (rainy) CDW meeting last week in Ottawa. It was great to see you all!

For your information, I have attached the PDF package of all the presentations from the meeting.

(See attached file: Cdw2017-05 (presentations) final.pdf)

Cheers,
Anne

Anne Vézina
Coordinator of the F/P/T Committee on Drinking Water
Coordonatrice du Comité F/P/T sur l'eau potable
Water and Air Quality Bureau
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Draft Agenda

FPT Committee on Drinking Water - May 2017 (269 Laurier West, Ottawa, Ontario)		
	Wednesday May 3rd, 2017	**Thursday May 4th, 2017**
8:30 am	1-A Opening 2-A Adoption of agenda 2-B Approval of minutes 2-C CDW status/checklist 2-D Bill C-326 2-E CDW priority list 2-F Withdrawal of old guidelines	4-D 1,4-Dioxane 4-E Chloramines 4-F Barium 4-G 2,4-D
10:30 am	Break	Break
11:00 am	3-A Protozoa 3-B Coliform 5-A Guidance for well owners	4-H Strontium 4-I Microcystins (recreational) 4-J Other chemical/radiological (atrazine, etc)
12:00 am	Lunch	Lunch
1:00 pm	3-C Enterococci 3-D Other microbiological (QMRA, viruses, etc.) 4-A NOM	6-A FNIHB report 6-B WHO report 6-C CHE report 6-D CCME report 5-B EHSRB update 5-C INAC update
2:30 pm	Break	Break
2:45 pm	4-B Lead 4-C PFOS, PFOA	7-A Member's reports 8-A Future meetings
5:00 pm	End of meeting	End of meeting
NB: Meeting will be held in room 7-086 and will run from 8:30 AM to Noon and from 1:00 PM to 5:00PM. The social dinner will be held on Wednesday.		

Item 2-C
CDW Status

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Guideline status by milestone

Last update -April 25th 2017

Dates in cells: Month-Year (ex: July 2013: 0713)

Parameter	A1	A2			A3	A4	A5	A6	A7	A8	B1	B2	B3	B4	B5	B6	C1	C2	C3	C4	D1	D2	D3	D4	D5	D6	D7	D8	E1	Comments
Viruses	0114	X	X	X	N/A	0216	0416	0416	0416	0416	1016	1216	N/A	0317	0317						1017	1117								Doc to be approved for cons posting
Protozoa	0914	X	X	X	N/A	0815	0916	1016	0116	1015	1115	0216	N/A	0816	0816	0916	1016	0117	0417	0417	0417	0517								With CDW for review
Bacteriological-Ecoli																													0613	
Bacteriological-Coliform	0816	0916	X	X	N/A					1017	1117																			Draft doc for November meeting
GMRA		X	X	X	N/A	0516	0716	0816	0816	0918	1016	1116	N/A									1117								Doc translated and to be posted for consultation
Enterococci	0216	X	X	X	N/A	0217	0317	0317	0417	0417	0517																			With CDW for review
Uranium	0412	X	X	X	0116	0216	0316	0416	0416	0416	1016	0916	N/A	1216	0317							1117								Doc to be approved for cons posting
Copper	1012	X	X	X	0516	0716	0916	1016	1016	1016	1016	0117	0417									1117								Doc translated and to be posted for consultation
PFOS	0113	X	X	X	0615	0715	0915	0915	0116	1015	1115	0316	0516	0516	0516	0516	0616	0916	0317	0317	0417	0517								With CDW for review
PFOA	0113	X	X	X	0615	0715	0915	0915	0116	1015	1115	0316	0516	0516	0516	0516	0616	0916	0317	0317	0417	0517								With CDW for review
NOM	0214	X	X	X	N/A	0117	0217	0417	0417	0417	0517											0516								
Strontium	1114	X	X	X	0916	1015	1216	0317	0517	0517	0517																			With CDW for review
Chloramines	1114	X	X							1017	1117																			Draft doc for November meeting

CDW Meeting May 2017 CDW Status

2

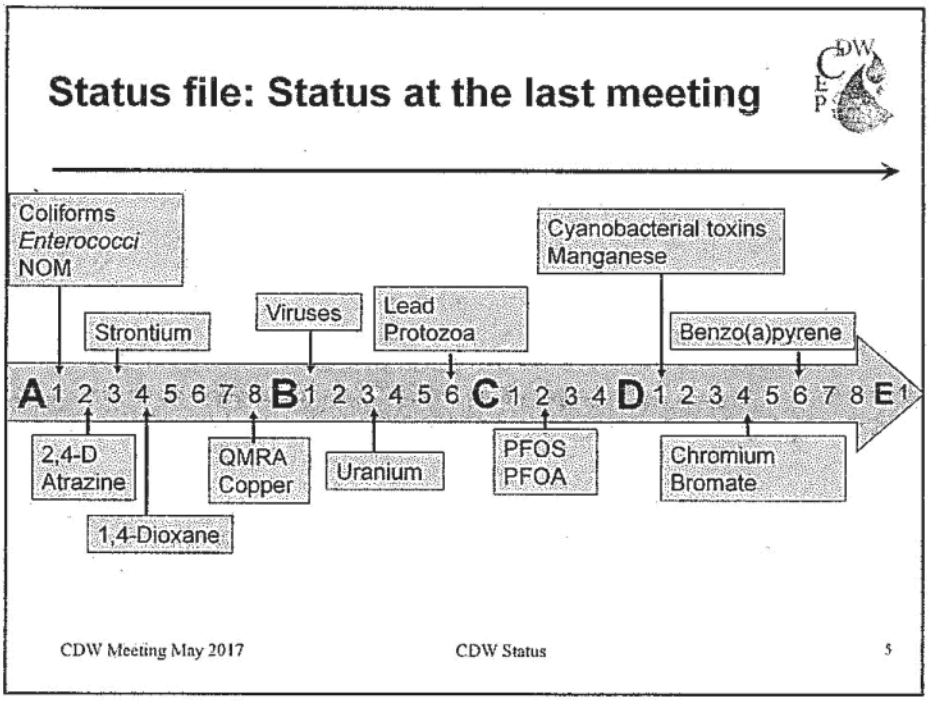
Guideline status by milestone (cont'd)

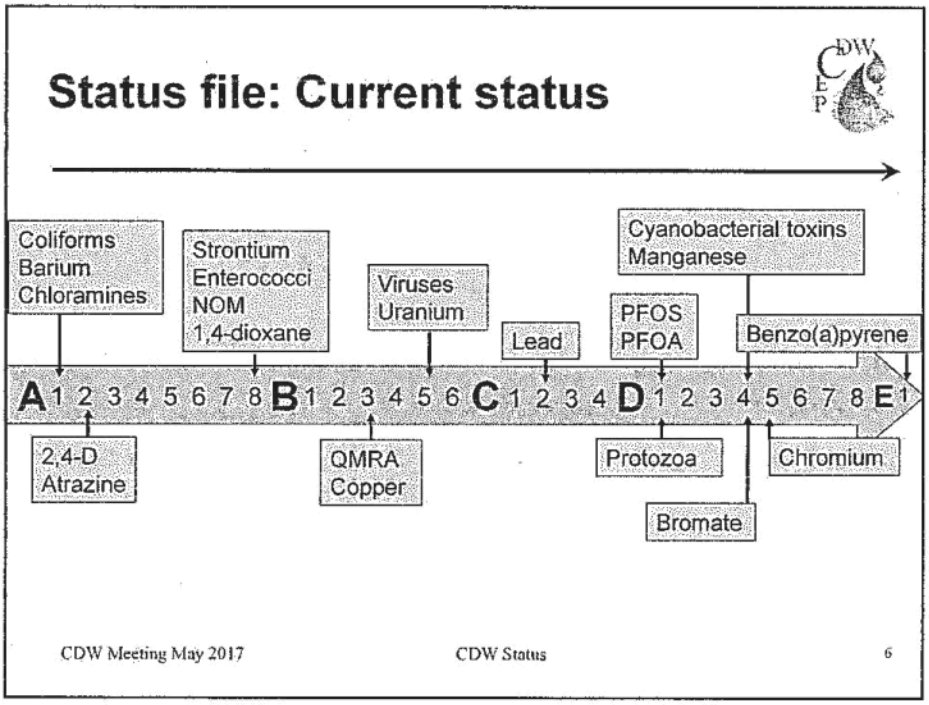
Last update -April 25th 2017 Dates in cells: Month+Year (ex: July 2013: 0713)																										Comments
Parameter	A1	A2		A3	A4	A5	A6	A7	A8	B1	B2	B3	B4	B5	B6	C1	C2	C3	C4	D1	D2	D3	D4	D5	D6	D7	D8	E1	
Barium	0116	0416							0917	1117																			Draft doc for November meeting
Cadmium									0416	0516																			Draft doc for May 2018 meeting
Dioxane, 1,4-	1214			0816		0816	1216		0417	0517																			With CDW for review
Chromium	0709	1214		0714	0814	0914	0915	0417	1014	1014	0515	EA		0515		0715		0715			0116	0316		0316					Doc CHE approved, to be finalized for posting
Dichlorophenoxyacetic acid, 2,4- (2,4-D)	0709								1017	1117											1116								
Lead	0416	0714		0714	0814	0115	0215	0915	0415	0515	0816										1117								Public consultation ended March 15th 2017
Bromate	0410	0714		0814	0914	1014	1014	1014	1014	1014	1216	EA		0915							0516	0616							Doc CHE approved, to be
Aluminum																													
Manganese	0410			0815		0815		0815	1015												1116	0117							CHE approved March 24th
Boron	0616									0516																			Draft doc for May 2018 meeting
Atrazine	0710																												PMRA special review
Cyanobacterial toxins	0112			0714		1214		0115	0415	0515																			CHE approved Feb 24th

CDW Meeting May 2017 CDW Status 3

Status of Approvals

	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
		2016				2017				2018			
Name of parameter	January - February - March	April - May - June	July - August - September	October - November - December	January - February - March	April - May - June	July - August - September	October - November - December	January - February - March	April - May - June	July - August - September	October - November - December	January - February - March
Final Document													
Aldicarb(s) (oxime)	CHE												
Atrazine													
2,4-D													
Cyanobacteria toxins				CDW	CHE								
PFOS						CDW	CHE						
PFOA						CDW	CHE						
Chromium	CDW/CHE												
Lead								CDW	CHE				
Bromate		CDW		CHE									
Uranium								CDW	CHE				
Manganese				CDW	CHE								
Protozoa						CDW	CHE						
Viruses								CDW	CHE				
Copper										CDW	CHE		
NDMA												CDW	CHE
CMRA										CDW	CHE		
Strontium												CDW	CHE
Dioxane, 1,4-												CDW	CHE
Total Cyanome													
Barium													
Cadmium													
Chloramines													
Cryptosporidium										CDW	CHE		
Public Consultation Document													
Cyanobacteria toxins	Feb												
PFOS		June											
PFOA		June											
Lead				December CDW									
Uranium						June							
Manganese		June											
Copper				CDW									
NDMA						CDW							
Protozoa				October CDW									
Viruses						June CDW							
Strontium						CDW							
Dioxane, 1,4-						CDW							
Chloramines								CDW					
Cryptosporidium						CDW							
Barium								CDW					
Cadmium										CDW			
Atrazine													
2,4-D													
CMRA				CDW									
Total Cyanome								CDW					
Boron										June			


Status file: Status at the last meeting
Coliforms
Enterococci
NOM
Strontium
Viruses
Lead
Protozoa
Cyanobacterial toxins
Manganese
Benzo(a)pyrene
A 1 2 3 4 5 6 7 8 B 1 2 3 4 5 6 C 1 2 3 4 D 1 2 3 4 5 6 7 8 E 1
2,4-D
Atrazine
1,4-Dioxane
QMRA
Copper
Uranium
PFOS
PFOA
Chromium
Bromate
CDW Meeting May 2017
CDW Status
5


Status file: Current status
Coliforms
Barium
Chloramines
Strontium
Enterococci
NOM
1,4-dioxane
Viruses
Uranium
Lead
Cyanobacterial toxins
Manganese
PFOS
PFOA
Benzo(a)pyrene
A 1 2 3 4 5 6 7 8 B 1 2 3 4 5 6 C 1 2 3 4 D 1 2 3 4 5 6 7 8 E 1
2,4-D
Atrazine
QMRA
Copper
Protozoa
Bromate
Chromium
CDW Meeting May 2017
CDW Status
6

Current priority list

1) Arsenic
2) Trihalomethanes (THMs)
3) Strontium
4) Chloramines
5) Dioxane, 1,4-
6) Haloacetic acids (HAAs)
7) Barium
8) Cadmium
9) Boron
10) Aluminum
11) Acrylamide
12) Trichloroethylene
13) Zinc
14) Iron
15) Formaldehyde
16) Hydrocarbons, F2, F3, F4
17) Odour (AO)
18) Perchlorate
19) Asbestos

Item 3-A
Protozoa

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Status

- Public consultation ended January 9th, 2017
- 11 sets of comments were received and addressed
- Document and table of comments were sent to CDW members for their review
- Seeking final CDW approval

Refresher

- Last publication date – 2012
- Guideline was not changed
- Changes from 2012 version include new information on:
  - Groundwater
  - *Cryptosporidium* genotypes
  - Impact of environmental conditions
  - Riverbank filtration

Consultation comments

- Overview
  - Generally positive
  - Mostly clarifications or requests for additional information on topics already included the document

Consultation comments Guideline statement

- *Where treatment is required for enteric protozoa, the guideline for* Giardia *and* Cryptosporidium *in drinking water is a health-based treatment goal of a minimum 3 log removal and/or inactivation of cysts and oocysts. Depending on the source water quality, a greater log removal and/or inactivation may be required. Treatment technologies and source water protection measures known to reduce the risk of waterborne illness should be implemented and maintained if source water is subject to faecal contamination or if* Giardia *or* Cryptosporidium *have been responsible for past waterborne outbreaks.*

- Modification from proposed consultation guideline – "watershed or wellhead protection" was replaced by "source water protection"

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Consultation comments Part I

- Executive summary
  - Included more specific advice from the main document to better reflect the recommendations in the guideline
- Application of the guideline
  - Clarified information on risk management for systems where protozoa monitoring is not being conducted
  - Included additional information on assessing the vulnerability of groundwater to faecal contamination
  - Added a section for the distribution system

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Consultation comments
Description, sources and exposure

- Description
  - Clarify the significance of detecting *Cryptosporidium* oocysts in water
  - Update *Cryptosporidium* taxonomy
- Sources and exposure
  - Included additional surface water data for Quebec and Ontario
  - Added additional detail from studies of enteric protozoa in groundwater and treated water
  - Expanded information on endemic illnesses and outbreaks
  - Added information on link between illness and weather events
  - Clarified use of indicator bacteria in surface, ground, and treated drinking water

Consultation comments
Analytical methods

- Analytical methods
  - Clarified details related to US EPA Method 1623(1623.1)
  - Clarified information on correcting for recoveries
  - Update information on staining methods

Consultation comments Treatment technology

- Groundwater
  - Additional exposure data, importance of classifying these sources, clarification of surrogates and riverbank filtration
- Membranes
  - Enhanced information on chemical cleaning, added note for direct integrity testing for NF/RO
- Disinfection
  - Added information on low temperature, clarified multi-disinfectant strategy
- Ultraviolet disinfection
  - Added information regarding fouling, clarified validation and dose

Consultation comments Health effects, assessment

- Health effects
  - Included information on new dose-response study
- Risk assessment
  - Further emphasis on characterizing source waters
  - Clarified use of *Cryptosporidium* genotyping information

CDW discussion / next steps

- Seeking CDW approval of the final guideline technical document for publication
- Next steps:
  - final CDW approval
  - final CHE approval
  - publication

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Item 3-B
Total coliform

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Background & Status

- Current version published in March 2012
- Little substantive change in the state of the science, therefore, full revision not required
- Instead, preparing an appendix containing updated technical information and references

Proposed updates

4.0 Significance of TC: lack of correlation with pathogens

5.0 Analytical methods: commercial method comparison, molecular methods, injured organisms

6.0 Sampling: large volume sampling, frequency and location

7.0 Treatment technology: system considerations re: distribution system/biofilms, materials impact, groundwater aquifers

8.0 International considerations: U.S. EPA's Revised Total Coliform Rule

Discussion / Next Steps

- Peer review
  - Late July
- CDW approval for consultation
  - Draft document to CDW in October
- Public consultation

Item 3-C
Enterococci

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Status

- Guidance document has been peer-reviewed, and comments incorporated
- The guidance document has been provided to CDW
- Seeking CDW approval for public consultation

Peer reviewers

- Dr. Philippe Cantin – Microbiologiste
  - Centre d'expertise en analyse environnementale du Québec (CEAEQ) - Ministère du Développement durable, de l'Environnement et de la Lutte contre les changements climatiques (MDDELCC)
- Dr. Norm Neumann – Professor
  - School of Public Health – University of Alberta
  - Alberta Provincial Laboratory for Public Health
- Dr. Murulee Byappanahalli – Research Microbiologist
  - Great Lakes Science Center – U.S. Geological Survey

Peer review comments

Some disagreement between reviewers about the usefulness of enterococci as an indicator

"Pro" side:

- The document makes a good case for enterococci as an indicator
- Enterococci may be a better faecal indicator than EC due to somewhat greater survival in the environment and post-treatment
- Less concerned about non-faecal occurrence: detection in environmental habitats has also been observed with *E. coli*

Peer review comments (cont'd)

"Con" side:

- The benefits of enterococci as an additional indicator are not convincingly demonstrated
- Potential for detecting enterococci that don't come from faecal contamination
- Variability among the methods
- Some methods take 48h

Response to peer review

- The overall direction taken:
  - The potential greater survivability of enterococci supports its further investigation as a fecal indicator.
  - Non-faecal sources are not a unique challenge. Confirmation and risk-based assessment is always important.
  - Positioning as a guidance document is fitting while more information is gathered.

Changes from peer review

- Clearer message about the survival of enterococci compared to *E. coli*
  - This is the rationale for why enterococci is a useful verification indicator
- More context about fecal and non-fecal sources
  - Recognizes that the use of other indicators , including *E. coli*, is also challenged by the presence of environmental strains.
- Emphasis on standardized methods and verification and the potential impacts these may have on time of analysis.
  - Standardized methods summarized in a table for ease of comparison
- Identified knowledge gaps and research needs

International considerations

- U.S. EPA
  - Under the Ground Water Rule, enterococci is one of three options as an indicator of faecal contamination that can be specified by the state for systems that have a total coliform-positive sample
- WHO
  - Fact sheet on intestinal enterococci; no guideline value.
- EU
  - Legislated in the EU Drinking water directive since 1980.
  - Used for "audit" monitoring, tested less frequently than "check" parameters (*E. coli*)
- Australia
  - Fact sheet on intestinal enterococci ; no guideline value.

Discussion / next steps



- Seeking CDW approval for 2 month public consultation period

Item 4-A
Natural Organic Matter

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Status

- Document has been peer-reviewed and comments incorporated
- Seeking CDW feedback on whether we continue to move forward as guideline or shift format to guidance document

Health effects of NOM

- Indirect effects on health are related to its impacts on drinking water processes:
  - Interferes with processes designed to remove or inactivate pathogens
  - Forms disinfection by-products
  - favours the development of biofilm in distribution systems
  - may affect corrosion and increase lead and/or copper concentrations in the treated water
  - contributes to taste, colour and odour

Operational challenges

- NOM can have significant operational impacts on water utilities, such as:
  - increased coagulant dose
  - poor floc formation or settling
  - shorter filter run times, more frequent backwashes
  - reduced hydraulic capacity
  - membrane fouling and shorter membrane life
  - reduced effectiveness of adsorption and anion exchange processes

Characterization

- NOM concentration and character (i.e., chemical, physical and biodegradability properties)
  - Important for selection of appropriate design and operation of water treatment facilities
  - Need to understand origin, occurrence and variation in the source water to minimize indirect health effects

Measurement of NOM

- NOM cannot be measured directly
- Other parameters used to provide an indication of the concentration and character of NOM
  - Dissolved organic carbon, UV absorbance, chemical oxygen demand
  - Specific UV absorbance
  - Chemical usage, DBP concentrations

Peer reviewers

- Dr. James Edzwald
  - Professor and Chair, Civil and Environmental Engineering, Clarkson University
- Dr. Graham Gagnon
  - Professor, Civil and Resource Engineering, Dalhousie University
- Dr. David Reckhow
  - Professor, Civil and Environmental Engineering, University of Massachusetts

Peer review: Corrosion

- Need to strengthen section on corrosion
- Addressed by adding information on corrosion impacts:
  - NOM can form protective film and decrease corrosion
  - NOM can also increase corrosion
    - Lead: impairs stable solid formation
    - Copper: interferes with pipe ageing
    - Iron: increased release of iron and trace inorganics
  - Complicated corrosion mechanisms, depending on surface charge, concentration, exposure time, pH, NOM characteristics

Peer review: Biofilm

- Need for additional context to the discussion of biofilms and the potential for *Legionella* growth
  - Strengthened discussion on biofilms and *Legionella*
- Clarification of the approaches used in North America and the Netherlands as they pertain to biological stability
  - Text on biostability has been clarified
- Clarification of the role of other compounds (e.g., phosphorus, ammonia, humic substances) in microbiological growth
  - Added information on compounds that can promote microbial growth

Peer review: Coagulation

- Enhance discussion on how NOM contributes to sub-optimal coagulation conditions
  - NOM exerts a coagulant demand that must be overcome before flocculation can occur
  - Pathogen log removal may be impacted if coagulant dose is not adjusted to account for an increase in NOM
- Need to focus on optimized coagulation
  - Strengthened text to indicate that NOM and turbidity removal must be viewed as an "integrated" process

Peer review: Occurrence

- Need more Canadian data and better characterization of occurrence and ranges
  - Included additional data from various regions in Canada
  - Median DOC: 1.24 – 14 mg/L
  - Clarified that NOM found in surface and ground water across Canada

Median ranges (CDW data)	Treated Groundwater	Treated Surface Water
TOC (mg/L)	1.1 - 2.7	1.9 - 7.4
Colour (CU)	4 - 9	<1 - 25

Proposed guideline statement

It is recommended that the concentration and character of natural organic matter be monitored in raw water as well as drinking water at the treatment plant and in the distribution system, in order to optimize treatment for its removal and the overall quality of the treated water.

International considerations

- U.S. EPA – treatment technique
  - Mandated percent TOC removal based on raw water quality
- WHO – operational parameter
  - Optimized NOM removal suggested to minimize biofilm
- EU – indicator parameter for supplies >10,000 m^3/d
  - No abnormal change
  - France – treated water quality reference guideline of 2 mg/L TOC
  - Netherlands – AOC target of 10 µg/L
- Australia – guidance on understanding and controlling impact of NOM

Discussion / next steps

- CDW Discussion
  - Guideline or guidance document
- Will be seeking CDW approval for 2 month public consultation period – either by conference call or at next meeting

Item 4-B
Lead

FPT Committee on Drinking Water

60th Meeting / May 3-4, 2017

Ottawa, Ontario

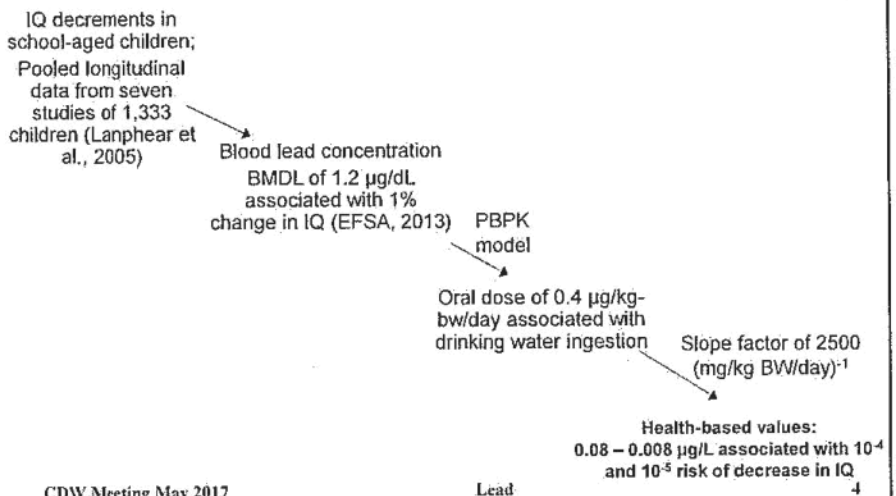
Status

- Guideline technical document underwent public consultation, ending March 15, 2017
- Consultation comments currently being addressed
- Revised classification and assessment section (10.2) sent to CDW in agenda package

Refresher

- Current guideline (1992) is 0.010 mg/L (after flushing), based on PQL
- Proposed MAC (2017) is 0.005 mg/L using exposure based sampling (30 MS or RDT), based on feasibility
- Lead exposure is associated with many health effects, including cancer and increased blood pressure; decreased IQ was retained as the critical effect:
  - Strongest evidence for a causal effect
  - Children were affected at the lowest blood lead levels studied

Risk assessment – consultation document



Revised section 10.2

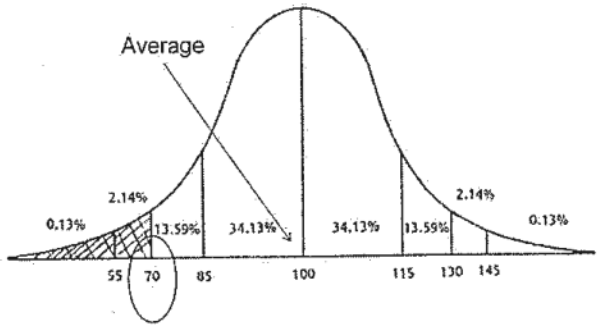
- Secretariat developed a new approach to better describe populational risk associated with exposure to lead in drinking water
  - Solves issues related to the use of negligible risk estimates (10^{-4} to 10^{-5}) for risks of IQ decrease (these type of risk estimates would typically be used for non-threshold cancer substances)
- These concerns were previously raised by CDW and more recently during public consultation
- New focus on increased cases of children with intellectual disability due to populational shifts in IQ
- No identified HBV and no impact on MAC value

IQ – populational distribution

- Variances in IQ within the population follow a normal distribution
- IQ = 100 represents average intelligence
- Approximately 2% of the population exhibits an intellectual disability (ID), generally seen as having an IQ of 70 or less
  - Decreasing average population IQ will increase the number of children expected to be affected with an intellectual disability
- Children with existing disability may exhibit greater intellectual impairment

IQ – populational distribution (con't)

Average IQ loss corresponding to exposure in drinking water → Expected cases of intellectual disability (IQ < 70)



Population Shift

Estimated impact

- Increased cases of children with an intellectual disability due to small population shifts in IQ associated with exposure to lead in drinking water can be calculated

Estimated additional cases of children with an intellectual disability associated with various lead concentrations in drinking water

DW concentration (µg/L)	% children expected to develop an ID*	Estimated increase in number of children expected to develop an ID*
0.1	0.004	5 in 100,000
1.0	0.045	5 in 10,000
3.0	0.137	1 in 1,000
5.0	0.232	2 in 1,000
10.0	0.483	5 in 1,000

*Over background of 2.27% or 2 cases per 100 children with an intellectual disability

Overview of consultation comments

- Comments were received from
  - 12 municipalities
  - 4 provinces (7 sets of comments)
  - Industry associations (7 sets of comments)
  - NGOs (2 sets of comments)
  - Federal departments (2 sets of comments)
  - Academia (1 set of comments)
- Generally, comments were supportive of lowering guideline

Overview of consultation comments (implementation)

- NGOs would prefer an even lower value
- Many comments regarding implementation of the guideline
  - Costs
  - Sampling protocols
  - Difficulties of sampling in homes, schools and daycares
  - Need for federal financial support to homeowners for replacement of their portion of LSL
  - Desire for additional guidance for municipalities and homeowners

Overview of consultation comments (health)

- Comments on risk assessment were generally related to:
  - Use of non-threshold cancer approach for low-dose extrapolation
  - Use of 10^{-4} and 10^{-5} risk estimates for non-cancer effects
  - Use of concurrent blood lead metric in key study
  - Age group considered for HBV calculation
  - Lack of information on populational impact

Next steps

- Address relevant public consultation comments and update document
- Revised document will be presented to CDW at November 2017 meeting for final approval

Item 4-C
PFOS, PFOA

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Status

- Public consultation ended September 2nd, 2016 for both documents
- 12 sets of comments were received and addressed for PFOS
- 12 sets of comments were received and addressed for PFOA
- Seeking final CDW approval

Refresher

- PFOS and PFOA are man-made compounds that do not occur naturally in the environment
- They are extremely persistent in the environment, with high partitioning to water
- They remain in the human body for years
- Contamination of drinking water sources has mostly occurred in Canada as part of firefighting foam discharge

Proposed MACs

- Calculation of both MACs is based on hepatocellular hypertrophy in rats and are protective of cancer and non-cancer effects
  - PFOS: 0.0006 mg/L (0.6 µg/L)
  - PFOA: 0.0002 mg/L (0.2 µg/L)
- Accounted for differences between humans and animals regarding how long PFOS/PFOA remain in the body (i.e., years for humans vs days/weeks for rodents).
  - Used a physiologically-based pharmacokinetic (PBPK)-derived chemical-specific adjustment factor (CSAF) approach as recommended by experts

Consultation comments – overview

- Comments were mostly supportive.
- Newly published scientific studies were highlighted for incorporation into the documents. These supported existing information in the document.
- Several concerns regarding implementation, treatment challenges and cost considerations were raised.
- Clarifications and minor editorial comments were suggested

Consultation comments – health

- Well-established toxicological effects that occur at doses far below the dose used as the basis for the proposed MAC were not considered
  - These are discussed in detail in section 10.2 and were not considered because of their lack of human relevance, inconsistencies in findings, lack of dose-response relationship, and lack of adversity
  - Consistent with other international agencies and comments from peer reviewers
- The endpoint selected as the basis for the MAC is not protective of infants and children
  - All reproductive and developmental effects occur at much higher doses

Consultation comments – health

- The assessments should have used BMD modeling for non-cancer PODs if possible
  - PFOS: the BMD approach did not provide a secure basis for risk assessment purposes
    - The text has been modified to reflect this information
  - PFOA: the POD was changed based on the comments received. The final health based value does not change
    - The text has been modified to reflect the change in POD

Consultation comments – health

- Why were external doses used instead of serum concentrations?
  - Modeling would be required to use serum concentrations, but the available models are not sufficiently validated to allow for their use
  - A PBPK-CSAF approach allows us to account for
    (a) species-specific differences in clearance,
    (b) chemical-specific differences in clearance, and
    (c) species-specific physiology

Additivity

- PFOS and PFOA are commonly found together in water
- The health effects used to establish their MACs are similar, affecting the same organ in the same way
- Based on internationally accepted principles, additivity should be used for these two substances, as follows:
  - The sum of the ratios of the detected concentration to the MAC for PFOS and PFOA should not exceed 1

$$\frac{\textit{PFOS concentration}}{0.6\ \mu g/L} + \frac{\textit{PFOA concentration}}{0.2\ \mu g/L} \leq 1$$

- This approach reflects current scientific knowledge associated with each substance and is protective of health

CDW Meeting May 2017 PFOS, PFOA 9

Consultation comments – treatment

- Requested information on monitoring of the treated water
  - Information added
- Potential sources of PFOA/PFOS contamination in distribution system
  - Information added in Section 5.1
- GAC would be expensive and impractical to operate strictly for PFOA/PFOS removal
  - GAC is well established and widely used technology, including small systems

CDW Meeting May 2017 PFOS, PFOA 10

International considerations

- Currently no regulatory limits

	PFOS	PFOA	Additivity
MAC	*0.6 µg/L*	*0.2 µg/L*	$\frac{[PFOS]}{0.6\ µg/L} + \frac{[PFOA]}{0.2\ µg/L} \leq 1$
US EPA health advisory (2016)	**0.07 µg/L** ↓Body weight in offspring	**0.07 µg/L** ↓ Ossification of proximal phalanges, accelerated puberty in offspring	[PFOS] + [PFOA] ≤ 0.07 µg/L
	Animal-to-human extrapolation using PK modeling & linear clearance-based scaling		
UK guideline (2007, 2009)	**0.3 µg/L** Thyroid effect in monkeys	**10 µg/L** Liver weight in rats	Additivity not considered
	Animal-to-human extrapolation using default UF of 10		
Australia Guidance (2017)	**0.07 µg/L** ↓Body weight in offspring	**0.56 µg/L** ↓Body weight gain in offspring	[PFOS] + [PFHxS] ≤ 0.07µg/L PFOA not considered
	Animal-to-human extrapolation using PK modeling & linear clearance-based scaling		

CDW discussion / next steps

- Seeking CDW approval of the final guideline technical documents for publication
- Next steps:
  - final CDW approval
  - final CHE approval
  - publication

Item 4-D
1,4-Dioxane

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Status

- Guideline technical document has been peer-reviewed and peer-review comments have been incorporated into the document
- Guideline technical document has been provided to CDW prior to meeting
- Seeking CDW approval for public consultation

Refresher

- 1,4-dioxane is a synthetic industrial chemical that is completely miscible in water, does not bind well to soils, and resists biodegradation
- Drinking water contamination usually results from chemical waste disposal practices, leaks from landfills, or wastewater discharges
- There is no current guideline for 1,4-dioxane in drinking water in Canada

Exposure

- Sources include contaminated food and drinking water, outdoor air, vapors from cleaning products, and consumer products
- Canadian exposure data for all sources is limited or unavailable
- Allocation factor = 0.2
- Multi-route exposure assessment
  - Contribution from inhalation and dermal exposure from drinking water is not significant

Levels in water

- Levels in drinking water across Canada are not well-characterized, information is limited

Province	# regions/ sites	% <limit of detection	Max (µg/L)	Mean (µg/L)	Median (µg/L)
Ontario	111	79 (0.02)	1.60	0.06	0.02
Québec	24	100 (0.03-0.5)	-	-	-

- Literature: levels are generally below the limit of detection, but levels up to 2000 µg/L have been detected in groundwater near waste disposal sites

CDW Meeting May 2017 1,4-Dioxane 5

Health effects

- Rats and mice: liver tumours and liver/kidney toxicity
- Humans: data are limited
- Mode of action for liver tumours was conducted
  - Multi-disciplinary/institutional consortium on 1,4-dioxane mode of action lead by independent TERA group
  - Liver toxicity precedes tumour formation in both dose and time
  - Selection of precursor event for tumour formation would be protective of non-cancer and cancer effects
  - Threshold risk assessment approach is appropriate

CDW Meeting May 2017 1,4-Dioxane 6

Peer reviewers - health

- Brittany Jacobs
  - Biologist, Environmental Protection Agency, Office of Water
- Michael Dourson, PhD, DABT, FATS, FSRA
  - Professor of Environmental Health, Risk Science Center, University of Cincinatti
  - President, Toxicology Excellence for Risk Assessment
- Kannan Krishnan, PhD, DABT, FATS
  - Senior Vice President, Chemical Risk Assessment, Risk Sciences International
- Various Health Canada programs
  - Consumer Products, Foods, Contaminated Sites, Existing Substances

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Peer review comments Health (1)

- Overall, the comments were positive
  - Document was thorough, well-written, and scientifically sound
- Additional information was requested
  - Inclusion of other studies that support existing information in the document
  - Clarification on outcomes of results from the consortium on 1,4-dioxane mode of action. In particular related to outlier results from one mouse study
  - Further details describing that the liver toxicity endpoint is protective of other health effects
- Minor editorial comments

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Peer review comments Health (2)

- Reviewers supported HBV derivation approach
  - Conclusions of mode of action analysis, choice of TDI approach, liver toxicity as basis for risk assessment, choice to not use available PBPK models, and AF of 0.2
  - EPA requested more detail in mode of action analysis to support the use of a TDI approach
- Use of BMD preferred to NOAEL for POD
  - BMD modeling of hepatocellular necrosis data was performed at 5% benchmark response
- More justification for use of 10x database deficiency UF
  - Poor characterization of reproductive and developmental toxicity; inadequate characterization of effects in second species (mice)

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Analytical & Treatment

- Analytical methods
  - Drinking water: EPA Method 522 & 541; solid phase extraction & GC/MS analysis with selected ion monitoring
  - MRLs: 0.07 µg/L; MDL: 0.010 µg/L
  - Surface/ Groundwater: EPA Methods 8260B (MDL = 12 µg/L) and 8015C (MDL = 15 µg/L); Broad list of analytes
- Treatment plant achievability
  - Advanced oxidation (UV/H_2O_2 or H_2O_2/O_3) typically achieves below 3 - 10 µg/L in treated water

CDW Meeting May 2017 1,4-Dioxane 10

Peer review comments Analytical and treatment

- Comments were supportive
  - Identified appropriate analytical methods
  - Accurate assessment of treatment achievability
- Requested additional information
  - Water reuse as a source of 1,4-dioxane in drinking water
  - Membrane filtration data from full-scale water reuse projects
  - Emerging technologies: Fenton's process, photocatalytic oxidation, and electro-peroxone
  - Activated carbon may be effective at residential-scale due to low flow rates, longer contact times

Peer review comments Monitoring

- 1,4-dioxane co-occurs with TCA, 1,1-DCE and TCE
  - Monitor at sites where chlorinated solvents are present
- Landfills and solvent recycling facilities are most common sources of 1,4-dioxane contamination in groundwater
  - Characterize sites that may be impacted by industrial wastes and/or landfill leachate

Proposed TDI

$$\text{TDI} = \frac{5.4 \text{ mg/kg bw per day}}{1000}$$

$$= 0.0054 \text{ mg/kg bw per day}$$

where:

- 5.4 mg/kg bw per day is the BMDL for a 5% response for hepatocellular necrosis using combined incidence data from male and female rats (Kociba et al., 1974; Dourson et al., 2014)
- 1000 is the uncertainty factor (x10 for interspecies variability, x10 for intraspecies variability, x10 for database deficiencies – i.e., poor characterization of reproductive and developmental toxicity, inadequate characterization of effects in a second species)

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Proposed HBV

$$\text{HBV} = \frac{0.0054 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L per day}}$$

$$= 0.05 \text{ mg/L}$$

$$= 50 \text{ µg/L}$$

where:

- 0.0054 mg/kg bw per day is the TDI
- 70 kg is the average body weight of an adult
- 0.2 is the allocation factor for drinking water
- 1.5 L per day is the estimated daily volume of tap water consumed by an adult

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Proposed MAC

- Proposed MAC = 0.05 mg/L (50 µg/L)
  - based on studies of early events of liver cancers in rats, which is protective of both cancer and non-cancer health effects
  - can be reliably measured by available analytical methods
  - is achievable by municipal and residential scale treatment technologies

International considerations

- Currently no regulatory limits

Agency	Year	Value (mg/L)	Basis
U.S. EPA Health Advisory	1987 (2012)	0.200 - lifetime 0.035 – 10^{-4} cancer risk	NOAEL 9.6 mg/kg bw per day based on liver toxicity (Kociba et al., 1974) Oral slope factor for liver tumours (Kano et al., 2009)
WHO Guideline	2005 (2011)	0.050	Average of approaches: -NOAEL 16 mg/kg bw per day (Yamazaki et al., 1994) -Oral slope factor for liver tumours (Yamazaki et al., 1994) at 10^{-5} cancer risk level

CDW discussion / next steps



- Seeking CDW approval for a 2-month public consultation period

Item 4-E
Chloramines

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Status

- For information only
- Risk assessment under development
- Draft document expected for CDW review and approval for public consultation at fall 2017 meeting
- Priority for update:
  - Both a disinfectant and a disinfection by-product
  - Identified by provinces and territories because of exposure and need

Background

- Current MAC (1995): 3.0 mg/L total chloramines, based on:
  - PQL
  - Level close to concentration (1.8 mg/L) calculated from NOEL (4.8 mg/kg bw/day) for monochloramine based on reduction of bodyweight gain in rats – 2 yr study
  - Natural ammonia levels are higher during cold weather, and may lead to higher levels of chloramines which may present control problem at lower level

Background

- Inorganic chloramines: 3 chemically related compounds:
  - Monochloroamine NH_2Cl preferred for use in disinfecting drinking water because of its biocidal properties and relative stability
  - Dichloroamine: $NHCl_2$
  - Trichloroamine: NCl_3

Sources and uses

- Sources in drinking water:
  - Non-intentional: disinfection by-product of chlorination
  - Intentional: ammonia added to chlorine to form inorganic chloramines; forms present dependent on pH, ratio (Cl: NH), temperature and contact time
- Uses:
  - Main: Residual disinfection - secondary disinfectant
  - Other uses:
    - Primary disinfection in some exceptional cases
    - Mono-: used in synthesis of amines & substituted hydrazines
    - Di-: used for preparation of diazirine

Exposure

- Air:
  - Mono- and di-chloramine: low potential of volatility
  - Trichloramine: very volatile
- Water:
  - Mono- and di-: soluble /Tri-: Limited to hydrophobic
- Soil/Food: no data
- Occupational exposure: trichloramines
  - Workers in food industry facilities - ambient air
  - Lifeguards/workers in indoor swimming pools – ambient air
- Consumer products: chloramine gas
  - bleach and ammonia accidentally mixed for cleaning purposes

Exposure in drinking water

- BC: Regional and Abbotsford Mission: 4 sampling points (2015-2016)
  - Dichloramine: 0-0.75 mg/L (min-max)
  - Monochloramine: 0-8.5 mg/L (min-max)
- QC: 11 distribution systems; 1 region, 3 sampling sites (2013-2015):
  - Chloramines: 0.07-1.5 mg/L (min-max)
- SK: Very limited use - 4 plants using chloramination
  - Allowed as primary disinfectant for true groundwater; not typically allowed as primary disinfectant for surface or GUDI systems
  - Chloramines (0.01-3.9 mg/L); di- (0.01-0.15 mg/L); mono- (0-8.33 mg/L)

Health considerations - Monochloramine:

- Chronic: 2 year study in rats and mice (NTP, 1992) found mononuclear cell leukemia (MCL):
  - Marginal increase in female rats:
  - Not present in male rats or in mice (both sexes)
  - No reduced latency/ historical controls
  - F344 rats more susceptible to MCL – NTP
  - NOAEL: 8.7 mg/kg/day (= highest dose of 200 ppm)*
- Mutagenicity: some mutagenic potential in *in vitro* studies, no significant evidence in *in vivo* studies
- Epidemiology: no adverse health effects, but study limitations

Health considerations Chloramines

- Very limited data on health effects of di and trichloramine:
  - Only 1 subchronic study each - Mild histological effects at doses 0.2 ppm in absence of clinical signs in rats
  - Risk assessment will be based on monochloramine
- Multiroute exposure:
  - to be considered - volatility of trichloramine
- Potential health effects of chloramine treated water used for dialysis:
  - decreased haemoglobin, formation of Heinz bodies, haemolytic anaemia, methaemoglobinaemia, decreased haptoglobin

Risk assessment - monochloramine

- Cancer classification:
  - IARC (2004): Group 3: not classifiable as to carcinogenicity to humans based on inadequate evidence in humans and in experimental animals
  - USEPA (1994): Group D: not classifiable as to human carcinogenicity based on inadequate human data and equivocal evidence of carcinogenicity from animal bioassays
- Non cancer risk assessment
  - 2 year study in rats; NOAEL of 8.7 mg/kg bw/day (200 ppm)

Analytical and treatment

- No approved U.S. EPA methods specifically for chloramines
- U.S. EPA approved methods for total and free chlorine
  - Total – free = combined
- Methods for characterization of chloramine species

Chloramine generation

- Mixing ratio (Cl_2:N) must be optimized to maximize monochloramine production
  - Typical range 3:1 – 5:1
  - Ideal range 4.5:1 – 5:1
- pH and temperature
- Minimize residual ammonia entering distribution system
  - Nitrification concerns
- Avoid di- and tri- chloramine formation

Treatment considerations

- Nitrification in the distribution system
- Generation of unwanted disinfection by-products
  - I-DBP, nitrosamines, hydrazine
- Shifts in microbial ecology in biofilms
  - nitrifying bacteria, opportunistic pathogens
- Interactions with materials
  - corrosion related issues
  - water quality changes
- Best management practices & disposal considerations

International considerations

- U.S. EPA (2001): MRDL of 4.0 mg/L as an annual average
- WHO (2004): Guideline of 3.0 mg/L
- Australia (2014): Guideline of 3.0 mg/L
- Cal EPA: MRDL of 4.0 mg/L (as Cl_2)
- EU: not regulated. A few countries may use it (Great Britain, Finland, Spain, and Sweden)

Next steps



- Complete the risk assessment
- Incorporate comments from peer reviewers
- CDW approval to be sought in fall 2017 for a 2-month public consultation

Item 4-F
Barium

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Status

- For information only
- Risk assessment under development
- Draft document expected for CDW review and approval for public consultation at fall 2017 meeting

Background

- Current MAC (1990): 1 mg/L
  - based on absence of effect on blood pressure or cardiovascular disease in humans
- Main use in mining and oil industries (drilling), but also:
  - Components/filler of plastic, rubber, textile, ceramic/brick, glass, paper, electronics, pharmaceutical, cosmetics, X-ray diagnostics
- Sources
  - Major source in groundwater is natural: leaching from sedimentary, ignous (granite), and manganese-rich rocks

Exposure

- Food:
  - Main source of exposure, accounting for ~85-95% of total exposure
  - Total intake of 5–25 µg/kg bw per day (TDS, 1993-2007)
  - Most food items contain low levels (~0.01–0.5 µg/g); highest in cereals, nuts, certain fruits/veggies (~1–5 µg/g)
- Water:
  - Contribution can be highly variable
  - Typically ~10–50 µg/L in most natural & treated waters, range ~10–500 µg/L; max of 10 000 µg/L
  - Soluble barium species: Ba chloride (375 g/L, mostly used in studies), nitrate, hydroxide, acetate
  - Low solubility: Ba sulfate and carbonate (< 0.02 g/L)
  - Additional inhalation/dermal exposure from showering or bathing is unlikely (very low volatility and skin permeability constant)

Levels in Canada

- National Survey of DBPs and Emerging Contaminants, 2009-2010:
  - Raw+treated surface water: mean = 26 µg/L; 2 samples >100 µg/L, max 120 µg/L
  - Raw+treated well water: mean of 104 µg/L; 24 samples >100 µg/L, max 510 µg/L
- Canadian Total Diet Study (TDS) : means of tap water in 9 cities (2000—2012)
  - Montreal 15-247 µg/L, St-John's <3.6-57 µg/L, Vancouver <11-62 µg/L, Winnipeg 1.2-14 µg/L, Toronto <1-14 µg/L, Halifax 5.9-73 µg/L, Ottawa 13-42 µg/L, Quebec city 21-61 µg/L, and Calgary 31-46 µg/L

Levels in Canada

- Data provided by CDW members: wide variability across the country

P/T	Source	Median (µg/L)
AB	5 river basins	91
NB	Crown lands distribution systems Municipal ground or surface water sources	53 15-76
ON	Ambient Groundwater Geochemistry project	65
QC	distribution systems	20
SK	Groundwater Treated water	14 72
YT	Raw drinking water Treated drinking water Groundwater	80 72 25

Health considerations

- Renal toxicity consistently observed in animal studies (Dietz et al., 1992; NTP, 1994; Elwej et al., 2016).
- Equivocal associations between barium intake from drinking water and cardiovascular disease in animals and humans (Brenniman et al., 1985; McCauley et al., 1985; Perry et al., 1985, 1989; Wones et al., 1990 ; NTP, 1994)

Analytical methods

- Approved methods
  - U.S. EPA
    - ICP-MS and ICP-AES
    - MDLs ranged from 0.05 µg/L to 1 µg/L
  - Standard methods
    - ICP-MS, GFAAS
    - MDLs ranged from 0.1 µg/L to 2 µg/L
- Existing U.S. EPA (1993) PQL of 150 µg/L

Treatment technologies

- Effective treatment technologies
  - Chemical precipitation
    - Lime softening – 93-95%
  - Ion exchange softening – greater that 94%
    - Two types of resin – SAC and WAC
  - Reverse osmosis – greater than 98%

Residential scale

- Certified residential treatment devices are available for reduction to 2.0 mg/L or less
- Applicable standards are:
  - NSF/ANSI Standard 44 - Residential Cation Exchange Water Softeners
  - NSF/ANSI Standard 58- Reverse Osmosis Drinking Water Treatment Systems
  - NSF/ANSI Standard 62- Drinking Water Distillation Systems

International considerations

- U.S. EPA
  - MCL (1991) = 2 mg/L based on possibility of increased blood pressure
  - RfD (2005) = 200 µg/kg bw per day based on nephropathy in a 2-year mouse study (NTP, 1994; and ATSDR, 2007)
- WHO (2004)
  - 0.7 mg/L based on absence of effect on blood pressure or cardiovascular disease in epidemiological study (Brenniman & Levy, 1985)

Next steps

- Complete the risk assessment
- Incorporate comments from peer reviewers
- CDW approval to be sought in fall 2017 for a 2-month public consultation

Item 4-H
Strontium

FPT Committee on Drinking Water

60th Meeting / May 3 & 4, 2017

Ottawa, Ontario

Status

- Draft guideline technical document has been peer reviewed
- Peer-review comments have been addressed and the document revised
- Document was provided to CDW prior to meeting
- Seeking CDW approval for public consultation

Refresher

- Strontium currently #3 on priority list
  - No existing MAC, but frequently detected in surface/drinking water in Canada
  - Drinking water screening values have been requested by more than one P/T (2010, 2013)
- Naturally occurring non-essential element
- Enters water through leaching from granites and sedimentary rocks
- Food is generally the main source of exposure

CDW Meeting May 2017 Strontium 3

Levels in drinking water

- Levels in Canadian drinking water are highly variable

	Mean (µg/L)	Maximum (µg/L)
National Survey	185	1600
Canadian Total Diet Study	5-150	
Newfoundland and Labrador	17-276	6320
Nova Scotia	19-231	2200
New Brunswick	187-297	3500
Quebec	857	47 000
Ontario	3528	87 832
Manitoba	84-454	7940
Saskatchewan	310-570	2100
Alberta	276-372	2820
British Columbia	860-8100	1 280 000

CDW Meeting May 2017 Strontium 4

Health effects

- Non-essential element
  - Natural health products have been licensed in Canada (support bone health), but none for osteoporosis
- Effects on bones in animal and human studies:
  - Skeletal defects in rats (>12 studies): Reduced calcification rate / bone ash weight and increase in osteoid thickness
  - Rickets in children
  - Beneficial effects in osteoporotic adults
- Stable strontium unassessed for carcinogenicity
  - No IARC assessment found
  - IRIS (U.S. EPA): "Not undergone a complete evaluation [...] for evidence of human carcinogenic potential."

Key study

- Key study in weanling rats via drinking water (Marie et al., 1985)
  - Bone defects: Reduced calcification rate, bone ash weight and increased osteoid thickness were observed (NOAEL of 425 mg Sr/kg bw per day)
- Choice of key study based on:
  - Exposure via drinking water (higher absorption via DW vs food)
  - Dose-response relationship
  - Bone parameters quantified
  - In weanling rats (with high absorption and bone remodelling)
  - Endpoint supported by MOA (related to its similarity with calcium) and other animal studies and human studies

Peer reviewers - health

- Dr. Kannan Krishnan, Université de Montréal
- Dr. Joyce Donohue and Jamie Strong, Office of Water, US EPA
- Dr. Lynne Haber, University of Cincinnati
- 4 reviewers from the Health Products & Food Branch, Health Canada

Peer review comments - health

- All peer-reviewers agreed with choice of key study and critical endpoint
- Some peer-reviewers challenged the choice of **sensitive sub-population**, since calcium deficiency is rare in young Canadian children but common in adolescents (>60% aged 9-18 years old) (Statistics Canada, 2010)
  - Response: The choice of infant sub-pop is protective (lower HBV) of adolescents and is another sensitive sub-pop given their high rate of bone turnover

Peer review comments - health

- Some challenged the UF of 3 for **intraspecies variability** since sensitivity can vary depending on calcium/vitamin D status, and it is not clear if the window of vulnerability was adequately captured
  - Response: We agreed with reviewers and changed the UF for intraspecies variability from 3 to 10

Peer review comments NOAEL vs BMDL approach

- Some challenged NOAEL approach and preferred BMDL option:
- Response: Both approaches were considered, but the NOAEL approach is deemed more appropriate based on:
  - Using the BMDL (328 mg/kg bw per day) was overly conservative, no effects were observed at 425 mg/kg per day (NOAEL), and the endpoint is considered a precursor, reversible effect.
  - BMD models had poor variance: not optimal in the current context.

Peer reviewers Analytical and treatment

- Dr. Dennis Clifford – Ph.D., P.E.
  - Department of Civil and Environmental Engineering, Gullen College of Engineering, University of Houston
- Darren Lytle – Ph. D; P.E.
  - U.S. EPA – Water Supply and Water Resources Division

Peer review comments – Analytical and treatment

- Minor clarification for chemical precipitation
  - Added early studies on strontium removal by lime softening
  - Recent work (2016) supports the early findings
    - calcium plays an important and necessary part of strontium removal
    - strontium co-precipitated with $CaCO_3$ (mixed crystals)
- Treatment of high strontium concentrations
  - Requires modified softening process
    - originally intended for radioactive strontium treatment but relevant to stable strontium
  - Multi-stage membrane processes

Proposed MAC

- Proposed MAC of 7 mg/L based on HBV
  - Protective of potential health effects
  - Can be reliably measured by available analytical methods
  - Achievable by municipal and residential scale treatment technologies
- HBV = $\frac{1.417 \text{ mg/kg bw per day} \times 7 \text{ kg} \times 0.50}{0.75 \text{ L}}$

  ≈ 7.0 mg/L (rounded)

  Where:
  - 1.417 mg/kg bw per day is the TDI, based on calcification defects and UF of 300;
  - 7 kg is the average body weight for infants 0–6 months of age;
  - 0.5 is the allocation factor (only two main sources)
  - 0.75 L is the mean daily water intake for infants 0–6 months of age.

International considerations

- No enforceable drinking water limit identified
- U.S. EPA
  - 2014: RfD of 0.3 mg/kg bw/d based on BMDL of 328 mg/kg bw per day for decreased bone calcification in rats (Marie et al., 1985)
    - Health Ref Level of 1500 µg/L
  - 1992: IRIS Lifetime Health Advisory of 4 mg/L based on rachitic rat bones from Storey et al. (1961) (RfD of 0.6 mg/kg bw per day)
- WHO (IPCS CICAD, 2010)
  - TDI of 0.13 mg/kg bw per day based on thyroid effects in young rats (Kroes et al., 1977)

CDW discussion / next steps

- Seeking CDW approval for a 2-month public consultation period

Fishwick, David HLTH:EX

From: Anne Vezina <anne.vezina@hc-sc.gc.ca>
Sent: April 7, 2017 12:53 PM
To: angelina.polegato@novascotia.ca; Caroline.Robert@mddelcc.gouv.qc.ca; Fishwick, David HLTH:EX; donald.reid@gov.ab.ca; Peter_Workman@gov.nt.ca; ghsomers@gov.pe.ca; hkhan@gov.nl.ca; Kevin.Gould@gnb.ca; Kim.Philip@gov.mb.ca; pat.brooks@gov.yk.ca; sam.ferris@wsask.ca; Satish.Deshpande@ontario.ca; MLeBlanc-Havard@GOV.NU.CA
Cc: John Cooper; Michele Giddings; Stephanie McFadyen; Richard Carrier; France Lemieux; Veronique Morisset; Tina Brennan; Wendy Enright; Philippa.cureton@canada.ca; kristina.taracha@hc-sc.gc.ca; Anca-Maria Tugulea; Rocio Aranda-Rodriguez
Subject: Agenda package - upcoming CDW meeting
Attachments: Cdw2017-05 (agenda package) 2017-0407 .pdf

CDW members,

The upcoming CDW meeting is in about four weeks from now (May 3 & 4), so you will find attached the information package for the meeting.
(See attached file: Cdw2017-05 (agenda package) 2017-0407 .pdf)
We will be sending the remaining documents for discussion at the meeting shortly, starting early next week, in this order:
1- strontium
2- protozoa
3- enterococci
4- 1,4-dioxane
5- NOM

We apologize for sending these other documents less than four weeks prior to the meeting but we are doing the best we can. Also, we currently do not have editors in the moment so please be gentle if you notice editorial mistakes in our documents!

Thank you all for your understanding and I hope you can attend the meeting!
Have a good weekend,
Anne

Anne Vézina
Coordinator of the F/P/T Committee on Drinking Water
Coordonatrice du Comité F/P/T sur l'eau potable
Water and Air Quality Bureau
Bureau de la qualité de l'eau et de l'air
Safe Environments Directorate
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Health Canada
Healthy Environments and Consumer Safety Branch

Santé Canada
Direction générale, Santé environnementale et sécurité des consommateurs

Your file Votre référence

Our file Notre référence

Federal-Provincial-Territorial Committee on Drinking Water Technical Secretariat
269 Laurier Avenue West (AL 4903D)
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Secrétariat technique du Comité fédéral-provincial-territorial sur l'eau potable
269 ave Laurier ouest (ia 4903D)
Ottawa (Ontario) K1A 0K9

April 7th, 2017

le 7 avril 2017

DISTRIBUTION

DISTRIBUTION

FEDERAL-PROVINCIAL-TERRITORIAL COMMITTEE ON DRINKING WATER

Enclosed you will find information for the next meeting of the Federal-Provincial-Territorial Committee on Drinking Water (CDW).

The CDW meeting will be held May 3 and 4, 2017 at 269 Laurier Ave W., Ottawa, Ontario. The meeting will be held in room 7-086 and will start at 8:30 am on each day.

If you have any questions, please contact me at (613) 957-3130.

COMITÉ FÉDÉRAL-PROVINCIAL-TERRITORIAL SUR L'EAU POTABLE

Vous trouverez ci-inclus l'information concernant la prochaine réunion du Comité fédéral-provincial-territorial sur l'eau potable (CEP).

La réunion du CEP aura lieu les 3 et 4 mai 2017, au 269 ave Laurier ouest, Ottawa (Ontario). La réunion se déroulera dans la salle 7-086 et débutera à 8h30h chaque jour.

Pour de plus amples renseignements, veuillez communiquer avec moi au (613) 957-3130.

Anne Vézina
Committee Coordinator / Coordonnatrice du comité

Canada

Federal Provincial Territorial Committee on Drinking Water

Sixtieth Meeting
May 3 & 4, 2017
Ottawa, ON

AGENDA PACKAGE

Federal Provincial Territorial Committee on Drinking Water
Sixtieth meeting – May 3 & 4, 2017
Ottawa, ON
AGENDA PACKAGE

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1 Opening

Reference/Action:

- Introduce CDW members and observers
- Attached, April 2017 CDW membership list
- Members to update the membership list

Notes:

CDW MEMBERSHIP LIST - LISTE DES MEMBRES DU CEP

VOTING MEMBERS – MEMBRES VOTANTS

Jurisdiction Compétence	***Member & Affiliation*** Membre & Affiliation	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* / NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Newfoundland and Labrador / Terre-Neuve et Labrador	Mr. Haseen Khan, P. Eng., Director, Water Resources Management Division Department of Environment and Climate Change	P.O. Box 8700 St. John's, NL A1B 4J6	Phone: 709 729-2563 Fax: 709 729-0320	Emergencies: 709 729-3703 / 709 772-2083 NEEC: 709 772-7745	Email: hkhan@gov.nl.ca Website: www.gov.nl.ca/env/water
Prince Edward Island / Île-du-Prince-Édouard	Mr. George Somers, Manager Drinking Water and Wastewater Management Environment Division Department of Communities, Land and Environment	11 Kent Street, 4th Floor P.O. Box 2000 Charlottetown, PEI C1A 7N8	Phone: 902 368-5046 Fax: 902 368-5830	Emergencies: 902 426-6030 NEEC: 902 426-6200	Email: ghsomers@gov.pe.ca Website: www.gov.pe.ca/infopei/Environment_and_Land/Water_Resources/Drinking_Water/
New Brunswick / Nouveau-Brunswick	Mr. Kevin Gould, P.Eng (Vice-Chair) Acting Director, Healthy Environments Branch Office of the Chief Medical Officer of Health New Brunswick Department of Health	520 King Street, 2nd Floor, HSBC Place Fredericton, NB E3B 5G8	Phone: 506 444-4096 Fax: 506 453-8702	Emergencies: 506 453-2133 NEEC: 902 426-6200	Email: kevin.gould@gnb.ca Website: http://www.gnb.ca/health
Nova Scotia / Nouvelle-Écosse	Ms. Angelina Polegato, Supervisor Drinking Water Management Unit, Science Division Nova Scotia Environment	1894 Barrington Street, Suite 1800 P. O. Box 442 Halifax, NS B3J 2P8	Phone: 902 424-1583 Fax: 902 424-0501	Emergencies: 902 426-6030 NEEC: 902 426-6200	Email: angelina.polegato@novascotia.ca Website: http://www.gov.ns.ca/nse/water/drinking.water.asp
Quebec / Québec	Ms. Caroline Robert (Chairperson) Chef de la division de l'eau potable Direction de l'eau potable et des eaux souterraines Ministère du Développement durable, de l'Environnement et de la Lutte aux Changements Climatiques	Édifice Marie Guyart, 8e Étage 675 blvd René-Lévesque Est Québec, QC G1R 5V7	Phone : 418 521-3885 (ext 4938) Fax : 418 644-2003	Emergencies: 866 694-5454 / 418 643-4595 NEEC: 866 283-2333 / 418 317-0513	Email: caroline.robert@mddelcc.gouv.qc.ca Website: www.mddelcc.gouv.qc.ca/eau/potable/

Jurisdiction Compétence	***Member & Affiliation*** Membre & Affiliation	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* / NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Ontario	Dr. Satish Deshpande, Team Leader, Water Standards Section Standards Development Branch, Ministry of the Environment and Climate Change	40 St. Clair Ave W, 9th Floor Toronto, ON M4V 1M2	Phone: 416-327-4689 Fax: 416-327-2936	Emergencies: 800 268-6060 NEEC: 416 994-2126	Email: Satish.Deshpande@ontario.ca Website: www.ene.gov.on.ca
Manitoba	Ms. Kim Philip, Director Office of Drinking Water Manitoba Sustainable Development	1007 Century Street Winnipeg, MB R3H 0W4	Phone: 204 945-7010 Fax: 204 945-1365	Emergencies: 204 944-4888 NEEC: 819 997-3742	Email: Kim.Philip@gov.mb.ca Website: www.manitoba.ca/drinkingwater/
Saskatchewan	Mr. Sam Ferris Executive Director Environmental & Municipal Management Services Division Saskatchewan Water Security Agency	420, 2365 Albert Street Regina, SK S4P 4K1	Phone: 306 787-6193 Fax: 306 787-0197	Emergencies: 800 667-7525 NEEC: 306 536-9991	Email: sam.ferris@wsask.ca Website: www.saskh2o.ca/browser.htm
Alberta	Dr. Donald Reid Drinking-water Quality Regulator Drinking-water and Wastewater Section Provincial Programs Branch Operations Division, Environment and Parks Alberta Environment	1504, 15th Floor, 9820-106 Street Edmonton, AB T5K 2J6	Phone: 780 644-8061 Fax : 780 422-4086	Emergencies: 800 222-6514 NEEC: 780 977-1559	Email: donald.reid@gov.ab.ca Website: www.environment.gov.ab.ca
British Columbia / Colombie Britannique	Mr. David Fishwick Drinking Water Manager, Ministry of Health Province of British Columbia	4-2, 1515 Blanshard Street Victoria, BC V8W 9P1	Phone: 250 952-1110 Fax: 250 952-1713	Emergencies: 800 663-3456 NEEC: 604 666-6100	Email: david.fishwick@gov.bc.ca Website: www2.gov.bc.ca/
Yukon	Ms. Patricia Brooks, Drinking Water Program Coordinator Health and Social Services, Government of Yukon	2 Hospital Road Whitehorse, YT Y1A 3H8	Phone: 867 667-8351 Fax: 867 667-8322	Emergencies: 867 667-7244 NEEC: 867 667-7244	Email: pat.brooks@gov.yk.ca
Northwest Territories / Territoires du Nord-Ouest	Mr. Peter Workman, Chief Environmental Health Officer Department of Health & Social Services Government of the Northwest Territories	5015 - 49th Street, 5th Floor - NGB P.O. Box 1320 Yellowknife, NT. X1A 2L9	Phone: 867 767-9066 ext. 49260 Fax: 867 669-7517	Emergencies: 867 920-8130 NEEC: 867 920-8130 Health Line: 867-920-8646	Email: peter_workman@gov.nt.ca Website: www.hss.gov.nt.ca

Jurisdiction Compétence	**Member & Affiliation** Membre & Affiliation	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* / NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Nunavut	Ms. Michele LeBlanc-Havard, Environmental Health Specialist Department of Health Government of Nunavut	Box 1000 Station 1000; 1107 Sivummut Bldg. Iqaluit, NU X0A 0H0	Phone: 867 975-5943 Fax: 867 975-5755	Emergencies: 867 222-0256 NEEC: 867 222-0256	Email: mleblanc-havard@gov.nu.ca Website: www.gov.nu.ca
Canada	Dr. John Cooper, Director Water & Air Quality Bureau Safe Environments Directorate Healthy Environments & Consumer Safety Branch, Health Canada	269 Laurier Ave West A.L. 4903D Ottawa, ON K1A 0K9	Phone: 613 948-2568 Fax: 613 952-2574	Emergencies: 613 954-6651	Email: john.cooper@hc-sc.gc.ca Website: http://www.hc-sc.gc.ca/ewh-semt/water-eau/index_e.htm

**Telephone number for emergencies ONLY that may impact drinking water quality (e.g., toxic chemical spill into source water). Numéro de téléphone à utiliser SEULEMENT pour les urgences pouvant avoir des répercussions sur la qualité de l'eau potable (p.ex. déversement de substances toxiques dans une eau d'approvisionnement).*
*** NEEC - Environment Canada's National Environmental Emergencies Centre. CNUE – Centre National des Urgences Environnementales.*

CDW LIAISONS MEMBERS – MEMBRES LIAISONS DU CEP

Liaison	**Member & Affiliation**	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* /NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Environment and Climate Change Canada Environnement et changement climatique Canada	Philippa Cureton Science & Risk Assessment Directorate Emerging Priorities Division National Guidelines and Standards Office Environment and Climate Change Canada	6th Floor Place Vincent Massey Annex 351 St-Joseph Blvd Gatineau, QC	Phone: 819 938-5078	NEEC:	Email: philippa.cureton@canada.ca

Liaison	Member & Affiliation	Address Adresse	Phone / FAX / Téléphone / Télécopieur	Emergencies* /NEEC** (24hr) Urgences* / CNUE (24 hres)	Email / Website Courriel / Site Web
CHE Committee Comité CSE	Mr. Peter Workman, Chief Environmental Health Officer Department of Health & Social Services Government of the Northwest Territories	5015 - 49th Street, 5th Floor - NGB P.O. Box 1320 Yellowknife, NT. X1A 2L9	Phone: 867 767-9066 ext. 49260 Fax: 867 669-7517	Emergencies: 867 920-8130 NEEC: 867 920-8130 Health Line: 867-920-8646	Email: peter_workman@gov.nt.ca Website: www.hss.gov.nt.ca
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2 Agenda/Minutes

2-A Adoption of agenda

Reference/Action:

- Tentative meeting agenda
- Attached, schedule for tentative meeting agenda
- CDW to approve agenda

Notes:

Draft Agenda

FPT Committee on Drinking Water - May 2017 (269 Laurier West, Ottawa, Ontario)		
	Wednesday May 3rd, 2017	**Thursday May 4th, 2017**
8:30 am	1-A Opening 2-A Adoption of agenda 2-B Approval of minutes 2-C CDW status/checklist 2-D Bill C-326 2-E CDW priority list 2-F Withdrawal of old guidelines	4-D 1,4-Dioxane 4-E Chloramines 4-F Barium 4-G 2,4-D
10:30 am	Break	Break
11:00 am	3-A Protozoa 3-B Coliform 5-A Guidance for well owners	4-H Strontium 4-I Microcystins (recreational) 4-J Other chemical/radiological (atrazine, etc)
12:00 am	Lunch	Lunch
1:00 pm	3-C Enterococci 3-D Other microbiological (QMRA, viruses, etc.) 4-A NOM	6-A FNIHB report 6-B WHO report 6-C CHE report 6-D CCME report 5-B EHSRB update 5-C INAC update
2:30 pm	Break	Break
2:45 pm	4-B Lead 4-C PFOS, PFOA	7-A Member's reports 8-A Future meetings
5:00 pm	End of meeting	End of meeting
NB: Meeting will be held in room 7-086 and will run from 8:30 AM to Noon and from 1:00 PM to 5:00PM. The social dinner will be held on Wednesday.		

2 Agenda/Meeting

2-B Approval of minutes

Reference/Action:

- Attached, draft October 2016 meeting minutes
- CDW to approve the minutes

Notes:

Federal-Provincial-Territorial Committee on Drinking Water

Fifty-ninth Meeting
October 19-20, 2016
Ottawa, ON

Draft Minutes

Draft minutes prepared by J. A. MacDonald, November 2016
Draft minutes revised by J. Mortimer and V. Morisset, March 2017
Minutes finalized, ? 2017

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FEDERAL-PROVINCIAL-TERRITORIAL COMMITTEE ON DRINKING WATER – 59th MEETING

October 19-20, 2016
Ottawa, Ontario

Members Present

Ms. C. Robert, Quebec – Chair
Mr. K. Gould, New Brunswick – Vice Chair
Dr. J. Cooper, Health Canada
Mr. P. Workman, Northwest Territories
Mr. D. Fishwick, British Columbia
Ms. K. Philip, Manitoba
Ms. M. Leblanc-Havard, Nunavut
Mr. H. Khan, Newfoundland and Labrador
Dr. D. Reid, Alberta
Dr. S. Deshpande, Ontario
Mr. G. Somers, Prince Edward Island
Ms. P. Brooks, Yukon
Ms. A. Polegato, Nova Scotia
Mr. S. Ferris, Saskatchewan (phone)

Secretariat

Mr. R. Carrier, Health Canada
Ms. F. Lemieux, Health Canada
Ms. V. Morisset, Health Canada
Ms. S. El-Kady, Health Canada (First Nations)
Ms. J. Mortimer, Health Canada (Coordinator)
Ms. J. MacDonald, Health Canada (Reporter)
Ms. M. Giddings, Health Canada
Ms. S. McFadyen, Health Canada
Dr. A-M. Tugulea, Health Canada (Research)
Dr. B. Sadi, Health Canada (Radiological)
Water quality staff, Health Canada

Guests

Mr. S. Ray, Truesdail Laboratories
Mr. M. Ngo, Truesdail Laboratories (phone)
Mr. P. Greiner, NSF (phone)
Mr. T. Spoden, WQA (phone)
Mr. B. Hatton, CSA (phone)
Mr. Jean Rousseau, BNQ (phone)

Regrets

Ms. P. Cureton, Environment Canada
Dr. R. Aranda-Rodriguez, Health Canada (Research)

1 Opening

The Chair called the 59th meeting to order and welcomed everyone to Ottawa. The Coordinator reviewed administrative details. The membership list was circulated for updating. Members, alternates, guests and staff introduced themselves.

Decision/Action:

- **Members to update the membership list.**

2 Agenda/Meeting

2-A Adoption of agenda

The Chair added a new item on the guideline development process (see Item 2-D), requested an update on the priority list under 2-C and a roundtable discussion on lead under 4-J. D. Reid asked that the Committee Terms of Reference be discussed.

Decision/Action:

- **Members approved the meeting agenda as amended.**

2-B Approval of minutes

The meeting minutes were discussed. J. MacDonald noted minor corrections under items 3-A and 4-F.

Decision/Action:

- **Members approved the minutes as revised.**

2-C CDW status/checklist

The Coordinator reviewed the status of documents. C. Robert asked about glyphosate, sodium and the radiological parameters. M. Giddings noted that the timing for the radiological parameters would need to be discussed with the Radiation Protection Bureau. M. Giddings indicated that the review of contaminants for the priority list will be contracted out next fiscal year and asked members to identify any new substances that are of interest to their jurisdictions. D. Reid asked when the committee will discuss the priority list. M. Giddings indicated that a preliminary update is possible for Fall 2017 and a full discussion at the Spring 2018 meeting. M. Giddings agreed to send the list of contaminants previously assessed.

Decision/Action:

- **M. Giddings to send the list of contaminants previously assessed.**
- **Members to identify new substances of interest.**

2-D Guideline development process

J. Cooper noted that cost implications and/or implementation issues can delay the publication of guideline technical documents. He requested feedback on how the committee can identify and discuss these issues earlier in the process before a maximum acceptable concentration (MAC) is selected for public consultation, particularly when the selected MAC may not be achievable in some parts of the country or the sampling is costly. K. Philip asked if this could be discussed when the exposure data is submitted. S. Deshpande was concerned that costs could be perceived as driving the process. J. Cooper noted that policy decisions based on cost implications have been used in the past to risk manage guideline values. S. Deshpande suggested a process whereby committee members and scientists agree on a value, identify issues that will result from this value, and then make a recommendation. S. Deshpande noted that Ontario can provide economic impacts earlier in the process. G. Somers noted that issues can be identified earlier but

his observation has been that, lately, in-depth discussions have been deferred when a document is going for consultation. K. Philip noted that when children are identified as the most sensitive population, it may be more appropriate to have special advice for this segment of the population. D. Reid suggested reviewing the Committee Terms of Reference to re-establish expectations. K. Gould asked for clarification regarding how the process would work when a health-based value (HBV) becomes a risk-managed MAC. It was noted that both values would be published in the document as we do currently. V. Morisset asked whether jurisdictions are able provide the information before the value is selected. S. Ferris indicated that Saskatchewan has a process for developing cost impacts and soliciting input; he also noted that streamlining the process would be helpful. C. Robert indicated that Quebec can identify impacts earlier in the process and agreed that it would be helpful to discuss these issues sooner. P. Brooks agreed that it would be good to enhance the process but also asked that it be recognized that the scale of economic impact is different in Northern Canada. K. Philip noted that it would be helpful to separate treatment achievability from economic feasibility. She also noted that it would help if documents were provided earlier. S. Deshpande noted that even providing the HBV calculation earlier would help; the complete edited document is not necessary to assess impacts. A discussion ensued on how to move forward. It was agreed to begin discussing impacts in more detail immediately and update the Terms of Reference to reflect the suggested process.

Decision/Action:

- **Members agreed to begin discussing economic impacts as early as possible in the guideline development process.**
- **Secretariat to begin the process of updating the Terms of Reference.**

3 Parameters: Microbiological

3-A QMRA

T. Brooks gave a presentation. S. Deshpande noted that the lack of a publicly available model is a concern. T. Brooks indicated that the model is available upon request. J. Cooper asked about the purpose of the document if the model is not available. S. McFadyen noted that users have requested a document to reference the model. S. Deshpande asked that it be clarified that very low risk values are meaningless. D. Reid expressed concerns regarding the use of the model by individuals who may not understand the results. He also asked that the following be considered: elevated risk from young cattle and annual versus short term risk. He noted that annual risk is suitable for guideline development but short term risk is more applicable for utility diagnostics. P. Brooks asked about the applicability to small systems and the required number of samples. T. Brooks noted that the model requires the mean and standard deviation of pathogen data. K. Gould asked if a minimum number of samples are required to be statistically significant. S. McFadyen noted that where data is not available, the WHO safety plan approach can be used to assess risk. C. Robert noted that the document is well written and structured. A discussion ensued on what would be translated. C. Robert highlighted a missing reference.

Decision/Action:

- **Members approved the document for public consultation.**

3-B Enterococci

G. Yasvinski gave a presentation. The document is scheduled to be presented to the committee for approval for public consultation at the May 2017 meeting. K. Gould asked if enterococci is a better indicator for groundwater. G. Yasvinski indicated that it provides different information.

D. Reid indicated that it was his understanding that it was a better indicator for groundwater. G. Somers questioned the need for a guideline document. K. Philip indicated preference for a guidance document. P. Brooks asked why the document was developed. G. Yasvinski indicated it was requested by the committee and it is a recreational water indicator. C. Robert indicated that Quebec requires monitoring for *E. coli*, enterococci and coliphage in untreated groundwater supplies that are close to a fecal source; all are considered fecal indicators and trigger follow-up action. S. McFadyen suggested that the document focus on groundwater supplies. A. Polegato requested clarification on the Quebec process. A discussion ensued on the Quebec process. D. Fishwick asked about the lab capacity for enterococci testing. It was noted that enterococci is used for recreational water quality monitoring and that lab capacity exists. H. Khan asked if it will be a guideline or guidance document. A majority of jurisdictions preferred a guidance document, 2 had no preference and one preferred a guideline technical document. K. Gould asked whether the document would include information for private wells. C. Robert indicated that Quebec recommends that homeowners test for *E. coli* and enterococci.

Decision/Action:

- **Members approved moving forward as a guidance document.**

3-C Total coliforms

G. Yasvinski gave a presentation. P. Brooks asked if the decision tree would be reviewed. G. Yasvinski answered in the affirmative but noted changes are not expected. D. Reid noted that holding times and sample volumes are being reviewed but since total coliforms and *E. coli* are analysed together, it will be important to maintain consistency with the *E. coli* document. D. Reid asked if the document will be a guideline or guidance. K. Philip asked if an update was necessary. S. McFadyen noted that the review may result in re-affirmation. S. Deshpande noted that keeping the document as a guideline was preferred. P. Brooks indicated that boil water advisories can be issued due to total coliforms so it would be problematic if it was a guidance document. K. Gould indicated that total coliforms are used to flag problems in New Brunswick and concerns would be raised if it was guidance. G. Somers indicated that it helps to have a guideline for private wells, particularly for real estate transactions. S. Ferris preferred that it remain a guideline and favoured the re-affirmation approach. A discussion ensued on the need for public consultation. It was agreed that targeted consultation would suffice. It was noted that the re-affirmation approach will need to be reflected in the guideline development process and Committee Terms of Reference.

Decision/Action:

- **Members approved moving forward with re-affirmation and targeted consultation.**

3-D Enteric viruses

D. Medeiros, J. MacDonald and A. Cherry provided a verbal update. A. Polegato noted that the new wording (revised to incorporate comments from QC and BC) was problematic for Nova Scotia. D. Reid agreed and requested that the wording "sources vulnerable to viral contamination" be deleted from the guideline statement and Section 3.2. C. Robert indicated that the added wording was not necessary in the guideline statement because the last sentence says the same thing. P. Brooks also requested that the wording be deleted. D. Medeiros suggested returning to the original wording. D. Fishwick raised concerns with deleting the text but recognized that jurisdictions require flexibility. K. Philip requested the development of a "WaterTalk" to educate and help explain the risks and requirements to owners of semi-public and private supplies. D. Reid indicated some advice exists for private supplies and offered to provide the information. He indicated that Table 1 is too scientific for general advice. S. McFadyen cautioned against making a "WaterTalk" too technical; she re-iterated the need to keep the information simple. S. El-Kady indicated that FNIHB has a tool kit for private wells that is very simple with lots of photos but it assumes wells are not GUDI. K. Philip and A. Polegato indicated that their jurisdictions assume the well is at risk and require proof that it isn't. A. Cherry noted that all the literature indicates that it is hard to assess a well for vulnerability; it is possible to determine high risk but difficult to show low or no risk. For example, it isn't as straight forward as setting a distance to a septic systems; it is very hard to simplify. P. Brooks indicated that owners know very little about their wells and educational material is needed. K. Philips indicated the information on page 14 would be helpful (i.e., septic system recharge based on lot size). J. MacDonald noted that hydraulic conductivity complicates matters. K. Philip suggested the fact sheet refer readers to the provincial/territorial jurisdictions to obtain that information. J. Cooper agreed it is complicated but noted the information needs to get out in simple "WaterTalk" form to educate private well owners. K. Gould suggested a holistic approach to include other parameters such as manganese. C. Robert suggested that existing guidance for private well owners be reviewed by the Secretariat and that a recommendation be made at the next meeting regarding a "WaterTalk" series for private well owners. Members approved the document for public consultation subject to the requested changes being made. D. Medeiros requested that members share their guidance material for private well owners.

Decision/Action:

- **Members approved the document for public consultation subject to the requested changes being made.**
- **Members to share their guidance material for private well owners.**
- **Secretariat to recommend a path forward regarding a "WaterTalk" series for private well owners.**

3-E Other microbiological

S. McFadyen provided a verbal update. The recreational water guideline is under review to incorporate new scientific information and to make it consistent with the cyanobacterial toxins document. She requested assistance in identifying working group members. S. McFadyen also noted that the Genome Canada cyanobacteria project has been approved. Members are encouraged to identify water systems with algal blooms for evaluation.

Decision/Action:

- **S. McFadyen to follow-up with members regarding the recreational water guideline update.**

4 Parameters: Chemicals

4-A Uranium

J. Carney gave a presentation. G. Somers asked what health benefit would be achieved by reducing the existing MAC of 20 µg/L to the calculated HBV of 14 µg/L. J. Carney noted that it is difficult to quantify the benefits. It was noted that the uncertainty factor is 100 which is considered relatively protective. M. Giddings noted that the kidney health effect is reversible (i.e., the kidney recovers if exposure to uranium stops). H. Khan asked what the ratio was for the doses for bone versus kidney effects. J. Carney noted that this is difficult to determine due to study limitations. A. Polegato asked if advice is still needed for children. J. Carney noted that given the new information, no special advice is needed for children. Most members agreed that minimal health benefits would be achieved by reducing the MAC from 20 to 14 µg/L given the uncertainty factor. K. Philip asked if those with pre-existing kidney conditions should be notified. V. Morisset indicated that this is not normally part of the guideline development process. It was agreed that no impact statements were necessary since the guideline is proposed to be risk-managed and remain at 20 µg/L. K. Philip requested that the HBV be included in the executive summary.

Decision/Action:

- **Members approved the guideline technical document for public consultation, re-affirming the MAC of 0.02 mg/L.**

4-B Lead

V. Morisset provided a verbal update. It is expected that the document will be posted for public consultation in November. A 'Water Talk' is scheduled to be posted to Health Canada's web site on Thursday, October 20. A new version of Qs&As will be provided to members. C. Robert asked if the Qs&As will be translated. V. Morisset answered in the affirmative. D. Reid noted that the delay has not been helpful and the sooner the document can be released, the better.

Decision/Action:

- **Secretariat to provide updated Qs&As to members.**

4-C Cyanobacterial toxins

R. Charron and A. Cherry gave a presentation. S. Deshpande asked whether there is sufficient information to develop a screening value for cylindrospermopsin if needed. R. Charron indicated that the information is limited but that a screening value could be developed if required. K. Gould asked for clarification regarding the NSF information. A. Cherry indicated that the information relates to residential systems and not for raw water. C. Robert requested that additional information be included in the document to justify the use of an uncertainty factor of 3 instead of 10. R. Charron noted that text will be added to explain that a factor of 3 is considered sufficient because the LOAEL and NOAEL are similar. D. Fishwick requested that the text explaining seasonal (i.e., spring to fall) be deleted. K. Philip requested clarification regarding the seasonal MAC. R. Charron explained that the short term value is protective of long exposure.

Decision/Action:

- **Members approved the final document subject to minor changes.**

4-D HAAs and THMs

S. Labib gave a presentation. D. Reid asked what the detection limits were for the HAA9 compounds. S. Labib indicated that they varied. D. Reid offered to provide a reference with additional exposure data. C. Robert asked if HBVs have been calculated for BCA and BDCA. S. Labib indicated that they have not been calculated yet. C. Robert asked which option (expanding the guideline to include BCA and BDCA or develop screening values for them) involved more work. S. Labib indicated that developing a guideline would involve more work. S. Deshpande asked if monitoring data is available to meet the committee's exposure requirement. A discussion ensued on the sixth HAA that is monitored as part of a standard HAA analysis. D. Reid indicated such data would be difficult to retrieve. S. Ferris noted that monitoring data may not be available but health effects cannot be ignored.

Decision/Action:

- **D. Reid to provide exposure data reference to the Secretariat.**
- **Secretariat to derive drinking water screening values for BCA and BDCA.**

4-E Copper

S. Chébékoué, S.J. Payne and F. Lemieux gave a presentation. D. Reid indicated he was comfortable approving the document for public consultation and provided the following comments: blue hair is an effect that should be added to the document; pig production facilities can be sources of copper; sample digestion is generally required, particularly if the sample is also used for lead analysis. D. Fishwick requested clarification on whether the exposure data are representative of tap or distribution system water quality. Members clarified their results. K. Philip requested additional information to explain pH and alkalinity adjustment in Section 7.7.1. K. Philip asked if the same bottle can be used for copper and lead sampling. F. Lemieux indicated additional information can be added to clarify requirements. K. Philip asked if lead and copper were the same exposures. F. Lemieux indicated that where water is corrosive, problem sites may be the same but copper exposure is different and sampling for copper may require fewer samples overall. K. Philip noted that it would be helpful to clarify that the sampling procedure and sample bottle can be the same as for lead. F. Lemieux indicated that the same bottle can be used but different sites should be selected for lead versus copper. K. Philip asked if additional text was planned in Section 3.1. F. Lemieux noted that "as discussed below" should have been deleted. S. Deshpande asked if the aesthetic objective (AO) should be linked to the corrosion control program. F. Lemieux indicated that different sites would typically be selected for lead and copper monitoring. S.J. Payne discussed plastic pipes and yellow brass. D. Fishwick requested clarification regarding sampling. C. Robert requested that additional information be added to explain the selection of the AO. S.J. Payne reviewed the taste considerations. C. Robert indicated that when the AO was selected for BTEX, the most sensitive population was considered but for copper, impacting up to 72% of the population is suggested. F. Lemieux indicated that a value less than 1 mg/L (AO) would be difficult to achieve. C. Robert indicated that it should be clarified that the AO is related to achievability versus aesthetic acceptance as complaints could be expected at lower values. V. Morisset indicated additional information can be added that some people may be more sensitive. C. Robert indicated that her Health colleagues will be submitting comments on the derivation of the HBV. C. Robert requested clarification on the monitoring of total copper. It was noted that it is being clarified that the guidelines apply to total concentrations. C. Robert noted that the document indicates in one location that sample

locations should focus on new copper "and" water quality problems whereas in another location it says "or". She requested that this be clarified.

Decision/Action:

- **Members approved the document for public consultation with minor changes.**

4-F 1,4-dioxane

S. Labib and A. Cherry gave a presentation. The document is scheduled to be presented for approval for public consultation at the May 2017 meeting. S. Deshpande asked whether the M. Dourson manuscript has been considered. S. Labib indicated that she is aware of the material. S. Deshpande asked what the HBV would be. S. Labib indicated that it is still in development but the screening value is 90 µg/L. S. Deshpande noted that 1,4-dioxane can cause issues with carbon filters at high concentrations. J. Cooper asked if 1,4-dioxane is found ubiquitously or just at contaminated sites. It was agreed that the Secretariat would consider this question and return to this item on Day 2.

Day 2 – Health Canada staff noted that CEPA considers 1,4-dioxane non-toxic because exposure is minimal. It was also noted that its use has been discontinued but it can be found due to historical use and/or contaminated sites. Members were asked if a guideline or guidance was preferred. S. Deshpande indicated that Ontario could live with guidance but a guideline was preferred. D. Reid suggested a slide be added to presentations to remind members why a parameter is being evaluated. A discussion ensued on the analysis cost. It was noted that it is expensive but the cost may be reduced if demand increases. K. Gould indicated that a guideline would be preferred if testing were to be required. D. Reid indicated that the water safety approach does not encourage testing for parameters that are unlikely to be found. S. Ferris concurred. He suggested that if a guideline document is prepared that monitoring only be recommended where risk exists. A discussion ensued on the potential for contamination, the persistence of 1,4-dioxane and the difficulty to treat. A guideline document was preferred by most members.

Decision/Action:

- **Members approved moving forward with a guideline document.**
- **Secretariat to include reasons for developing guideline in presentations to CDW.**

4-G Barium

P. Hamel gave a presentation. S. Deshpande noted that barium can enhance dental health. C. Robert asked if the HBV will go up or down. P. Hamel indicated that it is still in development. G. Somers noted that approximately 2% of wells in PEI are above the existing MAC and the most frequent question asked is related to the applicability of the higher U.S. guideline. A discussion ensued on treatment and softening. A discussion ensued on the adequacy of information to develop a guideline. P. Hamel indicated that sufficient information exists to derive a HBV based on kidney effects. C. Robert noted that Quebec's exposure data was summarized as it is representative of distribution system results. P. Hamel noted that other jurisdictions provided raw data. K. Gould asked if shale gas development has implications for barium and was answered in the affirmative.

Decision/Action:

- **For information.**

4-H Strontium

P. Hamel and N. Martinova gave a presentation. The document is scheduled to be presented for approval for public consultation at the May 2017 meeting. D. Reid noted that, similar to barium, softening is a treatment option but he asked that linkages to sodium be considered. S. Deshpande noted that calcium concentrations need to be considered and he offered to send the reference. J. Cooper asked if strontium is used in mineral supplements. P. Hamel answered in the affirmative and indicated that the Health Products and Food Branch has been consulted.

Decision/Action:

- **S. Deshpande to provide a reference on the calcium / strontium relationship.**

4-I Manganese

J. MacAulay, A. Cherry and S.J. Payne gave a presentation. D. Reid asked that Section 3.0 put an emphasis on the need to actively manage the distribution system (e.g., control biofilm, historical deposition). A. Cherry suggested that a distribution system section be added to Section 2. A. Polegato asked if the HBV applies to older populations in nursing homes given the U.S. EPA recommends a value of 300 µg/L. J. MacAulay noted that the childhood neurological effect continues to be observed in adulthood. C. Robert indicated that Quebec requires two to three weeks to review the document. A. Polegato indicated that the document was circulated while she was travelling and she has not reviewed it yet. A discussion ensued on the magnitude of guideline implementation issues. J. Cooper asked that CHE members be engaged.

Decision/Action:

- **Members to provide comments by November 4.**

4-J Other chemical

M. Giddings gave a verbal update. Boron, acrylamide, aluminum and chloramines have been started and comments were received on the PFOS/PFOA public consultation. C. Robert asked for an update on the withdrawal of old guidelines for pesticides. V. Morisset noted that the process to withdraw the guidelines will be developed when A. Vezina returns. M. Giddings requested permission to share the members contact details with principal investigators conducting a study on THMs and bladder cancer. Members answered in the affirmative. A roundtable discussion ensued on jurisdictional approaches for lead.

Decision/Action:

- **For information.**

5 Secretariat projects

5-A Standards

A written report was provided by F. Lemieux (see member's hand-out material).

Decision/Action:

- **For information.**

5-B National drinking water conference

S. Deshpande gave a verbal update and congratulated organizers on a great conference and technical program. He noted that during the debrief meeting, the Research Chairs indicated that the organization of the conference is too much for 2 people and that future conferences would need to be organized by experienced organizations such as the AWWA. Continuing education credits were suggested to help broaden outreach and increase registration. D. Reid also

congratulated conference organizers but noted that Western Canada was under-represented; he indicated that it would be a challenge if future conferences had to be held in Ottawa. G. Somers indicated it was a great conference and registration was good for a first time with the Research Chairs. He asked if copies of the presentations will be available. S. McFadyen agreed to follow-up but noted that many presenters arrived with their presentations on a memory stick. H. Khan requested a breakdown of attendees. S. McFadyen indicated that a report will be forthcoming from Dalhousie University on attendees, what went well and not so well. It was requested that this be an agenda item at the next meeting.

Decision/Action:

- **Members requested a discussion at the next meeting.**
  S. McFadyen to follow up on providing copies of presentations to CDW.

5-C Research group update

A-M. Tugulea gave a presentation.

Decision/Action:

- **For information.**

6 Committee Liaison Reports

6-A CRCP/CACP report

F. Lemieux provided a verbal update. Low lead requirements are being integrated into standards B125, B137, B64 and B483. The water efficiency committee is looking at water quality impacts. D. Fishwick asked about the rainwater committee. J. MacDonald provided an update. Greywater use is on hold due to lack of demand.

Decision/Action:

- **For information.**

6-B Certification body reports

F. Lemieux asked certification body representatives to introduce themselves and indicate which standards they are involved in. F. Lemieux gave a presentation. It was noted that NSF is accredited to write standards for Canada. K. Gould asked whether products must be certified to NSF 61 and 372. F. Lemieux indicated that plumbing standards and AWWA standards have low lead requirements. Plumbing is addressed through the plumbing codes but utilities need to specify their requirements for low lead. P. Greiner suggested that both be specified during the transition period for clarity.

Decision/Action:

- **For information.**

6-C FNIHB report

S. El-Kady reviewed the contents of the FNIHB report included in the hand-out material. J. Cooper suggested contacting T. Beattie for input on historical boil water advisories. The THMs sampling method was discussed. Members requested the training manual that FNIHB has developed. D. Reid noted concerns regarding how boil water advisories and the affected population are reported.

Decision/Action:

- **S. El-Kady to share the training manual.**

6-D CHE report

J. Cooper reported that the CHE mandate is under review. D. Reid asked about the timeline. J. Cooper indicated this has not yet been established.

Decision/Action:

- **J. Cooper to keep members apprised of progress.**

6-E WHO Report

A special meeting on cyanobacterial toxins was held in Singapore over the summer. R. Carrier indicated that he presented the Canadian approach and it was supported. The U.S. also presented their approach.. WHO remains interested in the Canada document on manganese.

Decision/Action:

- **For information.**

6-E CCME Report

A written report was provided by P. Cureton (see hand-out material).

Decision/Action:

- **For information.**

7 Members' Reports

Each jurisdiction provided a report on its program and legislative activities, training and outreach programs, publications and current key issues. Written reports were provided by Newfoundland and Labrador, Nova Scotia, Nunavut, Ontario and Saskatchewan.

Alberta

D. Reid indicated that regulatory revisions remain in the process mainly due to the Fort McMurray fire. Health Canada was thanked for their assistance. Post-fire discharge is being monitored for elevated carbon, turbidity, metals.

British Columbia

D. Fishwick indicated that work continues on the lead file. New non-potable water guidelines for flushing toilets and other lower risk uses have been developed. Also, work is continuing with system risk management plans, revamping operator qualifications and the outreach program with BCWWA. A first draft for setting up agreements amongst users and operators for point-of-entry and point-of-use systems has been prepared. New distribution system guidelines and emergency response guidelines have been prepared.

Manitoba

K. Philip indicated that a boil water advisory map has been prepared. It lists long term and short term boil water advisories. New fact sheets have been developed including one on zebra mussels. Stakeholders have been notified regarding lead. Program reviews are underway (e.g., red tape reduction).

New Brunswick

K. Gould indicated that the strategic review was concluded and the government lab will be closed.

Newfoundland and Labrador
The Department is now called "Department of Environment and Climate Change", and the Office of Climate Change has been merged with the Department of Environment. Drinking water safety remains a high priority for the Department. The Drinking Water Safety Action Plan has been developed and is under review by the Cabinet Secretariat. Once released, it will provide regulatory oversight to public, semi-public and private water systems. The Boil Water Advisory reduction initiative is making good progress. Its focus is on long-term boil water advisories, twelve of which have already been lifted. Three consultant contracts have been issued under this initiative during the current fiscal year. The regional water operators initiative is also making good progress with encouraging input from participating communities. The annual drinking water safety workshop will be held in March, 2017. The annual drinking water safety report for 2015-16 is being prepared. All regulatory permits issued by the Department are posted on-line. Flood risk maps are being updated to account for climate change. The Hurricane Flood Alert system informed communities about the potential rainfall associated with Hurricane Matthew. Two regulations dealing with water use charges and water power rental were gazetted in the last week. Work continues to update dam inventory in the province and the Department is actively involved in the regulatory oversight of the Lower Churchill Project. Recently, a NATO-funded project on real-time water and weather monitoring and reporting in Jordan was completed.

Northwest Territories
P. Workman indicated that an audit was concluded. Work continues on the database, arsenic, membrane filtration and the list of parameters to be analysed. It was noted that fluoridation of drinking water has been requested.

Nova Scotia
The evaluation of Nova Scotia's Drinking Water Program was completed in January 2016. The project team presented the recommendations of the evaluation to NSE's Environmental Policy Committee (EPC) in May 2016. The team was given permission to revise the *Water and Wastewater Facilities and Public Drinking Water Supplies Regulations*. The revisions will include a modification to the definition of a public drinking water supply to ensure owners of privately owned community type systems cannot use the "intent to provide potable water" portion of the definition as a loophole to avoid registering with the Department. In addition, NSE will create a clause to include mandatory laboratory reporting to the Department of sample results that exceed health based guidelines. The team recommended NSE define treatment requirements for registered supplies to ensure these systems deliver drinking water of comparable quality to our municipally owned systems. While EPC understood the increased risk attributed to these systems they asked that the team work with the Office of Regulatory Affairs to pilot their costing tool prior to delivering a final decision. The team is scheduled to report back to EPC on the results of the regulatory costing tool exercise in December 2016. Over the last two months, Nova Scotia has experienced extreme variability in weather conditions resulting in low water levels in southern and western portions of the province and flooding in the eastern portion of the province. These extreme weather events resulted in a number of challenges for municipally owned and private drinking water systems. The western and southern portions of Nova Scotia received less than half the normal precipitation for this time period. Agriculture Canada described the conditions in this part of the province as abnormally dry, moderate

drought, to severe drought. An estimated 2000 private wells went dry this summer. It is expected that this number may actually be higher as it is likely many were not reported. This resulted in a coordinated effort by the province and municipalities, as well as bottled water providers, to supply locations where residents could fill up water containers (potable and non-potable), have showers, do laundry, and obtain bottled water. Doors were opened at Provincial Parks, Fire Halls, Community Centres and other municipal buildings to assist residents. While the province assisted with this coordination and monitored the situation, NSE developed educational materials to ensure the safety of water used for drinking, cooking and oral hygiene, as well as actions for homeowners to take to bring their wells back on line once the water level is restored in their wells. In September, two municipal water utilities issued mandatory water conservation orders to their users, and subsequently noticed a drop in water consumption by customers. They also altered their own practices related to commercial bulk water hauling, water and wastewater line flushing. Other municipal water utilities continue to work with NSE to address challenges meeting the requirements of their water withdrawal permits for surface water supplies. Over the October Thanksgiving weekend, Nova Scotia experienced torrential rains with some areas exceeding 100–275 mm in a 24 hr period. This led to severe flooding events mainly in the northern and eastern parts of the province. Flooding of this magnitude can result in damage and contamination to water supplies. The extent of the damage remains to be seen. NSE continues to work with Dr. G. Gagnon from Dalhousie University on a proposal to assess the effectiveness of corrosion control programs at municipal water utilities throughout the province. Once the proposal is finalized, it will be presented to the Minister for final approval.

Nunavut

Many changes are occurring in Nunavut. The Department of Health is posed to launch the new *Public Health Act* and has made drinking water their first regulatory priority. A water regulations working group has been formed which includes representatives from the federal and territorial governments. This process is being led by the former Chief Medical Officer of Health, Dr. Maureen Baikie. The need for a comprehensive drinking water program has also been identified and it is recognized that work must begin to formally establish a structure for drinking water in the territory. There are new and emerging issues in drinking water and the issuing and rescinding of boil water advisories has been more frequent of late. Climate change is an ever present consideration and we continue to work towards putting in place a better structure for drinking water in Nunavut.

Ontario

S. Deshpande indicated the Climate Change Action Plan to implement the strategy over the next five years was released in June 2016. In June 2016, the Ministry established an Indigenous Drinking Water Projects Office. The Great Lakes Protection Act became law in November 2015. New drinking water standards are being consulted on along with lead sampling protocols. Thirteen outdated pesticides have been removed and the Ministry is consulting on a numerical value for any pesticide. In February 2016, the ministry launched the Source Water Protection Map (at www.applications.ene.gov.on.ca/swp/en/index.php), an innovative and interactive tool that provides the first province-wide view of the more than 970 wellhead protection areas and 150 intake protection zones. C. Robert asked if the map is available on the website. S. Deshpande answered in the affirmative.

Prince Edward Island
G. Somers indicated one round of public consultation was concluded on a proposed *Water Act*. The use of social media is encouraged. Re-organization of regulations is expected. The lab is streamlining water quality reporting by issuing them via email. Well inspectors are returning.

Quebec
C. Robert indicated that Quebec is consulting on a new 15-year water strategy with a link to drinking water quality. Best management practices for distribution systems are also out for consultation. C. Robert thanked members that provided information on non-potable water systems. Quebec is continuing to look at alternatives for small systems.

Saskatchewan
I would like to take the opportunity to thank R. Charron, F. Lemieux and V. Morisset and others at Health Canada for their assistance in provision of screening values and other advice for petroleum constituents in water in relation to the recent oil spill affecting the North Saskatchewan River in Saskatchewan. Contributions from Health Canada were integral to the health risk assessment that was developed to support reopening of the water intakes starting September 16, 2016 at three affected Saskatchewan cities and regional systems serving approximately 70,000 people. Saskatchewan continues with implementation of the new *Waterworks and Sewage Works Regulations* that took effect in Saskatchewan on June 1, 2015. One component of the regulations that waterworks owners must comply with is provision of a plan by July 31, 2017 outlining how they will comply with any applicable new water quality standards that come into force in 2020. This is tied to and utilizes information from the latest round of waterworks system assessments being completed by many waterworks owners at this time and work to bring upgrade plans continues at this time. Saskatchewan is currently considering the need for regulatory updates and this work could go forward with inclusion of revised *Guidelines for Canadian Drinking Water Quality* that have been updated since 2010. This and other minor fine tuning updates could proceed to conclusion within the next two years.

Yukon
P. Brooks indicated that the CNPHI tool is being implemented. Regulatory amendments remain in the process. An inspection tool is being piloted.
Decision/Action:
- **For information.**

8 Meetings

8-A Future Meetings
Members discussed future meeting dates. The original date of November 8-10 for the fall 2017 meeting was changed to November 7-9 2017.
Decision/Action:
- **Spring 2017: May 3-5, 2017**
- **Fall 2017: November 7-9, 2017**
- **Spring 2018: May 1-3, 2018**

The meeting adjourned at 5 p.m. on October 20, 2016.

2 Agenda/Meeting

2-C CDW status/checklist

Reference/Action:

- Oral presentation on the status of guideline/guidance documents
- Verbal update on the record of decision and checklist of action items
- Attached, record of decision sorted by subject
- Attached, checklist of action items from the October 2016 meeting
- Provided at meeting, CDW parameters status list
- For information only

Notes:

CDW Date	Subject	Decision
2011-05	Ammonia	• Secretariat to make links between the ammonia document and the nitrate/nitrite document • Operational considerations to be removed from the guideline statement • Public consultation to be done at the same time as the nitrate/nitrite document • Members approved the document in principle for public consultation
2013-05	Ammonia	• Members approved final document
2010-05	Bacteriological	• Secretariat to set up a working group meeting for June 2010.
2012-02	Bacteriological - *E. coli* & total coliforms	• Members approved by consensus e.coli and total coliforms documents with discussed changes on a conference call, Feb 14th, 2012
2010-11	Bacteriological - *E.coli*	• Members agreed to go forward with enzyme-based methods are 'recommended' and see what feedback comes back. • Members approved the E.coli document for public consultation.
2011-05	Bacteriological - Emerging	• Members approved the document in principle for consultation with minor adjustments to text to be made by Secretariat.
2016-10	Bacteriological - Enterococci	Members approved moving forward as a guidance document.
2010-05	Bacteriological - HPC	• Members approved document for a two month public consultation. • Secretariat to add a note in the consultation package asking participants to copy their comments to their provincial CDW rep.
2011-11	Bacteriological - HPC	• Members approved document with discussed changes
2016-10	Bacteriological - QMRA	Members approved the document for public consultation.
2010-11	Bacteriological - Total coliforms	• Members approved the document for public consultation in principle. The Secretariat to make changes and circulate the document for final approval.
2015-05	Bacteriological - Total coliforms	• Members approved moving forward with a guideline technical document for total coliforms with a MAC.
2016-10	Bacteriological - Total coliforms	Members approved moving forward with re-affirmation and targeted consultation.
2012-10	Bacteriological - WBP	• Members approved document in principle, awaiting confirmation from Quebec. The approval from Qc was received one month after the meeting by email (Nov 2012).
2013-11	Benzo(a)pyrene	• Members approved the document for consultation with the modified purpose of consultation section. Secretariat to include context in the purpose of consultation section of the document, noting that the lack of information on Canadian laboratory capacity and methods in this area is a gap.
2014-05	Benzo(a)pyrene	• Members approved the document in principle with proposed changes for public consultation.
2015-11	Benzo(a)pyrene	• Members approved the final document.
2013-11	Boil Water Advisories	• Members approved the document, amended as discussed, for consultation. Secretariat to work with C Robert on wording changes.
2014-10	Boil Water Advisories	• Members approved the document in principle for publication.
2014-10	Bromate	• Members approved the document in principle for public consultation.
2016-05	Bromate	• Members approved the final document with minor corrections noted in the meeting
2010-05	Carbon Tetrachloride	• Members agreed to approve the document for publication.
2013-05	CDW Administration	• Members agreed to contribute to the cost of providing light refreshments at meetings.
2014-05	CDW Administration	• Secretariat to maintain the collaboration centre on CNPHI for CDW use • Members approved the use of carbamazepine data by CCME.
2012-05	CDW collaborating centre	• Members agreed to try using CNPHI as a tool for CDW communication, especially as an archive and a place for approved documents. Alternates and CHE reps will have access, as will working group members who are not CDW members (to appropriate sections only). • Secretariat to continue to send the latest versions of the documents by email.
2010-11	CDW Stuff	• Members agreed that the conference is a venue for presentations. The committee is a working committee with business to cover. • Members agreed that for the time being, presentations from outside groups will be considered on a case-by-case basis and that there is a need to deal with questions from lobby groups.
2014-10	Chromium	• Members approved the document in principle for public consultation.
2015-11	Chromium	• Secretariat to circulate the document for final CDW approval when ready. A conference call will be convened, if needed, to obtain final CDW approval
2016-01	Chromium	• Members approved the final document via email (11 of 13 jurisdictions responded)
2016-10	Copper	Members approved the document for public consultation with minor changes.
2011-11	Cyanobacterial Toxins	• Members agreed to rolling revision of the guideline technical document • Secretariat to draft letter to jurisdictions alerting them to the need to review the guideline and that in the meantime, the recommendation is to test for total microcystins
2015-05	Cyanobacterial Toxins	• Members approved the document for public consultation in principle, subject to the changes noted at the meeting.
2016-10	Cyanobacterial Toxins	Members approved the final document subject to minor changes
2011-05	DBPs publication	• Members agreed on need to develop a plan of action to address false or misleading clains regarding Guidelines
2010-11	DCM	• Members approved the guideline with a MAC of 0.05 mg/L.
2012-05	Dichloroethane 1,2-	• Members approved the document for a two month consultation. • Members agreed that no impact paragraphs are needed since the proposed guideline value is unchanged.

CDW Date	Subject	Decision
2013-11	Dichloroethane 1,2-	• Members approved the guideline for publication.
2016-10	Dioxane, 1,4-	Members approved moving forward with a guideline document.
2010-05	Election of Chair and Vice-Chair	• Members elected J. MacDonald as Chair and C. Robert as Vice-Chair.
2014-05	Election of Chair and Vice-Chair	• Members elected S.Ferris as Chair and C.Robert as Vice-Chair.
2016-05	Election of Chair and Vice-Chair	• Members elected C. Robert as Chair and K. Gould as Vice-Chair.
2010-11	Enteric Viruses	• Secretariat to send revised document with highlighted changes to members. • Members to review the changes in the document by email.
2016-05	Enteric Viruses	• Members approved the document for public consultation in principle, subject to revisions.
2016-10	Enteric Viruses	Members approved the document for public consultation subject to the requested changes being made.
2013-11	Enterococcus	• Members asked Secretariat to pursue option 2 (develop more formal guidance on the use of Enterococcus as an indicator)
2015-05	*Enterococcus*	• Members approved moving forward with a guideline technical document for *enterococcus*.
2010-11	Fluoride	• Members approved the document.
2010-05	Future meetings	• 2010 Fall - Saskatoon, Nov 3,4,5 (National Conference Oct 30 - Nov 2) • 2011 Spring - Ottawa, May 4,5,6 • 2011 Fall - Halifax • 2012 Spring - Ottawa
2012-05	Future meetings	• Next meeting in Kelowna - October 2012 • May 2013 - Ottawa • November 2013 - Edmonton
2013-11	Future meetings	• April 30 - May 2, 2014 Ottawa • Oct 30 – 31, 2014 Ottawa (after National Conference) – members requested to start the meeting in the afternoon on the 29th from 2 to 6 pm.
2014-05	Future meetings	• Spring 2015: May 6-8, 2015 in Ottawa
2014-10	Future meetings	• Spring 2015: May 6-8, 2015 in Ottawa, Fall 2015: November 4-6, 2015 in Ottawa
2015-05	Future meetings	• Fall 2015: November 4-6, 2015 in Ottawa; • Spring 2016: May 4-6, 2016 in Ottawa with possible workshop
2015-11	Future meetings	• Spring 2016: May 4-6, 2016 in Ottawa with possible lab or treatment plant tour; • Fall 2016: October 19-20, 2016 (conference October 16-18, 2016); • Spring 2017: May 3-5, 2017
2016-05	Future meetings	• Fall 2016: October 19-20, 2016 (conference October 16-18, 2016); • Spring 2017: May 3-5, 2017; • Fall 2017: November 8-9, 2017
2016-10	Future meetings	Spring 2017: May 3-5, 2017; Fall 2017: Date of the November meeting was changed to 7-9, 2017 (instead of Nov 8-10); Spring 2018: May 1-3, 2018
2012-05	Guideline booklet	• Members agreed the guideline booklet should be published as a companion to the summary table. • Members agreed that the title of the summary table should match what is referenced in provincial and territorial legislation and regulations. Members to provide the Secretariat with specific wording
2016-10	Guideline development process (impact paragraphs?)	Members agreed to begin discussing economic impacts as early as possible in the guideline development process.
2015-11	HAAs	• Secretariat to draft problem formulation
2015-05	Hydraulic fracturing	• Hydraulic fracturing to remain as a standing item on the agenda.
2015-05	Lead	• Members approved the document in principle for public consultation, subject to the above noted changes being made.
2015-11	Manganese	• Members approved the document for public consultation subject to discussed changes
2016-11	Manganese	Members approved the document (by email) for posting
2014-10	Minutes	• Members approved changing the name of the "notes" to "minutes". Members agreed with the Technical Secretariat to no longer prepare the summarized version of the notes/minutes.
2010-05	Monitoring Framework	• Members to provide comments on the monitoring framework by May 31. P Brooks to provide comments after June 1. • Conference call to be set up for the 3rd week in June, a week apart from the turbidity call. • S. Deshpande to take P. Brooks place on the working group.
2010-05	National Drinking Water Conference	• The next National Drinking Water Conference is Oct 30 to Nov 2, 2010. • Members agreed to proceed with WaterNet publication of the conference papers.
2013-05	National Drinking Water Conference	• Members agreed to change location of next conference to Ottawa
2010-11	NDMA	• Members approved the document in principle, with the understanding that members will see Appendix 2 before it is posted.

CDW Date	Subject	Decision
2011-05	Nitrate / Nitrite	• Members approved the document for public consultation in principle, subject to the communications process to be developped Secretariat to follow up about the levels in soy-based infant formula • Secretariat to make links between the nitrate/nitrite document and the ammonia document • Secretariat to look into the need to monitor for both nitrate and nitrite in the distribution system (section 3.1 of the document) • Members agreed that information about bottle fed infants needs to be up front in the document. • Secretariat to look into additional information on limitations for using ion exchange at residential scale • Members approved the document for public consultation in principle, subject to the communications process to be developed
2011-07	Nitrate / Nitrite	• Members approved document in principle for public consultation with discussed changes on a conference call, July 12
2011-09	Nitrate / Nitrite	• Members approved document for public consultation with discussed changes on a conference call, Sept 21st
2012-05	Nitrate / Nitrite	• Members approved the document in principle for consultation. • Members agreed to remove ALARA from the guideline statement and from the rationale, and to add a sentence to the effect that for nitrate "it is recommended that levels be kept as low as reasonably practicable" in the Application of the Guideline section.
2013-05	Nitrate / Nitrite	• Members approved final document pending minor changes
2015-11	Old guidelines	• Secretariat will move forward with the proposed approach for the path forward for old guidelines and will prepare a draft consultation document for the May 2016 meeting
2012-10	Other Chemical / Radiological	• Members agreed the Technical Secretariat should develop the benzo(a)pyrene guideline technical document (even if lower on priority list)
2014-10	Other Chemical / Radiological	• The members approved the following parameters for the priority list: strontium, chloramines, 1,4-dioxane, barium and cadmium.
2013-01	Overarching microbiological document	• Conference call Jan 15th: Members approved the document in principle with discussed changes
2014-10	Pentachlorophenol	• Members approved withdrawing the guideline and removing it from the priority list.
2015-11	PFOS and PFOA	• Members approved the PFOS and PFOA documents for public consultation
2014-05	pH	• Members approved the document in principle with proposed changes for public consultation.
2015-05	pH	Members approved the document in principle for publication, subject to the above noted changes.
2010-05	Priority List	• (B)TEX to be listed as one document/one priority. • Members agreed on the following priority list: 1. Atrazine and metabolites 2. (B)TEX 3. Uranium 4. Copper 5. TOC 6. Microcystin 7. Pentachlorophenol 8. Cadmium 9. Benzo(a)pyrene 10. Boron 11. Dichlorophenol; 2,4- 12. Chloramines 13. Colour 14. Dioxane 1,4- 15. Barium 16. Acrylamide 17. Cyanide 18. Tetrachlorophenol; 2,3,4,6 19. Trichlorophenol; 2,4,6 20. Cyanogen chloride 21. Dimethoate 22. Zinc 23. Malathion 24. Dichloroethylene; 1,1- 25. Total Dissolved Solids (TDS)
2011-05	Priority List	• Members declined to put sodium higher on the priority list
2014-05	Priority list	• Members approved the priority list.
2014-10	Priority List	Members approved waiting for the IRIS assessment before beginning work on arsenic.
2015-05	Priority List	Members agreed switching the priority of aluminum and cadmium.
2015-11	Priority List	s-metolachlor will be included in the next prioritization exercise
2011-11	Protozoa	• Members approved the document by concensus
2015-11	Protozoa	• Members approved the document for public consultation
2014-10	Regulatory Frameworks	• Sub-committee to scope the discussion for a special meeting in May 2015 to compare regulatory frameworks. D. Reid to chair the process.
2014-05	Safe Drinking Water for First Nations Act	• Safe Drinking Water for First Nations Act is to be kept as a standing agenda item for CDW meetings.
2012-10	Selenium	• Members agreed that the guideline should be for total selenium • Members approved the document for public consultation, with the changes discussed.
2013-11	Selenium	• Members approved the document in principle if MAC value remains as proposed. Secretariat and Quebec to discuss concerns about the document ASAP and report back to members.
2011-11	Summary table	• Members agreed that the new summary table should replace the summary table currently on the Health Canada website, with a publication deadline of March 2012 • Members agreed to not include the summary table within the guideline booklet, but rather a summary of guideline development considerations • Members agreed that the summary table would be updated each year, and dated for version control • Members agreed that the information in the table replaces the paragraph version in the guideline booklet and that the guideline booklet will include a link to the summary table.
2012-10	Tetrachloroethylene	• Members approved approach taken to develop the guideline.

CDW Date	Subject	Decision
2013-06	Tetrachloroethylene	• Conference call June 18th: Members approved the document for consultation in principle with some changes
2014-10	Tetrachloroethylene	Members approved the document in principle for publication.
2012-10	TEX	• Members agreed the Technical Secretariat should proceed with developing the document as a Guideline Technical Document rather than a Guidance Document
2013-06	TEX	• Conference call June 18th: Members approved the document for consultation in principle with some changes
2014-05	TEX	• Members approved the final document.
2014-10	Trihalomethanes	• Members approved the amended document in principle.
2015-11	Trihalomethanes	• Secretariat to draft problem formulation by May 2016
2010-05	Turbidity	• Secretariat to make links to turbidity in the distribution system more prominent, provide
2010-06	Turbidity	• Members approved the document for public consultation on a conference call.
2012-05	Turbidity	• Members agreed to use the wording "health-based treatment limits" rather than MAC since turbidity is not measured as a concentration. Secretariat to revise document accordingly.
2012-09	Turbidity	• Members approved by consensus the document on turbidity with discussed changes for final posting on a conference call, September 18th, 2012
2016-05	Uranium	• Members approved the document for public consultation.
2016-10	Uranium	Members approved the guideline technical document for public consultation, re-affirming the MAC of 0.02 mg/L.
2011-11	Vinyl chloride	• Members agreed with including ALARA in the guideline statement • Secretariat to add consideration about age of pipes in distribution system to the document and add monitoring section • Members approved the document in principle. C.Robert and J.MacDonald to confirm with their jurisdictions that they can approve the document. Note: approvals from Quebec and Nova Scotia were confirmed by emails following the meeting Nov 14th and 29th respectively.

CDW meeting October 2016 - action items

Item	Action Item	Status/comment
1 Opening	Members to update the membership list	Done
2-B Minutes	Item 3-A (page 3, fifth last line) should note that "there have been no 'waterborne' outbreaks caused by adenovirus".	Done
	Item 4-F, line one, the word "dicussed" should be changed to "discussed".	Done
2-C CDW Status/Checklist	Members to identify new substances of interest for their jurisdictions, that they would like to be considered for the priority list	On-going
2-D Guideline development process	Secretariat to begin the process of updating the Committee Terms of Reference	To do
	The re-affirmation approach will need to be reflected in the guideline development process and Committee Terms of Reference	To do
3-D Enteric viruses	Members to share their guidance material for private well owners (incl D. Reid AB and S. El-Kady FNIHB).	On-going
	Secretariat to recommend a path forward regarding a "WaterTalk" series for private well owners.	On-going
3-E Other microbiological	S. McFadyen to follow-up with CDW to identify P/T working group members for the recreational water guideline update.	Done
4-B Lead	Secretariat to provide updated Qs&As to members.	Done
4-D HAAs and THMs	D. Reid to provide reference with additional data on DBPs to the Secretariat	Done
	Members requested that the derivation of drinking water screening values for BCA and BDCA be provided.	On-going
4-H Strontium	S. Deshpande to provide a reference to the technical secretariat on the calcium / strontium relationship	Done
4-I Manganese	Members to provide comments on the final GTD for manganese in drinking water by November 4 2016.	Done
5-B National drinking water conference	S. McFadyen to follow up on providing copies of presentations to CDW.	Done
	Members requested that the debrief report from Dalhousie University regarding the 2016 national drinking water conference be discussed at the spring 2017 CDW meeting.	Verbal update to be provided at the May 2017 meeting
6-C FNIHB report	S. El-Kady to share the training manual	Done
6-D CHE report	J. Cooper to keep members apprised of progress regarding the review of the CHE mandate.	On-going

2 Agenda/Meeting

2-D Bill C-326

Reference/Action:

- Verbal update on the Bill C-326 and potential implications for CDW and Secretariat
- Attached, copy of Bill C-326
- For information only

Notes:

First Session, Forty-second Parliament,
64-65 Elizabeth II, 2015-2016

HOUSE OF COMMONS OF CANADA

BILL C-326

An Act to amend the Department of Health Act (drinking water guidelines)

FIRST READING, DECEMBER 5, 2016

Mr. Scarpaleggia

Première session, quarante-deuxième législature,
64-65 Elizabeth II, 2015-2016

CHAMBRE DES COMMUNES DU CANADA

PROJET DE LOI C-326

Loi modifiant la Loi sur le ministère de la Santé (lignes directrices relatives à l'eau potable)

PREMIÈRE LECTURE LE 5 DÉCEMBRE 2016

M. Scarpaleggia

421310

SUMMARY

This enactment amends the *Department of Health Act* to require the Minister of Health to conduct a review of drinking water standards in member countries of the Organisation for Economic Co-operation and Development and, if appropriate, to make recommendations for amendments to national guidelines respecting drinking water.

SOMMAIRE

Le texte modifie la *Loi sur le ministère de la Santé* afin d'exiger du ministre de la Santé qu'il examine les normes relatives à l'eau potable en vigueur dans les pays membres de l'Organisation de coopération et de développement économiques et, s'il y a lieu, qu'il formule des recommandations visant à modifier les lignes directrices relatives à l'eau potable au Canada.

Available on the Parliament of Canada Web Site at the following address:
http://www.parl.gc.ca

Disponible sur le site Web du Parlement du Canada à l'adresse suivante :
http://www.parl.gc.ca

1st Session, 42nd Parliament,
64-65 Elizabeth II, 2015-2016

HOUSE OF COMMONS OF CANADA

BILL C-326

An Act to amend the Department of Health Act (drinking water guidelines)

Preamble

Whereas it is essential that drinking water in Canada be of the highest quality;

Whereas the Government of Canada recognizes that national guidelines respecting drinking water are required to ensure such quality;

Whereas the main responsibility of the Federal-Provincial-Territorial Committee on Drinking Water is to protect the quality of drinking water in Canada, including by developing and maintaining national guidelines;

And whereas the Minister of Health acknowledges the need for the national guidelines to be in keeping with the highest international standards respecting drinking water;

1996, C. 8

Now, therefore, Her Majesty, by and with the advice and consent of the Senate and House of Commons of Canada, enacts as follows:

1 The *Department of Health Act* is amended by adding the following after section 5:

Definition of *member country*

5.1 (1) In this section, *member country* means a country that is a member of the Organisation for Economic Co-operation and Development, or a subdivision of such a country.

Annual review of standards in member countries

(2) The Minister shall, within three months after the end of each calendar year, conduct a review of the standards respecting drinking water in member countries in the

1re session, 42e législature,
64-65 Elizabeth II, 2015-2016

CHAMBRE DES COMMUNES DU CANADA

PROJET DE LOI C-326

Loi modifiant la Loi sur le ministère de la Santé (lignes directrices relatives à l'eau potable)

Préambule

Attendu :

qu'il est essentiel que l'eau potable soit de la plus haute qualité au Canada;

que le gouvernement du Canada reconnaît que la garantie d'une telle qualité est tributaire de lignes directrices nationales relatives à la qualité de l'eau potable;

que le principal mandat du Comité fédéral-provincial-territorial sur l'eau potable est d'assurer la qualité de celle-ci au Canada, notamment par l'élaboration et le maintien de recommandations nationales;

que le ministre de la Santé reconnaît qu'il faut que les lignes directrices nationales équivalent aux plus hautes normes internationales relatives à l'eau potable,

1996, ch. 8

Sa Majesté, sur l'avis et avec le consentement du Sénat et de la Chambre des communes du Canada, édicte :

1 La *Loi sur le ministère de la Santé* est modifiée par adjonction, après l'article 5, de ce qui suit :

Définition de *pays membre*

5.1 (1) Pour l'application du présent article, *pays membre* s'entend d'un pays membre de l'Organisation de coopération et de développement économiques et de ses subdivisions.

Examen annuel des normes des pays membres

(2) Dans les trois mois suivant la fin de chaque année civile, le ministre examine les normes relatives à l'eau potable en vigueur dans les pays membres au cours de

previous calendar year and prepare a report on the review.

Recommendations

(3) If the Minister is of the opinion that standards respecting drinking water in a member country provide for a higher level of water quality than the guidelines respecting drinking water in Canada and that it would be in the best interests of Canadians that those guidelines be amended accordingly, the Minister shall include recommendations for the amendments in the report prepared under subsection (2).

Tabling of report

(4) The Minister shall cause a copy of the report to be laid before each House of Parliament on any of the first 15 days on which that House is sitting after the report is completed.

Publication of report

(5) The Minister shall publish the report on the Department's website within 30 days after the day on which the report is laid before each House of Parliament.

l'année civile précédente et établit un rapport sur l'examen.

Recommandations

(3) Si le ministre estime que les normes relatives à l'eau potable d'un pays membre permettent d'assurer une meilleure qualité de l'eau potable que les lignes directrices en vigueur au Canada et qu'il serait dans l'intérêt des Canadiens de modifier celles-ci, le ministre assortit le rapport de ses recommandations de modification.

Dépôt du rapport

(4) Le ministre fait déposer le rapport devant chaque chambre du Parlement dans les quinze premiers jours de séance de celle-ci suivant son achèvement.

Publication du rapport

(5) Le ministre publie le rapport sur le site Web de son ministère dans les trente jours suivant la date de son dépôt devant chaque chambre du Parlement.

2 Agenda/Meeting

2-E CDW Priority list

Reference/Action:

- Oral presentation on the prioritization process for guideline development
- CDW to discuss

Notes:

2 Agenda/Meeting

2-F Withdrawal of old guidelines

Reference/Action:

- Verbal update on the status of the withdrawal of old guidelines
- For information only

Notes:

3 Parameters - Microbiological

3-A Protozoa

Reference/Action:

- Oral presentation on the guideline technical document on protozoa
- Technical document sent prior to meeting: *Enteric Protozoa in Drinking Water: Giardia and Cryptosporidium*
- Status: The work on the protozoa document update was initiated in August 2014. The draft document went through internal and external peer-review processes which were completed in September 2015. The document was approved by CDW members to undergo public consultation at the November 2015 meeting and the document was posted for a 2-month consultation period which ended in January 2017. Comments from the public consultation were addressed and the document revised accordingly. The updated document is now presented to CDW members for a final approval for posting.
- For CDW discussion/approval

Notes:

3 Parameters - Microbiological

3-B Total coliforms

Reference/Action:

- Oral presentation on the draft guideline technical document on total coliforms
- Status: The work on the guideline technical document for total coliforms was initiated in August 2016 to update the current version. The document is being updated and an appendix with changes since the last version will go through internal and external peer-review processes in summer 2017. The document is expected to be sent to CDW members late summer/early fall of 2017 for approval for public consultation.
- For information only

Notes:

3 Parameters - Microbiological

3-C *Enterococci*

Reference/Action:

- Oral presentation on the draft guideline technical document on Enterococci
- Status: The work on Enterococci was initiated in July 2015 to develop a guideline technical document. The document was drafted and went through internal and external peer-review processes in winter 2017. Peer-review comments were addressed and the document was revised accordingly. The draft document is presented at this meeting for approval by CDW for a 2 month public consultation period. Document to be sent prior to meeting.
- For CDW discussion/approval

Notes:

3 Parameters - Microbiological

3-D Other microbiological

Reference/Action:

- Verbal update on other microbiological documents and review of other work in the area of water microbiology
- For information only

Notes:

4 Parameters - Chemical

4-A NOM

Reference/Action:

- Oral presentation on the draft guideline technical document on natural organic matter (NOM) in drinking water
- Status: The work on the NOM document was initiated in March 2014. The document was drafted and went through an external peer-review process which ended in February 2017. Comments from peer-reviewers were addressed and the document was revised accordingly. The document is presented to CDW members for approval for a 2-month public consultation period.
- To be sent prior to meeting: Draft guideline technical document for natural organic matter in drinking water
- For CDW discussion/approval

Notes:

4 Parameters - Chemical

4-B Lead

Reference/Action:

- Oral presentation on a summary of the comments received during the public consultation on the draft guideline technical document on lead in drinking water
- Status: The draft document on lead went through internal and external peer-review processes, ending in January 2015. Comments from peer-reviewers were addressed and the document revised and presented to CDW members at the May 2015, which approved the document for a 2-month public consultation period which ended March 15, 2017. Relevant comments from public consultation will be addressed in the spring/summer 2017, and the document will be presented at the fall 2017 meeting for final approval by CDW. In the meantime, some changes were made to the classification and assessment section to address some concerns from public consultation with the approach to calculate the proposed health based value (HBV).
- Attached: Section 10.2 of the guideline technical document for lead in drinking water, with proposed changes highlighted.
- For CDW discussion

Notes:

10.2 Non-cancer risk assessment

BLLs below the current intervention level of 10 µg/dL have been associated with several adverse health effects in humans, including: reduced cognition in adults, especially seniors (see Section 9.1.2.1); increased systolic blood pressure in adults, especially in African Americans and postmenopausal women (see Section 9.1.2.2); decreased renal function, especially in diabetic and hypertensive individuals (see Section 9.1.2.3); reproductive effects, including delayed puberty and early menopause in women (see Section 9.1.3.1); and developmental neurotoxicity, including decreased intelligence and attention in infants and children (see Section 9.1.3.2). There is extensive evidence in experimental animals to support the observations made in humans (see Section 9.2). Of the endpoints considered, developmental neurotoxicity has been the most widely studied effect of lead exposure. The relationship between IQ and BLLs in school-aged children specifically was the most sensitive endpoint and can be characterized with greatest certainty due to the large database of relevant information. Effects on IQ represent an important social determinant of health, as lowered IQ in children has been conclusively linked to poorer academic achievement and earning potential later in life (Herrnstein and Murray, 1994; Schwartz, 1994b; Nevin et al., 2000; Gross et al., 2002; Health Canada, 2013a). Given the strong weight of evidence for lead-induced decreases in IQ and the lack of a known threshold of toxicity for this endpoint, IQ loss in children was selected as the critical health effect on which to base the non-cancer risk assessment.

The loss of IQ points is not expected to be distributed equally across the population, due to inter-individual variability in intellectual functioning. Variances in IQ within the population follow a normal distribution, in which an IQ of 100 represents average intelligence and approximately 2% of the population exhibits an intellectual disability (see Figure 10.1). A mild intellectual disability (MID) is defined as having an IQ of 70 ± 5 points, among other diagnostic criteria, and is characterized by delayed learning as well as cognitive and behavioral problems that can greatly affect an individual's quality of life (American Psychiatric Association, 2013). By decreasing the average population IQ even slightly, the number of children expected to be diagnosed with a MID will increase and children with an existing disability may exhibit more significant intellectual impairments. This assessment focuses on increased cases of children with a MID due to small population shifts in IQ associated with exposure to lead through drinking water.

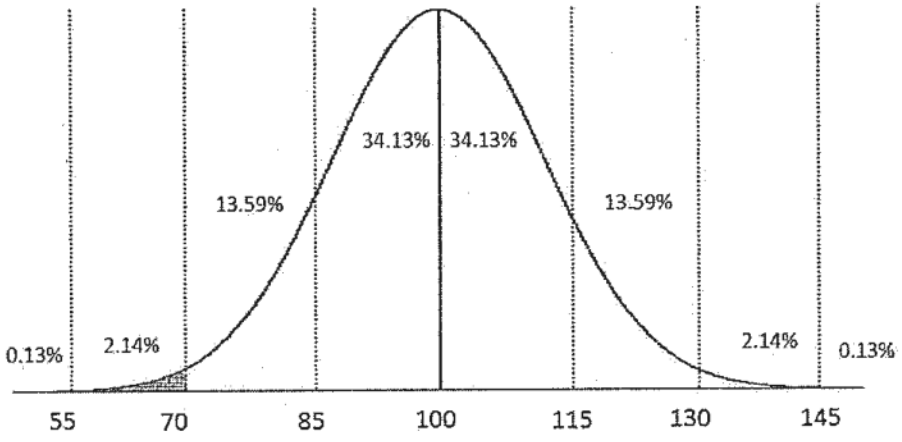

Figure 10.1. Normal distribution of IQ presented as frequency within the population vs. IQ score (modified from Weiss, 1988). The hashed line section under the curve represents the 2.27% of the population with an intellectual disability.

The critical study selected for this assessment consists of an analysis of pooled data from seven longitudinal prospective studies initiated prior to 1995, which followed children from birth or infancy until 5–10 years of age (Lanphear et al., 2005). The study involved 1333 children from Boston, Massachusetts, Cincinnati and Cleveland, Ohio, Rochester, New York, Mexico City, Mexico, Port Pirie, Australia, and Kosovo, Yugoslavia. Of the existing studies on IQ decrements in children (see Section 9.1.3.2), the meta-analysis performed by Lanphear et al. (2005) has the highest number of individuals and diversity of subjects. Full-scale IQ was assessed using age- and language-appropriate versions of the Wechsler Intelligence Scales for Children. Ten covariates were examined overall and were available for most subjects, including maternal IQ, education, marital status, prenatal alcohol use, prenatal tobacco use, HOME inventory score, sex, birth order, birth weight and ethnicity. Four blood lead indices were used in the analysis: (1) concurrent BLL (closest to testing), (2) maximum BLL, (3) lifetime average BLL and (4) early-childhood BLL (mean BLL from 6 months to 2 years of age). Concurrent BLL was selected by Lanphear et al. (2005) as the primary lead exposure index because it exhibited the strongest relationship with IQ. Health Canada agrees with the choice of concurrent BLL as the dose metric for further analysis.

Individual data from concurrent BLLs of the Lanphear et al. (2005) study have been acquired by EFSA (2013) and by JECFA (2011) to establish BMDs associated with a 1% change on human intellectual function. Overall, EFSA provided extensive detail pertaining to its BMD analyses with thorough justification for the choice of the piece-wise linear model as the best fit model associated with the least uncertainty (EFSA, 2013; Budtz-Jorgensen et al., 2010). Thus, the BMDL01 of 1.2 µg/dL associated with a benchmark response of 1 IQ point was used to estimate the corresponding oral dose.

In order to determine corresponding external oral doses associated with exposure from drinking water, PBPK modelling was done using all three of the available models (i.e., IEUBK, Leggett, and O'Flaherty) (see Section 8.5). Equivalent oral administered doses for a five year old child were determined to be 0.4, 0.2 and 0.8 µg/kg bw per day for the IEUBK, Leggett and O'Flaherty models, respectively. Because the Leggett model has been shown to overestimate BLLs at lower exposures (Pounds and Leggett, 1998), it was not considered any further in our analysis. The IEUBK model, however, was considered to be an excellent model, as it is specific to children and has been more extensively validated than other models; the external oral dose of 0.4 µg/kg bw per day (or 0.0004 mg/kg bw per day) was thus used as a point of departure in this assessment and corresponds to the external oral dose associated with the average loss of 1 IQ point.

At the population level, the average loss of 1 IQ point, or an approximate change of 1% in human intellectual functioning, is associated with significant public health implications. These include substantive increases in cases of children with a MID, increased severity of existing intellectual disabilities and decreases in "gifted" children, as well as impacts on socioeconomic status and productivity in general (EFSA, 2013; Health Canada, 2013a). As discussed in section 9.1.3.2, lead exposure significantly affects IQ even at very low BLLs and the lowest BLL associated with adverse neurodevelopmental effects in children has not been identified (section 9.1.3.2). Moreover, data suggest that the damage caused by lead at very low doses is completely,

or at the very least mostly, irreversible (WHO, 2010). For these reasons, it was determined appropriate to calculate a slope factor. A slope factor of 2500 $(mg/kg\ bw/day)^{-1}$ was derived by dividing the benchmark response by the external oral dose of 0.0004 mg/kg bw/day.

The average loss of intelligence associated with various drinking water concentrations of lead can be calculated using the following equation:

$$\text{Average IQ loss} = \frac{\text{drinking water concentration} \times \text{daily water intake}}{\text{body weight}} \times \text{slope factor}$$

Where:

- 0.9 L is the daily water intake for children 5-11 years of age (Health Canada, 1994)
- 18.2 kg is the average body weight for a 5-year-old child, as determined using data from the IEUBK PBPK model (U.S. EPA, 1994a, 1994b; White et al., 1998); and
- 2500 $(mg/kg\ bw\ per\ day)^{-1}$ is the slope factor

The standardized normal distribution of IQ presented in Figure 10.1 is used as a reference for variances in intelligence across the Canadian population. The anticipated average IQ loss associated with various drinking water concentrations of lead is used to estimate the corresponding proportion of individuals with IQ scores expected to drop below 70 IQ points and hence to estimate the resulting additional cases of children with an intellectual disability above background (Walker et al., 2017), as provided in Table 10.1.

Table 10.1. Estimated additional cases of children with an intellectual disability associated with various lead concentrations in drinking water

DW concentration (µg/L)	% children expected to develop an MID[a]	Estimated increase in number of children expected to develop an MID[a]
0.1	0.004	5 in 100,000
1.0	0.045	5 in 10,000
3.0	0.137	1 in 1,000
5.0	0.232	2 in 1,000
10.0	0.483	5 in 1,000

[a]Over background of 2.27% or 2 cases per 100 children with an intellectual disability (see figure 10.1)

The consensus in the scientific literature is that a safe level of exposure to lead in children has not been identified. The estimates presented above provide an indication of cases of intellectual disabilities in children above background associated with the respective levels of lead in drinking water in order to inform risk assessment and/or risk management decisions. Although this assessment focuses on intellectual disabilities in a sensitive sub-set of the population (i.e., children with a borderline MID), it should be noted that there are significant health and socioeconomic implications of even small generalized losses in IQ regardless of intellectual functioning (Health Canada, 2013a). Moreover, this assessment focuses on children as the most sensitive population but it should be noted that reduced intellectual functioning, among other health effects, is expected to occur in all age groups at low levels of exposure.

References to add:

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders, fifth edition (DSM 5). Neurodevelopmental Disorders. Washington, D.C.

Grosse, S.D., Matte, T.D., Schwartz, J. and Jackson, R.J. (2002). Economic gains resulting from the reduction in children's exposure to lead in the United States. Environmental Health Perspectives. 110(6): 563-569.

Walker, M. (2017). Probability of MMR for an unexposed population. Internal document available upon request.

Weiss, B. (1988). Neurobehavioral toxicity as a basis for risk assessment. Trends in Pharmacological Sciences. 9(2): 59-62.

WHO. (2010). Childhood lead poisoning. World Health Organization, Geneva, Switzerland.

4 Parameters - Chemical

4-C PFOS, PFOA

Reference/Action:

- Oral presentation on the draft guideline technical documents on PFOS and PFOA in drinking water
- Attached: Revised guideline technical document on PFOS in drinking water and table of comments and responses from public consultation
- Attached: Revised guideline technical document on PFOA in drinking water and table of comments and responses from public consultation
- Status: The draft guideline technical documents for PFOS and PFOA in drinking water have gone through a public consultation ending in September 2016. The comments from the consultation have been integrated, where relevant, and the documents are presented at the meeting for final approval by CDW
- For CDW discussion/approval

Notes:

Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Perfluorooctane Sulfonate (PFOS)

Prepared by the
Federal-Provincial-Territorial Committee on
Drinking Water
of the
Federal-Provincial-Territorial Committee on
Health and the Environment

Health Canada
Ottawa, Ontario

July, 2017

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The document was prepared by the Federal-Provincial-Territorial Committee on Drinking Water of the Federal-Provincial-Territorial Committee on Health and the Environment.

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Other Guideline Technical Documents for the Guidelines for Canadian Drinking Water Quality can be found on the following web page: www.healthcanada.gc.ca/waterqualite

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July 2017

Perfluorooctane Sulfonate

Part I. Overview and Application

1.0 ~~Proposed guideline~~Guideline

~~A~~The maximum acceptable concentration (MAC) ~~of 0.0006 mg/L (0.6 µg/L) is proposed~~ for perfluorooctane sulfonate (PFOS) in drinking water is 0.0006 mg/L (0.6 µg/L). The MAC is based on exposure solely to PFOS.

As the toxicological effects of PFOS and perfluorooctanoic acid (PFOA) are considered to be additive, the sum of the ratios of the detected concentration to the MAC for PFOS and PFOA should not exceed 1.

2.0 Executive summary

PFOS is a man-made compound that does not occur naturally in the environment. It is no longer manufactured, imported, sold, offered for sale or used in Canada, but is still found in the environment because of its extremely persistent nature. PFOS was used for water, oil and/or stain resistance on surface and paper-based applications, such as rugs and carpets, fabric and upholstery. It was also used in specialized chemical applications, such as fire-fighting foams, hydraulic fluids, and carpet spot removers.

This guideline technical document reviews and assesses all identified health risks associated with PFOS in drinking water. It incorporates available studies and approaches and takes into consideration the availability of appropriate analytical methods and treatment technology. Based on this review, the ~~proposed~~ drinking water guideline for PFOS is a maximum acceptable concentration (MAC) of 0.0006 mg/L (0.6 µg/L~~).~~), based on the general population.

~~During its fall 2015 meeting, the Federal-Provincial-Territorial Committee on Drinking Water reviewed the guideline technical document on PFOS and gave approval for this document to undergo public consultation.~~

2.1 Health effects

The carcinogenicity of PFOS has not been evaluated by the International Agency for Research on Cancer (IARC). Some cancer effects were observed in humans after exposure to PFOS, but no clear links could be made due to various study limitations. Tumours were observed in the liver, thyroid, and mammary gland of rats following long term exposure to PFOS. Non-cancer effects occurring at the lowest level of exposure to PFOS in animals include effects on the immune system, liver effects, effects on the thyroid and changes in serum lipid levels.

Both cancer and non-cancer endpoints were considered in the derivation of the ~~proposed~~ MAC for PFOS in drinking water. The non-cancer approach, based on liver effects in rats, was used to calculate a ~~proposed~~ MAC that is protective of human health from both cancer and non-cancer effects.

2.2 Exposure

Canadians can be exposed to PFOS through its presence in food, consumer products, dust, and drinking water. Exposure is mainly from food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Although PFOS is not regularly monitored at water treatment plants in Canada, the analysis has been performed for a few locations. When detected in drinking water, it is usually found below ~~1 ng~~0.001 µg/L.

2.3 Analysis and treatment

To date, the United States Environmental Protection Agency has not approved any analytical methods for the analysis of PFOS in drinking water. There are some methods that can be used to measure PFOS in drinking water at levels well below the proposed MAC. However, they require good quality control procedures to get accurate results.

The selection and effectiveness of a treatment strategy for PFOS removal is driven by several factors, including source water chemistry, concentration of PFOS and/or other perfluoroalkyl substances and pre-existing treatment processes. Conventional treatment is not effective for PFOS removal. Other treatment methods are promising, although full-scale studies are limited. Granular activated carbon (GAC) adsorption can achieve treated water concentrations of PFOS below the ~~proposed~~ MAC. However, proper operation of the system is essential to ensure that the performance of GAC is not affected by the presence of natural organic matter in the source water. Membrane filtration techniques (reverse osmosis and nanofiltration) and anion exchange may also be effective. Although there are no residential treatment devices certified to remove PFOS, it is expected that the same treatment technologies would also be effective at the residential scale.

2.4 Additivity

The health effects of PFOS and PFOA are similar and well documented. Recent scientific evidence shows that PFOS and PFOA affect the same organ in similar ways. Thus, when PFOA and PFOS are found together in drinking water, the best approach to protect human health is to consider both chemicals together when comparing to the screening values. This is done by adding the ratio of the observed concentration for PFOS to its MAC with the ratio of the observed concentration for PFOA to its MAC; if the result is below or equal to one, then the water is considered safe for drinking. Science currently does not justify the use of this approach for other PFAS.

3.0 Application of the guideline

~~———~~*Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.*

~~3.1 Monitoring~~

PFOS ~~is~~ and perfluorooctanoic acid (PFOA) are typically found in ~~groundwater~~groundwaters and surface waters impacted by aqueous film-forming foam (AFFF) (i.e., fire-fighting foams). ~~water~~ They may also be found in groundwaters and surface waters

contaminated by: discharges from industrial facilities; ~~discharge~~effluents from wastewater treatment plants treating domestic ~~and~~or industrial waste; storm water runoff; ~~land application~~or applications of ~~biosolid amended soils as well as groundwater and surface water sources that are or may have been~~ biosolids from a municipal wastewater treatment plant to agricultural land. ~~impacted by aqueous film-forming foam (AFFF) (i.e., fire-fighting foams).~~ Like other groundwater contaminants, PFOS can reach drinking water wells through migration of a contaminated groundwater plume. It can also reach ~~groundwater~~surface waters from air emissions of industrial facilities. Particle-~~bounded~~bound volatile perfluoroalkyl substances ~~(PFASs)~~ PFAS) including PFOS may be carried ~~by wind~~ from disposal sites by the wind and deposited on ~~the~~ land or ~~the~~ surface water, thus explaining ~~the~~their presence ~~of these anthropogenic chemicals in~~ in remote locations and, in waters not impacted by a point source. PFOS migrates very slowly through the soil to groundwater.

For drinking water supplies that occasionally experience short-term exceedances above the MAC, it is suggested that a plan be developed and implemented to address these situations. For more significant long-term exceedances that cannot be addressed through treatment, it is suggested that alternative sources of drinking water be considered.

3.1 Monitoring

~~and may not be detected in the source water~~It is important to note that the analysis for ~~years~~PFOS is highly specialized and should be conducted by a laboratory that is accredited or that has a stringent quality assurance/quality control (QA/QC) program in place to ensure data quality.

3.1.1 Source charcterization

Utilities should characterize their source water to assess PFOA and PFOS concentrations. ~~In~~, particularly if source waters ~~where PFOS~~are impacted by firefighting training areas, military bases, airports, manufacturing sites and/or waste disposal sites. Once contamination is ~~present at levels exceeding the proposed~~ detected, the source should be sampled semi-annually to confirm that the sum of the ratios of the observed concentration to the MAC ~~quarterly~~ for PFOA and PFOS does not exceed 1. If treatment is required, the source should be sampled in conjuction with compliance monitoring ~~of surface water and semi-annual monitoring of groundwater should be conducted.~~

~~The monitoring frequency of the treated water depends on the treatment technology the utility employs.~~ Utilities that ~~use a granular activated carbon (GAC) system for PFOS removal may want to enhance monitoring of the treated water in order to assess the performance of the GAC system and to determine the timing of the regeneration. Utilities may consider reduced monitoring when they have data indicating that PFOS does not occur in the source water. However, if the main source of groundwater~~have baseline data showing the absence of PFOA and PFOS may conduct less frequent monitoring.

If the main source of contamination is suspected to be from the use of AFFF, utilities may want to consider monitoring for other ~~perfluorinated alkyl acids PFAAs (i.e.,~~PFAS, including shorter chain compounds such as perfluorobutanoic acid and perfluorobutane sulfonate~~).~~. These other ~~PFAA compounds~~PFAS are likely to co-occur at AFFF-impacted sites and are typically more mobile. As such, they can serve as an early warning sign of PFOA and PFOS contamination of a groundwater source. ~~Utilities should be aware that ozone or AOPs may oxidize~~

~~polyfluorinated precursor chemicals present in the raw water, which could result in an increased concentration of PFOS in the finished water.~~

3.1.2 Operational monitoring

Treatment systems should be specifically designed, operated and maintained for removal of PFOA and PFOS. The operational monitoring frequency will depend on the treatment technology the utility employs. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance. Utilities that use a GAC system for PFOA and PFOS removal may require quarterly monitoring of the treated water in order to assess the performance of the GAC system and to determine the timing of the regeneration or replacement. Utilities should also be aware that ozone or advanced oxidation processes (AOPs) may oxidize polyluorinated pecursors present in the source water, which could result in an increased concentration of PFOA in the finished water.

3.1.3 Compliance monitoring

When treatment is in place for PFOA and PFOS removal, semi-annual monitoring of the treated water is recommended. Samples should be collected after treatment, but prior to distribution, typically at the entry point to the distribution system. Paired samples of source and treated water should be taken to confirm the efficacy of the treatment. The sum of the ratios of the measured concentration to the MAC for PFOA and PFOS should not exceed 1.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Perfluorooctane sulfonate (PFOS) is an anthropogenic compound with a chain length of 8 perfluorinated carbons. PFOS, its salts and its precursors form part of a larger chemical class of fluorochemicals typically referred as perfluorinated alkyl acids (PFAAs). PFOS can occur under several forms, including the acid ($C_8HF_{17}SO_3$; 500.03 g/mol; CAS number 1763-23-1), the potassium salt (K^+PFOS; 538.23 g/mol; CAS number 2795-39-3), the ammonium salt ($NH4^+$ PFOS; CAS number 29081-56-9), the diethanolamine salt ($C_8F_{17}SO_3NH$; CAS number 70225-14-8), and the lithium salt (Li^+PFOS; 29457-72-5). The main synonyms of PFOS are 1-perfluorooctanesulfonic acid, heptadecafluoro-1-octanesulfonic acid, heptadecafluorooctan-1-sulphonic acid, perfluorooctane sulfonate, perfluorooctylsulfonic acid and 1-octanesulfonic acid (ATSDR, 2009).

PFOS is soluble in water, with solubility values reported at 570 mg/L and 519 mg/L (at 20°C) in pure water (OECD, 2002; Brooke et al., 2004) and at 370 mg/L in freshwater (OECD, 2002); the solubility decreases when the water salt content increases (OECD, 2002). The solubility depends on the acid dissociation constant (pKa) of the acid form; the pKa value for PFOS has been estimated at -3.27 (no direct measurement of the pKa has been located) and PFOS is considered to be a strong acid, suggesting that the environmental partitioning of PFOS will be dominated by the anionic form (Brooke et al., 2004).

PFOS contains both hydrophobic and hydrophilic functional groups and is thus expected to behave differently than traditional hydrophobic chemicals. Due to its surfactant properties, the octanol:water partition coefficient ($LogK_{ow}$) cannot be determined directly because multiple layers are formed in octanol/water. Moreover, the parameters usually estimated from the K_{ow} (e.g. K_{oc}, K_d, bioconcentration factor) cannot be calculated using this method (OECD, 2002), nor using conventional quantitative structure-activity relationship models (QSAR) (Beach et al., 2006).

PFOS is essentially non-volatile, with a vapour pressure of 3.27×10^{-9} atm at 20°C (OECD, 2002; Brooke et al., 2004; ATSDR, 2009); its Henry's Law constant was estimated at approximately 3.1×10^{-9} atm-m^3/mol. Attempts to measure the air–water partition coefficient using the potassium salt indicate no volatilization to any measurable extent; the air-water partition coefficient was thus considered to be $< 2 \times 10^{-6}$, and to be essentially zero (OECD, 2002; Brooke et al., 2004). Nevertheless, some of the PFOS-containing substances have considerably higher vapour pressure and are more likely to be volatile to some extent. This may allow the wider transport of potential PFOS precursors through the air than is possible for PFOS itself (Brooke et al., 2004).

The principal applications for PFOS were for water, oil and/or stain resistance for use on surface and paper-based applications, such as rugs and carpets, fabric and upholstery. PFOS was also used in specialized chemical applications, such as fire-fighting foams, hydraulic fluids, carpet spot removers, mining and oil well surfactants and other specialized chemical formulations (OECD, 2002; Health Canada, 2006). PFOS was produced in the U.S. until 2002, when the 3M Company phased out its PFOS production (ATSDR, 2009). Although there are no known Canadian manufacturers of ~~PFAAs~~PFAS, including PFOS, almost 600,000 kg of ~~PFAAs~~PFAS were imported into Canada between 1997 and 2000 (PFOS represented a very small proportion of this total) (Health Canada, 2006). ~~In 2009, PFOS and its salts were added to~~ Regulations

established under the *Canadian* ~~Virtual Elimination List compiled under subsection 65(2) of CEPA~~*Environmental Protection Act, 1999*~~, as required by subsection 3(1) of the Act (SOR/2009-15) (Government of Canada, 2009). The Canadian regulations~~ prohibit the manufacture, ~~import~~use, sale, offer for sale ~~and use of PFOS~~, or ~~products containing PFOS~~import of PFOS and its salts or compounds, unless ~~incidentally present, with certain exemptions~~designed for ~~aviation hydraulic fluids under certain conditions, and some products used in photographic or photolithographic processs~~specific uses (Government of Canada, ~~2008).~~ 2012).

4.1 Sources to water

A source of ~~PFAAs~~PFAS in water is the discharge of aqueous film-forming foam (AFFF) for extinguishing fires. Discharge of AFFF was presumed to have resulted in increased levels of PFOS in water surrounding the Toronto International Airport, based on spatial and temporal trends of ~~PFAAs~~PFAS in water (Awad et al., 2011). However, as of 2013, most uses of AFFF containing PFOS at concentrations of >0.5 ppm have been banned (Government of Canada, 2008). Data supporting the possibility of contamination in the vicinity of firefighting training areas include measurements of elevated PFOS concentrations in groundwater near a Michigan air force base (Moody et al., 2003), at a firefighting training ground in Australia (Baduel et al., 2015), and in private drinking water wells proximate to an industrial site in Cologne, Germany (Weiß et al., 2012).

Elevated PFOS concentrations measured in surface water downstream from fluorochemical manufacturing plants have also been used as indications of the potential for industrial sources of PFOS in water (Hansen et al., 2002).

Mass balance studies of ~~PFAAs~~PFAS at wastewater treatment plants commonly report similar or higher PFOS concentrations in the effluent in comparison to the raw influent, suggesting that the degradation of other fluorinated organic compounds (i.e. fluoropolymers) into PFOS may take place during wastewater treatment (Clarke and Smith, 2011). This also indicates that conventional wastewater treatment plants are not effective for removal of ~~PFAAs~~PFAS (Ahrens, 2011).

Although measures are in place in North America and Europe to restrict the production, use and/or the major exposure risks to PFOS, the ubiquitous use of ~~PFAAs~~PFAS within the built environment still causes their transfer to biosolids (sludge) (Clarke and Smith, 2011). The use of biosolids as fertilizers may thus represent a source of soil and water contamination with PFOS (Clarke and Smith, 2011). Drinking water contamination was reported after the widespread use of soil conditioner mixed with industrial waste containing ~~PFAAs~~PFAS (e.g., 8,600 ng PFOS/g d.w.) in the region of Arnsberg, North Rhine Westphalia, Germany (Hölzer et al., 2008). PFOS was also measured in surface and well water in Decatur, Alabama, after biosolids from a municipal wastewater treatment plant (at which waste from local fluorochemical facilities were received) were applied in agricultural fields (Lindstrom et al., 2011).

4.2 Environmental fate

The elevated water solubility of PFOS and the negligible volatility of its ionized species suggest that PFOS species will partition primarily to the aquatic environment. PFOS is a strong acid and most likely forms strong bonds in soils, sediments, and sludge via chemisorption mechanism (3M Company, 2001; Brooke et al., 2004; Beach et al., 2006), with greater adsorption under anaerobic conditions than aerobic conditions (Beach et al., 2006). PFOS does not partition

into lipids but instead binds to certain proteins in animals (Beach et al., 2006). PFOS bioaccumulates in tissues of aquatic and terrestrial living organisms including humans. Data for the marine food web from the Eastern Canadian Arctic (from 1996 to 2002) indicate that PFOS biomagnifies through the entire food web with a trophic magnification factor of 3.1 (Butt et al., 2010).

Under environmental conditions, PFOS does not hydrolyze, photolyze or biodegrade, and it is considered extremely persistent in the environment (OECD, 2002; Beach et al., 2006; Environment Canada and Health Canada, 2012). The estimated half-lives for PFOS (as the potassium salt) are > 41 years in water (ATSDR, 2009) and 114 days in the atmosphere (Brooke et al., 2004); the indirect half-life of PFOS was estimated (using an iron oxide photoinitiator model) to be ≥ 3.7 years (OECD, 2002; Beach et al., 2006). No study was able to demonstrate the biodegradation of PFOS under aerobic or anaerobic conditions (Beach et al., 2006) and PFOS is considered resistant to microbial degradation (Health Canada, 2006). Moreover, the abiotic degradation of certain PFOS precursor molecules can lead to PFOS as the end stage metabolite product (Martin et al., 2010). Hydrolysis rates (varying from days to weeks) for PFOS precursors are provided in 3M Company studies (Mendel, 1977; 3M Company, 1996; Hatfield, 1999).

The adsorption of PFAS onto natural sediments with varying organic carbon and iron oxide content, onto kaolinite, alumina and geothite was investigated in aqueous solution (Higgins and Luthy, 2006; Johnson et al., 2007; Pan and Yu, 2010; Tang et al., 2010; Wang et al., 2011; Xiao et al., 2011; 2015). Higgins and Luthy (2006) and Johnson et al. (2007) reported that the adsorption of PFAS on sediments collected from various riverines and lacustrine sites was influenced by the organic carbon, rather than the mineral content, of the sediment. Other studies demonstrated that the adsorption of PFOA/PFOS onto minerals was influenced by pH, ionic strength and the type of the cations present in the aqueous solution (Tang et al., 2010; Wang et al., 2011; Xiao et al., 2011).

5.0 Exposure

Canadians can be exposed to perfluorinated compounds present in food, consumer products, dust, and drinking water. The major sources of ~~PFAAs~~perfluorinated compounds are expected to be food and consumer products, including solution-treated carpeting and treated apparel (Tittlemier et al., 2007); however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water.

The estimated total daily intake of ~~PFAAs~~PFAS (estimates not provided for individual ~~PFAAs~~PFAS) in Canadians was reported to be 410 ng/day for the general population of Canada (Tittlemier et al., 2007). Drinking water ingestion, estimated at 0.3 ng/day, contributed only a minor amount to the overall estimated exposure ~~(estimated at 0.3 ng/day).~~ Although some exposure data are available, they are considered insufficient to justify modifying the default allocation factor for drinking water of 20%. ~~Twenty percent is the~~This default allocation factor for drinking water ~~which~~ is used as a "floor value" when drinking water is not a major source of exposure (Krishnan and Carrier, 2013); therefore, this value is applicable for PFOS, even though water is expected to be only a minor contributor to PFOS exposure for the general population.

5.1 Water

Although PFOS is not regularly monitored at drinking water treatment plants in Canada, the analysis has been performed for a few locations. PFOS was not detected (method detection limit [MDL]= 0.85 ng/L) in raw or finished water from samples obtained in 2012 from two drinking water treatment plants in Calgary (Alberta Environment and Water, 2013). In Quebec, raw and treated water samples were obtained monthly between April 2007 and March 2008 from seven sites (a total of 84 samples each of raw and treated water). PFOS was detected in 52% of treated samples (MDL of 0.3–0.6 ng/L), with a median value of 1.0 ng/L. (maximum value of 36.0 ng/L). The detection rate and median concentrations were higher in treated water than in raw water, for which the detection rate and median were 40% and <1 ng/L, respectively (Ministère du Développement durable, de l'Environnement, de la Faune et des Parcs, 2012). The reported PFOS concentration in 5 tap water samples from Niagara-on-the-Lake, Ontario was 3.3 ng/L (Mak et al., 2009).

As part of a national survey of emerging contaminants in drinking water (including PFOS) conducted by Health Canada, treated and raw water from groundwater and surface water sources (rivers and lakes) were monitored in winter and summer at 35 locations in 2009 and 30 locations in 2010. In the four sampling periods, only one sample contained PFOS above the method detection limit (MDL) of 0.077 ng/L; the PFOS concentration in that sample was 0.082 ng/L, and was obtained in the winter of 2009 (Health Canada, 2013a). PFOS levels in Etobicoke Creek, ON (a tributary of Lake Ontario) ranged from not detected (limit of quantification: 17 ng/L) to 2210 µg/L following a fire alarm malfunction that released flame retardants containing PFAS (Moody et al., 2002).

5.1.1 Co-occurrence with other PFAS

Limited data show that PFOS is co-detected with other substances in several locations across Canada. In all of these studies, PFOS and PFOA were the predominant PFAS detected. PFOS is co-detected with:

- PFOA, perfluorohexane sulfonate (PFHxS), perfluoroethanesulfonate (PFEtS), perfluorooctanesulfonamide (PFOSA), perfluoroundecanoic acid (PFUDA), perfluorodecanoic acid (PFDA), perfluorononanoic acid (PFNA), perfluoroheptanoic acid (PFHpA), perfluorohexanoate (PFHxA), perfluoro-n-pentanoic acid (PFPeA), and perfluorobutanoate (PFBA) in tap water in Niagara-on-the-Lake, Ontario (Mak et al., 2009);
- PFOA, PFNA and PFUDA in treated and raw water in Québec (Ministère du Développement durable, de l'Environnement, de la Faune et des Parcs, 2012);
- PFOA, PFBA, PFPeA, PFHxA, PFHpA, PFNA, PFBS, and PFHxS in groundwater at former fire-fighting training areas in British Columbia, Alberta, Nova Scotia, and Ontario (Paterson et al., 2008; Environmental Sciences Group, 2015);
- PFOA and PFDA in Nova Scotia and Ontario, and PFUDA, PFDoA, and PFOSA in Nova Scotia (Environmental Sciences Group, 2015).

5.2 Food

Food is generally considered to be the main source of ~~PFOS~~ exposure to PFOS for the majority of the Canadian population, but exposure from food is still well below what is considered unsafe to humans. PFOS was measured in a selection of Canadian food composite

samples (samples from the Canadian Total Diet Study (TDS) conducted in 2004 and additional samples collected between 1992 and 2001) to estimate dietary intake (Tittlemier et al., 2007). PFOS was detected in 7 out of 54 food composites (average detection limit: 0.5 ng/g). The quantified concentrations ranged from 2.0 to 2.7 ng/g wet weight (w.w.; in marine and freshwater fish, ground beef and beef steak). Concentrations lower than the limit of quantitation (LOQ) were reported for microwave popcorn, luncheon meats and cold cuts, and freshwater fish. Values were used to estimate the average dietary daily exposure of Canadians; food was estimated to contribute 250 ng/day of perfluorinated compounds, of which approximately 110 ng was attributed to PFOS (Tittlemier et al., 2007).

Store-bought and restaurant foods commonly consumed by Canadians were collected in Whitehorse (Yukon Territory, Canada) in 1998 and analyzed for ~~PFAAs~~PFAS (Ostertag et al., 2009a). PFOS was detected in only 2 samples (regular and processed cheese) and quantifiable in one sample (processed cheese: 1.14 ng/g w.w.; Ostertag et al., 2009a).

The marine ecosystem of the Eastern Canadian Arctic represents a source of food for the local population. In this region, the PFOS levels (on a w.w. basis) were reported to range from 0.28 to 1.8 ng/g w.w. in zooplankton and invertebrates, from 1.3 to 1.4 ng/g w.w. in fish, and from 2.4 to 122 ng/g in marine mammals (whales and pinnipeds) (Butt et al., 2010). The concentrations of ~~PFAAs~~PFAS in the traditional foods of Inuit in Northern Canada were measured in order to estimate their dietary exposure (Ostertag et al., 2009b). PFOS was detected in 39% of the 68 traditional food samples collected from Chesterfield Inlet, Igloolik, Pond Inlet and Qiqiktarjuak in Nunavut, between 1997 and 1999. PFOS was detected in both aquatic food (0.1–7.6 ng/g in ringed seal, polar bear (meat), beluga, narwhal, bearded seal, walrus, eider and black duck, or lake trout) and terrestrial food (5.0 ng/g in baked caribou liver, 0.1–0.2 ng/g in caribou bone marrow, heart, blood, kidney, stomach, tongue or meat). PFOS concentrations in the other samples (arctic char, seaweed, clams, ptarmigan, artic hare, snow goose, berries) were below the detection limit (<0.1 to <0.5 ng/g) (Ostertag et al., 2009b).

An Australian study quantified ~~PFAAs~~PFAS in food packaging and polytetrafluoroethylene (PEFT) sealant tape. PFOS was not detected in any of these samples, including in microwave popcorn bags (Dolman and Pelzing, 2011).

5.3 Air

In an assessment designed to estimate total daily intake of perfluorinated compounds in Canadians, the inhalation intake of PFOS was considered negligible due to its low volatility (Tittlemier et al., 2007).

The levels of ~~PFAAs~~PFAS in outdoor air were determined in a Canadian study conducted in 2007 in Vancouver (Shoeib et al., 2011). PFOS samples were collected using outdoor passive samplers deployed in residential yards for approximately 3 months. PFOS levels were below the detection limit (< 0.02 pg/m^3) in all samples (n = 6) (Shoeib et al., 2011). In another study, PFOS was detected in 4 out of 8 air samples (particulate-phase) collected over Lake Ontario, at levels varying between 2.5 and 8.1 pg/m^3 (PFOS remained undetected in gaseous-phase samples) (Boulanger et al., 2005). PFOS was also detected in the Canadian Arctic (Resolute Bay, Nunavut) with a mean concentration of 5.9 pg/m^3 in the gas and particulate phase of atmospheric air (2004 sampling) (Fromme et al., 2009; Butt et al., 2010).

In indoor air, the levels of PFOS mainly depend on PFOS concentration in air particulates and are thus related to PFOS levels in indoor dust, as well as the number, type and age of the

potential sources (e.g. carpeting, furniture and paint) (Fraser et al., 2012). To date, data on indoor air concentrations of PFOS are limited to those reported in the aforementioned residential study (Shoeib et al., 2011). The authors collected PFOS in indoor air using passive samplers deployed for approximately 4 weeks in bedrooms of 59 participants. PFOS levels (available for 39 homes) were below the detection limit (< 0.02 pg/m^3) in all samples (Shoeib et al., 2011).

5.4 Consumer products

Owing to the use patterns of PFOS, human exposure to PFOS would likely result from contact with, or the use of, certain consumer products (Health Canada, 2006). Estimates of the contribution of solution-treated carpeting and treated apparel to Canadians' daily intakes of perfluorinated compounds were 120 ng/day and 12 ng/day, respectively (Tittlemier et al., 2007). PFOS has been measured in a variety of consumer products, including paint, printed circuit boards, carpet, leather, non-stick ware, and aqueous firefighting foams (Herzke et al., 2012).

5.5 Soil and household dust

~~Estimated~~The estimated contribution of dust to Canadians' daily intakes of total perfluorinated compounds was 28 ng/day (Tittlemier et al., 2007). The study did not estimate the total daily contribution of soil to perfluorinated compound exposure.

PFOS concentrations in dust in 67 Ottawa, Ontario, homes were between <4.6 and 5,065 ng/g, with a median value of 38 ng/g and a mean value of 444 ng/g ~~(Kubwabo et al., 2005).~~ House age and fraction of floor covering were reported to be significantly correlated with the concentration of ~~PFAAs~~PFAS in dust—older houses and those with smaller fractions of the floor covered with carpet were characterized by lower concentrations of ~~PFAAs~~PFAS (Kubwabo et al., 2005).

In another Canadian study conducted in ~~the City of~~ Vancouver, BC, PFOS was detected in all household dust samples analyzed for this compound (n = 132). The PFOS concentrations ranged from 1.5 to ~~4,661 ng/g (median: 71 ng/g, mean: 280 ng/g) (Shoeib et al., 2011).~~4661 ng/g (median: 71 ng/g, mean: 280 ng/g) (Shoeib et al., 2011). PFOS levels in dust collected from homes in Toronto, Ontario, (n=19) ranged from 42 ng/g to 1300 ng/g (median: 140 ng/g, mean: 290 ng/g) (Goosey and Harrad, 2011). Another Canadian study investigating PFAS levels in household dust in a family home in Edmonton, Alberta, found PFOS in the housedust (1090.0 ng/g) and carpets (42.0–1170.0 ng/g) (Beesoon et al., 2012). The authors attributed the high levels of PFOS to carpet treatment with Scotchgard™ carpet protector.

No study reporting background PFOS levels in soils was found. Some data are available in soils surrounding perfluorochemical industrial facilities (as reviewed by ATSDR, 2009).

5.6 Human biomonitoring data

The Canadian Health Measures Survey (CHMS), Cycle 1 (2007–2009) indicates that PFOS plasma levels in adult males (geometric mean [GM]: 11.13 ng/mL; 95% CI: 10.03–12.36, 95th percentile: 31.31 ng/mL, n=1,376) are higher than in adult females (GM: 7.07 ng/mL; 95% CI: 6.30–7.93, 95th percentile: 20.05 ng/mL, n=1,504) (Health Canada, 2010). This effect persisted in Cycle 2 of the study (2009–2011), which observed a decline in plasma concentrations compared with Cycle 1 (Males—GM: 8.3 ng/mL, 95% CI: 7.4–9.3, 95th percentile: 19 ng/mL, n=511; Females—GM: 5.7 ng/mL, 95% CI: 4.9–6.6, 95th percentile: 19 ng/mL, n=506) (Health Canada, 2013b).

PFOS was detectable in all serum samples (n = 86) collected from 2006–2008 in a study of Inuit children attending childcare centers in Nunavik (Turgeon O'Brien et al., 2012). The geometric mean of PFOS in serum was 3.369 ng/mL with a range of 0.93–31 ng/mL. A separate study of 621 Nunavik Inuit adults reported PFOS serum levels of 0.480 to 470 ng/mL (GM: 18.28 ng/mL, 95% CI: 17.19–19.44 ng/mL) (Dallaire et al., 2009). Other Canadian studies have reported similar levels of PFOS in serum ranging from 3.7 to 63.1 ng/mL (Tittlemier et al., 2004; Kubwabo et al., 2004). Similar results have been shown elsewhere—the overall range of mean PFOS concentrations (in males or females) was from 1.7 to 73.2 ng/mL in serum samples collected in 10 countries (Kannan et al., 2004). PFOS concentrations in human serum/plasma collected worldwide (America, Asia, Australia, and Europe) over a period from 1998–2007 reported mean concentrations ranging from 2.1 to 62 ng/mL (Ingelido et al., 2010). In the U.S., data from the National Health and Nutrition Examination Survey (NHANES) for the period 2007–2008 indicate a median serum PFOS level of 13.6 ng/mL in the general population (≥ 12 years of age), with a downward temporal trend noted for the period 1999–2008 by Kato and colleagues (2011).

5.7 Multi-route exposure through drinking water

The multi-route exposure assessment process applied is not applicable for PFOS, due to the compound's high molecular weight and low volatility (Krishnan and Carrier, 2008); therefore, the relative contributions of exposure to PFOS from both inhalation and dermal routes during showering and bathing were not estimated. Based on the high molecular weight of 500.03 g/mol and the ionic properties of PFOS at pH levels typical in drinking water, volatility and dermal penetration are expected to be low. Moreover, dermal permeability coefficients estimated in *in vitro* studies predict that ~~PFOS~~the skin is impermeable to ~~skin~~PFOS under typical conditions (Fasano et al., 2005; Franko et al., 2012). Consequently, exposure to PFOS via inhalation and dermal routes during showering or bathing is expected to be negligible.

6.0 Analytical methods

To date, the United States Environmental Protection Agency (U.S. EPA) has not approved any analytical methods for the analysis of PFOS in drinking water. There are some methods that can be used to measure PFOS in drinking water at levels well below the ~~proposed~~ MAC. However, they require good quality control procedures to produce accurate results.

6.1 Available methods

U.S. EPA Method 537 ver. 1.1, International Standard Organization (ISO) Method, 25101 (ISO, 2009) and 3M Method ETS-8-154.3 (3M Company, 2008) can all be used for the analysis of PFOS in drinking water (3M Company, 2008; ISO, 2009; U.S. EPA, 2009). All methods use a solid phase extraction (SPE) technique followed by a liquid chromatograph (LC) coupled to electrospray ionization (ESI) tandem mass spectrometry (MS/MS) operated in negative ion mode. For the purpose of trace quantitation of PFOS in drinking water, the chromatographic conditions are selected such that all isomers (linear and branched) are co-eluted together.

In the EPA method, a water sample is fortified with labelled internal standards and passed through a SPE cartridge to extract target analytes in addition to their corresponding internal

standards. The compounds are eluted from the SPE cartridge, concentrated and injected into a LC-MS/MS. The mass spectra and retention times of the analytes are identified by comparison to internal standards. The method detection limit (MDL) of PFOS is 1.4 ng/L (0.0014 µg/L) and the Lowest Concentration Minimum Reporting Level (LCMRL) is 6.5 ng/L (0.0065 µg/L) (U.S. EPA, 2009a). PFOS has been included in the third Unregulated Contaminant Monitoring Rule (UCMR3), which stipulates that using Method 537 ver. 1.1, an MRL of 40 ng/L (0.04 µg/L) for PFOS must be achieved and reported by the utilities during monitoring (U.S. EPA, 2012b).

The results of an inter-laboratory trial (Taniyasu et al., 2013), conducted in 2006, were used to establish whether ISO Method 25101 was reliable for the analysis of PFOS and PFOA in environmental water samples, including drinking water. The intra- and inter laboratory precisions were in the range of 3–4% and 16–27%, respectively for PFOS for all environmental water samples analyzed. The recovery of the internal standards for PFOS ranged from 90 to 96%. These results confirmed that this analytical method was reliable and can be used for the analysis of PFOS in environmental water samples. The method uses SPE, LC-MS/MS and is applicable for the quantification of the linear and branched isomers of PFOS and PFOA. The branched isomers can be separated from the linear isomers by using specific chromatographic column and optimized conditions. ISO Method 25101 was found to be appropriate for determination of PFOS levels in unfiltered samples of drinking water, groundwater and surface water with concentrations in the range of 2 – 10,000 ng/L (0.002 – 10 µg/L) (ISO, 2009).

Method (ETS-8-154.3) was developed and validated by 3M for PFOS analysis in drinking water, groundwater and surface water samples. The analytical steps are similar to EPA Method 537 Ver 1.1 and the method has an LOQ of 25 ng/L (0.025 µg/L) for PFOS (3M Company, 2008).

6.2 Analytical challenges

In spite of the significant improvements in the analytical methods for the determination of PFASs in environmental water samples, challenges, uncertainties and drawbacks still remain. Major challenges associated with the trace quantitation of PFASs included matrix effects and a background contamination in the analytical blanks. In order to generate accurate data, quality control ~~(QC)~~ procedures (matrix spikes, duplicates, spike-recovery experiments, surrogate recovery checks) are critical. In addition, the use of isotope-labelled internal standards is a standard practice and must be used in the analysis of PFASs. As such, PFOS analyses should be conducted by an accredited laboratory or by a laboratory with a stringent quality assurance/quality control (QA/QC) program in place to ensure data quality.

6.2.1 Matrix effect

Although LC-MS/MS is a highly selective and sensitive technique, it is susceptible to matrix effects which is one of the major uncertainties in the trace quantitation of PFOS in environmental water samples (Martin et al., 2004; Yamashita et al., 2004; Taniyasu et al., 2005; van Leeuwen et al., 2006; Arsenault et al., 2008). Matrix effects result from the co-extracted components from the sample, which affect the signal intensity of the target analyte and either suppress or enhance the spectral signal. The extent of the matrix interference varies, depending on the nature of the samples. Although the matrix interferences are negligible for drinking water and groundwater (ISO, 2009), the PFOS quantification requires efficient extraction and clean-up procedures. The aim of these procedures is to separate the compounds in the sample by their

chemical and physical properties, to concentrate the target analyte and to purify the extract prior to the instrumental determination. The most frequently used technique for the extraction of PFASs from drinking water samples includes SPE cartridges with different packing material such as reverse phase (C18) cartridge (Loewen et al., 2005; Wolf and Reagen, 2011; Zainuddin et al., 2012), mixed hydrophobic/polar (Oasis HLB) cartridges (Yamashita et al., 2004; Taniyasu et al., 2005; Villaverde-de-Saa et al., 2015) and a weak anion exchange (WAX) cartridges (Taniyasy et al., 2005; 2013). Several studies conducted a liquid-liquid extraction (LLE) technique to extract and concentrate PFASs in different environmental aqueous matrices prior to LC-MS/MS (Gonzales-Barreiro et al., 2006; Szostek et al., 2006; Backe et al., 2013). A laboratory study (Gonzales-Barreiro et al., 2006) used an LLE to extract 7 PFASs (C6-C12) from tap water. The recovery of the PFASs with a carbon chain greater than C7 was in the range 80-93%. The authors indicated that the method was less efficient in extracting short-chained PFASs when compared to the SPE technique (Gonzales-Barreiro et al., 2006).

The clean-up procedures involved a washing step after the sample enrichment on the SPE cartridge and a filtration to remove solids from the final extract (Yamashita et al., 2004; Larsen and Kaiser, 2007; van Leeuwen and Boer, 2007). Care should be taken to avoid contamination of the extract or losses of PFASs during the clean-up procedures. Prior to a SPE, a sample pre-treatment (filtration) may be required to facilitate extraction or to remove matrix constituent that will interfere with analyses (van Leeuwen and Boer, 2007; Ding et al., 2012).

The most suitable approach to assist in the quantification of PFASs is to use of isotopically-labelled internal standards (isotope dilution). It is important that the appropriate isotope-labelled internal standards are used for the quantitation of the corresponding native compound. Isotope-labelled internal standards will have the same retention time as the target analytes (excluding isomeric separation) and the monitoring of their signals will determine whether the analytes signal are suppressed or enhanced. The application of surrogates or isotopically-labelled internal standards early in the sampling or the sample preparation steps will compensate for the inefficiency/losses in the extraction and other sample preparation steps (Martin et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007). Wolf and Reagen (2011) reported that an addition of isotope-labelled internal standards prior to sample collection simplified the sample preparation procedures. The method demonstrated an accuracy of 109% and a precision of 10% for PFOS in laboratory Milli-Q water samples (Wolf and Reagen, 2012).

If isotope-labelled internal standards are not available, a standard addition quantitation, which involves spiking known quantities of a standard into the sample, is an alternative to use when matrix effects are unavoidable (Weremiuk et al., 2006; Furdui et al., 2007; van Leeuwen et al., 2009).

The use of MS/MS for analysis of PFOS enables the detection of product (daughter) ions. Although the transition m/z 80 (product ion SO_3^-) is the most abundant product ion used for determination of PFOS, m/z 99 (product ion FSO_3^-) is also used for PFOS identification (ISO, 2009; U.S. EPA, 2009a).

6.2.2 Background contamination in the analytical blanks

A known source of background contamination is the presence of fluoropolymers, such as polytetrafluoroethylene (PTFE) and perfluoroalkoxy compounds in various laboratory consumables. Ammonium perfluorooctanoate and ammonium perfluorononanoate are used as fluoropolymer processing aids and are common components in the laboratory products. These

fluoropolymers may lead to quantifiable background levels in the analytical blanks especially when quantifying trace levels in water samples. Contacts with such laboratory materials and products during analysis of PFOS should be avoided (Martin et al., 2004; Yamashita et al., 2004; ISO, 2009).

Yamashita et al. (2004) studied the sources of background contamination at various analytical steps, including sample collection, extraction and sample clean up prior to the instrumental analysis. Polypropylene bottles used for sample collection and storage, in addition to different types of SPE cartridges and purified reagent water, were found to be sources of PFASs contamination in the analytical blanks. Taniyasu et al. (2005) and Berger et al. (2011) found that the polypropylene containers are unsuitable for collection and storage of water samples intended for analysis of long-chain perfluorocarboxylic acids (PFCAs) such as perfluoroundecanoic and perfluorododecanoic acids, because of the adsorption of the compounds on the containers' surface. The authors recommended the use of high density polyethylene or glass containers. However, ISO method 25101 and EPA Method 537 recommended against the use of glassware for sampling due to the potential adsorption of PFOS on the walls (ISO, 2009; U.S. EPA, 2009a). The storage and sample preservation steps prior to the instrumental analysis should prevent changes in composition of the sample matrix and the concentration of the analyte (van Leeuwen et al., 2007).

SPE cartridges can also be a source of contamination and the U.S. EPA (2009a) recommends that SPE devices be tested prior to using them for analysis to ensure that there is no contamination of the sample. Several studies ~~performed on~~were conducted with a direct injection (DI) of the water samples into ~~LC-MS/MS~~liquid chromatograph. The method avoids the use of additional materials and sample preparation processes, which may limit possible contamination and target compound losses (Schultz et al., 2006; Furdui et al., 2008; Dickenson and Higgins, 2013).

HPLC tubing, nylon filters, auto-sampler vial caps made of Teflon or Viton fluoropolymers, valve seals and degassers were identified as the potential sources of contamination of the instrumental blanks with PFOA (Yamashita et al., 2004; Taniyasu et al., 2005; Schultz et al., 2006; Larsen and Kaiser, 2007) and to lesser ~~extend~~extent with PFOS (Yamashita et al., 2004). The instrumental background contamination can be reduced by replacing or bypassing the fluoropolymers parts such as a degasser (Arbuckle et.al, 2013) with offline degassing of mobile phases; replacing fluoropolymer components with stainless steel, polyetheretherketone (PEEK) tubing, installing an upstream guard column, extensively flushing of the LC system or reducing the LC-column equilibration time (Martin et al., 2004; Yamashita et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007; Nakayama et al., 2007; Shoemaker et al., 2009; Arbuckle et.al, 2013).

6.3 Analytical performance

The preferred analytical method for the determination of PFOS in environmental water samples, including drinking water, uses SPE followed by LC-MS/MS with electrospray ionization operating in a negative ion mode (Martin et al., 2004; Yamashita et al., 2004; Villagrassa et al., 2006; Larsen et al., 2007; van Leeuwen and Boer, 2007; Furdui, et al., 2008; Hansen et al., 2010; Sun et al., 2011; Wolf and Reagen, 2011; Post et al., 2013; Villaverde-de-Saa, 2015). Recent analytical improvements have been realized through the availability and use of high quality standards and stable isotope internal standards to compensate for the matrix effect and for

inefficiencies in the extraction procedure and/or other sample preparation steps (Yamashita et al., 2004; Lowen et al., 2005; Taniyasu et al., 2005; Nakayama et al., 2007; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). There are currently, a number of high quality analytical-grade standards that are commercially available and the list of these standards continues to expand (van Leeuwen et al., 2009, Berger et al., 2011).

In the early 2000s, quantification of PFASs was biased by the lack of proper analytical standards, isotopically labelled surrogates and reference material and there was a significant analytical variability between laboratories. Two inter-laboratory studies were conducted to analyze PFASs, including PFOS and PFOA, in environmental water samples and found a varying degree of accuracy. In the first study (van Leeuwen et al., 2006), conducted in 2004/2005, factors resulting in poor agreement between participating laboratories, were determined to be low PFOA/PFOS concentrations (below 20 ng/L) in water samples; the use of low purity standards, high matrix effect, and a high background contamination in the analytical blanks. The relative standard deviation (RSD) reported in the study was 95% for PFOS (van Leeuwen et al., 2006). In the second inter-laboratory study, the performance of the participating laboratories improved due to the minimization of the matrix effects; the use of higher quality (purity and isomeric composition) shared standards (provided by a single source), and the use of mass-labelled internal standards. The reported RSD value in this study was 29% for PFOS.

Methods using SPE and DI procedures followed by LC/ESI/MS/MS have been reported in the literature for the determination of ~~PFAAs~~PFAS, including PFOS in water samples (Yamashita et al., 2004; 2005; Taniyasu et al., 2005; 2013; Furdui et al., 2008; Hansen et al., 2010; Berryman et al., 2012; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). Details regarding the preconditioning procedures of the SPE cartridges, eluent, clean-up procedures, MS quantification parameters and QC procedures specific to each method are available in the cited reference.

A study reported a limit of detection (LOD) [signal-to-noise (S/N) = 3:1] of 0.2 ng/L and a limit of quantitation (LOQ) (S/N= 10:1) of 0.66 ng/L using an SPE followed by LC-MS/MS for analyzing PFOS in surface water. A water sample of 500 mL was loaded on the Oasis WAX cartridge, a target fraction was eluted, dried under nitrogen gas and before the analysis the samples were filtered. The recovery value of 109±4% for PFOS was calculated by isotopically-labelled internal standards calibration (Sun et al., 2011; Li et al., 2011).

Villaverde-de-Saa et al. (2015), using an SPE followed by LC–MS/MS, developed a method for the determination of seven PFCAs (C6–C12) and PFOS in environmental waters samples. A water sample of 1.0 liter, fortified with internal standards, was loaded on the Oasis HLB cartridge. The method reported a LOD of 0.04 ng/L and a LOQ of 0.12 ng/L for PFOS, (LOD and LOQ were calculated as 3 and 10 times the standard deviation, respectively). The recovery value of 99±7% for PFOS was calculated by isotopically-labelled internal standards calibration.

Furdui et al. (2008) investigated the concentration of PFASs in water samples from the Great Lakes. The analysis of nine target contaminants including PFOS, were performed by directly injecting the samples into LC-MS/MS. Quantification was performed using internal standard correction and standard addition. An isotope dilution provides the most accurate and precise results. The method had a LOQ (signal-to-noise [S/N] =10:1) of 0.5 ng/L for PFOS (Furdui et al., 2008).

The province of Québec reported results of the monitoring PFASs at 16 sites, including seven drinking water treatment plants. A total of 226 water samples (84 raw, 84 treated and 58

surface water samples) were analyzed. Both raw and treated water were sampled monthly for a period of one year. Sampling of the surface water was limited through the year. The samples were analyzed using C18 cartridges and LC-MS/MS in positive ionization mode. Reported DLs ranged from 0.5 to1.0 ng/L and 0.3 to 0.6 ng/L for untreated (250 mL analysed sample) and finished water (500 mL sample), respectively. In order to compensate and correct the instrumental variations and the matrix effect, isotopically-labelled internal standards were added prior to the LC (Berryman et al., 2012). Although the photoionization technique is less sensitive than the electrospray ionization, it is less prone to matrix effect (Martin et al., 2004).

Berger et al. (2004) compared different mass spectrometric techniques (time-of-flight [TOF] high resolution MS, triple-quadrupole tandem MS, and IT-MS) coupled with a high performance liquid chromatography (HPLC) for analysis of PFASs including PFOA. The instrument parameters such as vaporizer temperature, collision energy, and cone voltage fragmentation were optimized for each mass spectrometry technique. Negative electrospray ionization was selected as the ionization mode for all instruments. The study indicated that both TOF high resolution MS and triple-quadrupole tandem MS methods had higher sensitivities than IT-MS for all tested PFASs. Although IT-MS had a higher DL and smaller linear range, it provided the best results for tentative structure elucidation and qualitative analysis of branched PFASs isomers (Berger et al., 2004; Jahnke and Berger, 2009).

The analysis of PFASs in environmental water samples has been dominated by the use of LC coupled to MS or MS/MS, although other techniques such as ^{19}F nuclear magnetic resonance (NMR) and gas chromatography (GC)–MS have also been explored. ^{19}F NMR analysis is a less sensitive and non-specific method due to the determination of the presence of CF_2 and CF_3 moiety in the sample. Gas chromatography (GC) can be used to determine neutral and volatile PFASs and fluorotelomer alcohols. ~~PFAAs~~PFAS are derivatized in order to be amenable for GC analysis. However, the use of the derivatization techniques is limited for PFOS analysis due to the instability of the PFOS derivatives (Moody et al., 2001; Villagrassa et al., 2006).

7.0 Treatment technology

The available data and calculated pKa (–3.27) values indicate that PFOS is a strong acid which predominantly dissociates to a negatively charged form (anion) at environmentally relevant pH values (Brooke et al., 2004). Given the hydrophobic and oleophobic nature of the fluorinated alkyl chain and the hydrophilic nature of the sulfonic group, hydrophobic and electrostatic effects likely influence PFOS adsorption (Higgins and Luthy, 2006; Xiao et al., 2011). Due to the shorter carbon-fluorine bond length and high electronegativity of fluorine atoms in the PFOS structure, Senevirathna et al. (2010) suggested that higher adsorption of PFOS could occur on anion exchange resins. The nature of the chemical structure of PFOS (i.e., strong carbon–fluorine [C–F] bonds) makes it resistant to hydrolysis and biodegradation as well as to photolysis and several chemical treatment processes (3M, 1999; Lange et al., 2006; ATSDR, 2009).

7.1 Municipal scale

Dickenson and Higgins (2013) evaluated the ability of wide range of full-scale treatment techniques to remove PFASs, including PFOS and PFOA, from raw water and potable water reuse plants. The treatment trains varied, but generally included coagulation followed by physical separation, aeration, chemical oxidation, UV irradiation, and disinfection. Regardless of the

treatment train applied, there was little or no decrease in PFOS and PFOA concentrations and the authors concluded that these treatment methods are not effective in removing PFASs.

GAC adsorption and membrane filtration techniques appear promising for removal of PFOS in drinking water, achieving treated water concentrations below 0.6 µg/L (Tang et al., 2006; Lampert et al., 2007; Deng et al., 2010; Takagi et al., 2011; Appleman et al., 2014). In order to achieve a PFOS concentration below 0.6 µg/L, the GAC system must be specifically designed and appropriately operated for PFOS removal in drinking water. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance by directly competing for adsorption sites and preloading (fouling) the GAC beds. Therefore, the effectiveness of GAC to remove PFOS in drinking water appears to be dependent on the regeneration frequency and/or replacement of the carbon (Kolstad 2010; Takagi et al., 2011; Appleman et al., 2014). Membrane filtration such as reverse osmosis (RO) and bench-scale nanofiltration (NF) studies demonstrated effective removal of all tested short-and long-chain PFASs including PFOS in drinking water. Although the RO process is effective, it is likely to be an expensive treatment method (Steinle-Darling et al., 2008); Quinones and Snyder, 2009; Appleman et al., 2013; Flores et al., 2013). Anion exchange resins may also be effective in removal of PFOS. However full-scale evaluation of this technology has not been conducted specifically for PFOS removal in drinking water.

The selection and effectiveness of each treatment strategy is driven by several factors, including source water chemistry, concentration of PFOS and/or other PFASs and pre-existing treatment processes. If long-chain PFASs are detected in the drinking water sources, the utility may consider the implementation of treatments such as GAC. However, utilities that have shorter chain PFASs in their raw water source may choose to implement RO. The treatment technologies need to be designed specifically for PFASs removal and operated appropriately in order to achieve contaminants removal objectives in drinking water (Dickenson and Higgins, 2013).

The ability of various drinking water treatment processes and treatment trains to remove PFOS have been summarized by Dickenson and Higgins (2013) and Rahman et al. (2014). Appendix A summarizes the percentage removal of PFOS in full-scale plants where both raw and finished water concentrations were reported (Rahman et al., 2014). Data show that the treatment technologies employed by these plants (with the exception of GAC, RO and NF) did not appreciably remove PFOS. They also show that in some cases concentrations in the finished water were higher than in the raw water, likely due to the breakdown of precursor compounds to form PFOS during the treatment (Takagi et al., 2008; Shivakoti et al., 2010). Takagi et al. (2011) also postulated that these higher finished water levels may result from desorption from GAC filters used for long periods of time without reactivation.

7.1.1 Conventional treatment

Conventional drinking water treatment processes generally incorporate coagulation, flocculation, sedimentation, and filtration, followed by primary and secondary disinfection. Common coagulants used in drinking water include aluminum sulfate (alum), ferric hydroxide, ferric chloride, polyaluminum chloride and coagulant aid polymers. Filtration media can consist of sand (single media); sand and anthracite (dual media); or sand, anthracite, and garnet (multi or mixed garnet media). GAC may also be used as the filter media.

Conventional full-scale drinking water treatment techniques have been found ineffective in removing PFOS from source waters. Samples collected from several full scale conventional

treatment plants indicated essentially no difference in the PFOS concentrations between plants influent and concentrations in water following the coagulation, sedimentation, and sand filtration steps (Loos et al., 2007; Shivakoti et al., 2009; Takagi et al., 2011; Thompson et al., 2011). Similarly, Eschauzier et al. (2012) reported that slow- and rapid- sand filtrations were ineffective for PFOA and PFOS removal. The inability of conventional water treatment to remove PFOS and PFOA may be due to their extremely low concentrations in water and their hydrophilicity which renders them unamenable to removal by conventional treatment processes (Rahman et al., 2014). These findings are in agreement with recently conducted bench-scale studies of the removal of PFOS from water (Deng et al., 2011; Xiao et al., 2013).

Jar tests (Xiao et al., 2013) achieved an approximately 3% removal of an influent concentration of 0.1 µg/L (100 ng/L) of PFOS, with an alum dose of 30 mg/L and pH of 7.9. A removal efficiency below 10% was reported under a range of alum doses ranging from 10 to 60 mg/L and pH levels ranging from 6.5 to 8.0. Removal rates of approximately 25% were observed using enhanced coagulation with alum doses greater than 60 mg/L and pH 4.5 – 6.5. In general, the removal efficiencies were below 35% under the examined coagulation conditions (alum doses 3-110 mg/L and pH 4.5-8.0). Ferric chloride coagulation exhibited similar results. The authors indicated that removal rates were higher for PFOS than PFOA in both conventional and enhanced coagulation conditions, possibly due to PFOS having a higher molecular size and a potential for being more hydrophobic.

7.1.2 Adsorption

Adsorbents typically used in drinking water treatment include activated carbon, resins, activated alumina, zeolites, clays, metal oxides, hydroxides, and carbonates (AWWA, 2011; U.S. EPA, 2012a). GAC is used in a fixed bed, while PAC is generally added directly to the raw water as a powder or mixed with water to form a slurry.

Several laboratory studies of PFOS and PFOA adsorption kinetics indicate that PAC reached sorption equilibrium in 4 hours while GAC reached equilibrium in 168 hours, (Yu et al., 2009) and that PFASs removal percentages were generally higher for PAC than for GAC (60–90% versus 20–40%, respectively) for 10 minutes adsorption time (Hansen et al., 2010). These results may be due to PAC's smaller particle size, and higher specific surface area per volume of carbon when compared to GAC (Yu et al., 2009; Hansen et al., 2010). If PFASs are present in the raw water year round, Rahman et al. (2014) suggested that GAC adsorption may be the preferred method for PFASs removal, while PAC may be more appropriate for short-term spill response remediation.

7.1.2.1 Granular activated carbon

Full-scale evaluations of the effectiveness of GAC adsorption for the removal of PFOS in drinking water sources have been mixed. Several full-scale studies, specifically designed and operated for PFASs removal in drinking water, observed successful removal of PFOS by GAC with a long empty bed contact time (EBCT) and an appropriate regeneration regime (MDH, 2008a; Takagi et al., 2011; Appleman et al., 2014). Other water treatment plants found similar PFOS levels in both source and finished water, suggesting that GAC treatment only partially removes this contaminant, if at all. These treatment plants were not specifically designed for PFASs removal in drinking water. As the GAC had been in place for a variable period of time, it was likely that the preloading by NOM had deteriorated the GAC performance leading to similar

PFOS levels in the influent and treated water (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012, Flores et al., 2013).

A full-scale GAC treatment system with a flow rate of 1.5 m^3/minute was specifically designed for PFASs removal in groundwater. The system used two GAC contactors in a lead/lag configuration with an EBCT of 13 minutes each. The lead vessel operated for approximately 18 months and treated 59,483 bed volumes (BVs) before the concentration of PFOS exceeded 0.05 µg/L. The GAC unit was capable of reducing an influent PFOS concentration in the range of 0.53–1.38 µg/L to below 0.05 µg/L, in the treated water from the lag vessel, for 72,775 BVs (approximately 22 months). At that point, the lead vessel water reached 0.11 µg/L PFOS, its carbon was replaced with virgin media and the vessel was put in the lag position (Appleman et al., 2014).

A monitoring survey conducted in UK indicated that the contaminated groundwater with an influent concentration ranging between 1.7 and 3.8 µg/L PFOS was reduced to below 0.2 µg/L using GAC treatment. The five GAC contactors were operated in a parallel-staggered mode with an EBCT of 110 minutes and a regeneration frequency of 12 months. A PFOS concentration of 0.3 µg/L (breakthrough) was found to occur between 8,000 and 9,000 BVs. However, the breakthrough concentration was reported for the period of time prior to the increase of the regeneration frequency of 24 months to 12 months (Rumsby et al., 2009).

The behaviour and fate of PFASs, including PFOS and PFOA, was assessed by analyzing influent and treated water from several drinking water treatment plants that included GAC in the treatment train. These plants were not specifically designed for PFASs removal in drinking water. The hydraulic retention time of individual treatment steps was considered when the efficiency of each these steps was assessed (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013). The studies found that only the GAC step was capable of removing PFASs in drinking water. Removal of between 63% and 97% of PFOS was reported when a GAC process was included in the treatment train (Shivakoti et al., 2010; Flores et al., 2013; Appleman et al., 2014). The paragraphs below provide more details on some of these studies.

A full-scale 5 million gallons per day (MGD) treatment plant, designed to remove trace levels (ng/L) of organic contaminants in surface water, consisted of river bank filtration, softening, UV/H_2O_2, biologically-active GAC filtration and six GAC contactors. The GAC system operated in parallel mode with an EBCT of 10.5 minutes. Water samples analyzed before and after the GAC system demonstrated reduction of an influent PFOS concentration of 2.3 ng/L to 0.25 ng/L (89% removal) (Appleman et al., 2014).

Eschauzier et al. (2012) monitored the concentrations of PFOS and PFOA in a drinking water treatment train consisting of coagulation, rapid sand filtration, dune passage (water slowly passed through sand dunes), softening, ozonation and GAC treatment. Only the GAC step was effective for PFASs removal. The system used two-stage GAC contactors in a lead/lag configuration. Of the 40 filters, 20 were used in parallel mode as a first stage and the other 20 were used as a second stage filter. Each GAC filter operated at a flow rate of 348 m^3/hour and an EBCT of 20 minutes, resulting in a total EBCT of 40 minutes. Each virgin GAC filter was installed as a second stage filter and was switched to the first stage after 15 months of operation. After another 15 months, the carbon was reactivated and put back in service as a second stage filter. The GAC system effectively removed perfluorononanoic acid (PFNA), PFOS and perfluorohexane sulfonic acid (PFHxS). The GAC step was capable of reducing an average influent PFOS concentration of 11 ng/L in the feed water to the first GAC stage to below the

LOQ of 0.23 ng/L (approximately 98 % removal) after the second stage GAC filter (Eschauzier et al. 2012). Flores et al. (2013) reported 64% removal of PFOS in a water treatment plant, which had 24 GAC contactors installed and that were regenerated approximately once a year.

Takagi et al. (2008, 2011) investigated the behaviour, fate and removal efficiency of PFOS and PFOA in drinking water treatment processes from several drinking water treatment plants that included GAC in the treatment train. The removal efficiency of PFOS and PFOA were less than 50% in many of the water treatment plants. A negative removal rate in certain plants suggested that desorption from GAC filters, used for long periods of time without reactivation, may be responsible for these observations. The negative removal rates could also result from the formation of PFOS and PFOA from the degradation of the precursor compounds found in the raw water (Takagi et al., 2011). However, PFOS was effectively removed for 8 months in a 1.5 MLD water treatment plant after the replacement of its activated carbon in the GAC unit. The treatment train consisted of a coagulation/sedimentation, rapid sand filtration and two GAC contactors (coal and coconut-shell carbon) in parallel mode. Both GAC contactors were capable of reducing the PFOS concentrations in the range of 2.3–3.9 ng/L to below the LOQ of 0.5 ng/L during the 8 month study period.

Rapid small-scale column tests (RSSCTs) are a common bench scale test used to evaluate GAC. Using RSSCTs, Appleman et al. (2013) compared the effectiveness of three different types of GAC for removal of several PFASs including PFOS and PFOA. The column experiments were conducted with an EBCT of 0.38 minutes using de-ionized water and surface water [dissolved organic carbon (DOC) of 1.7 mg/L], both spiked with 1.0 µg/L of each PFASs. The tests were run for a total of 125,000 BVs (approximately 33 days). Carbon performance varied based on the type of carbon and water chemistry, with GAC being more effective at removing PFASs in deionized water. Of the three carbons, F300 achieved the best results. In the experiments conducted with deionized water, a PFOS concentration in the filtered water was less than 0.02 µg/L (less than 2% of influent C_0), after 98,000 BVs. However, the filtered water concentration reached 0.2 µg/L (20% of C_0) after 11,000 BVs (3 days) in spiked surface water. Although RSSCTs are not suitable for evaluating the effect of preloading/fouling of GAC columns by DOC, the observed rapid breakthrough in the spiked natural water demonstrated that the presence of DOC affects the GAC performance in the removal of PFASs by directly competing for adsorption sites (Appleman et al., 2013).

The efficiency of PFOS removal by GAC adsorption is impacted by NOM in source water which competes for the carbon adsorption site and will adsorb irreversible, causing the carbon's capacity for the target compound to be reduced. When the adsorption capacity of the GAC is exhausted, it must be removed from the contactor and replaced with fresh or reactivated carbon. GAC is used in a fixed bed reactor, as a substitute for existing filtration media (i.e., sand) in a conventional filter, as a layer in a multi-media rapid filter, or in a separate contactor. The reactor can be located at the beginning of the treatment train in a dual-media or sand-replacement mode, or later in the treatment train as a second-stage contactor. The rate of GAC exhaustion will vary substantially for the same water source depending in which configuration GAC will be employed. A dual media (GAC and sand) is used when turbidity removal and the adsorption/removal of the contaminants are combined in a single unit process. The dual media filter (typically located after sedimentation) is likely to be exposed to higher DOC concentrations, and this filter will be exhausted faster. A GAC contactor located at the end of a treatment train will likely experience slower preloading/fouling, since the treatment steps prior to a GAC contactor will reduce the

DOC influent concentrations. This treatment strategy will assist in completely utilizing the entire GAC capacity and reducing operating cost (i.e., carbon replacement cost) (Crittenden et al., 2012).

Close monitoring of PFOS breakthrough (treatment objective) is necessary for efficient operation of GAC unit. Studies indicated that PFOS was successfully removed from drinking water when the frequent regeneration or replacement of the GAC was performed (e.g., Wilhelm et al., 2008; Rumsby et al., 2009; Takagi et al., 2011). Takagi et al. (2011) observed that GAC regenerated over periods greater than one year were not effective in removing PFOS and PFOA and suggested regenerating the carbon 2 to 3 times per year. A full-scale 2,500 gpm GAC treatment plant, using two GAC contactors in series observed breakthrough of PFOA and PFOS after 286 days and 550 days, respectively. With the replacement of the GAC at the earliest time of PFOA breakthrough, the system was able to treat 1.9 million gallons of water for 23 months (MDH, 2008a; Kolstad, 2010).

Eschauzier et al. (2012) observed that the removal efficiencies of PFASs by GAC increased with increasing carbon chain length and that sulfonate compounds were removed for a longer period of time than the carboxylate compounds. Shorter-chained PFASs (especially perfluorobutanoic acid ([PFBA] and perfluorobutane sulfonate [PFBS]) were not removed by GAC. These findings were in agreement with previous batch experiments showing that the sorption of PFASs on activated carbon decreased with decreasing the carbon chain-length and perfluorosulfonates adsorbed stronger than perfluorocarboxylates with the same carbon chain length (Ochoa-Herrera and Sierra-Alvarez, 2008; Hansen et al., 2010; Dudley et al., 2012; Appleman et al., 2014). Branched isomers of PFOS and PFOA were found to be less sorbable to GAC than linear isomers. Desorption of shorter chain PFASs due to competition for sorption sites with longer chain PFASs or NOM (i.e., DOC) may result in higher levels of shorter chain PFASs in the treated water (Eschauzier et al. (2012).

7.1.2.2 Powdered activated carbon

No full-scale data were reported on the efficacy of PFOS removal by PAC. Most published studies on the efficacy of PAC were conducted at the bench-scale. PFOS concentrations in some of these bench-scale studies were order of magnitude higher than the concentration observed in natural waters. However, trends observed for PAC in terms of preferential adsorption (chain-length dependence) and competition with NOM were similar to that documented for GAC (Hansen et al., 2010; Dudley et al., 2012).

Dudley et al. (2012) evaluated the adsorbability of ten PFASs with different carbon chain lengths (from C4 - C10) on commercially available PACs (coconut shell, lignite, wood, and bituminous coal) and superfine PACs (S-PACs) obtained by wet-milling the commercially obtained PACs. Sulfonate substances were found to be more adsorbable than carboxylate substances and sorption kinetics were faster with S-PACs when compared to PACs. The removal efficiencies of ~~PFAAs~~PFAS increased with increasing carbon chain length (i.e., negligible removal of C4 compounds but greater than 90% removal for C7-C10 compounds). The presence of NOM was found to decrease the effectiveness of PFAS removal by PAC in batch studies. The authors also concluded that significant removal of smaller chain PFASs may not be achievable at practical PAC dosages (Dudley et al., 2012).

Yu et al. (2009) investigated the sorption kinetics and isotherms of PFOS and PFOA on PAC, GAC and an anion-exchange resin. The anion exchange resin had the highest sorption

capacity for PFOA while PAC was found to be the adsorbent of choice for PFOS. Another laboratory experiment reported 97% and 24% removal of PFOS by PAC and GAC, respectively, based on an initial concentration of 1.4 µg/L in groundwater. The study also observed that PFOS sorption on PAC was faster than on GAC, suggesting that the sorption kinetics were influenced by the size of the activated carbon (Hansen et al., 2010).

7.1.3 Membrane filtration

There are four main types of membrane filtration processes in drinking water treatment applications: microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO). Low pressure membranes such as MF and UF are not capable of rejecting PFASs since their pores sizes are larger than the effective diameter of the PFASs molecules (~1 nm) (Tsai et al., 2010; Rahman et al., 2014). Bench-scale studies indicated that the membrane molecular weight cut-off (MWCO) of NF/RO is probably the most important factor for removal of PFASs for these technologies. In general, NF membranes have a lower rejection (95%) than RO (greater than 99%), which is consistent with the fact that NF membranes have larger pores (Tang et al., 2006, 2007; Steinle-Darling and Reinhard, 2008; Lipp et al., 2010; Appleman et al., 2013; Rahman et al., 2014).

The available scientific information on the removal of PFOS and PFOA from drinking water supplies by membrane filtration is limited to one full-scale RO drinking water utility (Flores et al., 2013) and several indirect potable water reuse plants (Quinones and Snyder, 2009; Appleman et al., 2014). Due to the physical location of these indirect potable water reuse plants, they were considered to be major potential contributors to the drinking water facilities' source water in the conducted studies (Quinones and Snyder, 2009).

Although a full-scale conventional treatment was reported as being ineffective for PFOS removal in surface water; a greater than 99% removal of PFOS was achieved when RO followed the conventional treatment train (Flores et al., 2013). Samples were collected, taking into consideration the hydraulic retention time of each step, to assess the efficiency of each step of treatment train. The RO system's feed water was filtered by the conventional treatment process and blended with untreated groundwater. Feed water PFOS concentration ranged from 61 to 86 ng/L and the RO system was capable of reducing these concentrations to an average concentration of 0.7 ng/L (Flores et al., 2013).

Two indirect potable water reuse plants with RO units in their treatment trains were capable of reducing a PFOS concentration to below 0.25 ng/L in the RO treated water. Both RO systems had a flux rate of 12 gallons per square foot per day (gfd) (20 $L/m^2/h$) and water recovery in the range 80-85%. The feed PFOS concentrations to the RO units ranged from 3 to 18 ng/L (Dickenson and Higgins, 2013; Appleman et al., 2014). A survey of several drinking water utilities and indirect potable water reuse plants showed that the PFOS concentrations in the treated water were comparable to the levels found in the raw water samples in almost every case. However, removal was only observed in one planned potable reuse facility when an integrated membrane treatment consisting of MF and RO was employed. The membrane system was capable of rejecting a feed PFOS concentration of 41 ng/L to below 1 ng/L (Quinones and Snyder, 2009).

Bench-scale experiments evaluated the rejection behaviour of unfouled and fouled NF membranes on the removal of PFASs, including PFOS (Appleman et al., 2013). The study found that a polyamide thin film composite flat-sheet NF membrane was capable of rejecting all of tested compounds in the range of 93 to 99%. Greater than 99% rejection of an average influent

PFOS concentration of 866 ng/L (LOQ of 10 ng/L) was observed in all experiments using virgin membranes and spiked de-ionized water; virgin membranes and spiked groundwater; and fouled membranes and spiked groundwater. The fouling layer on the NF membrane showed no negative effect on PFOS rejection (Appleman et al., 2013). Another bench-scale study was conducted on one RO (MWCO of 100 Da) and three NF (MWCO range of 200 – 360 Da) membranes for the removal of PFOS in water. The RO membrane achieved a 99.9% rejection of PFOS from the feed water concentration of 2100 ng/L with a permeate PFOS concentration in the range of 2–3 ng/L. The RO system was operated with a flux rate of 30–40 L/m^2/h and a feed pressure of 8 bars (116 psi). All tested NF membranes achieved a rejection in the range of 99.8–100% of an average feed PFOS concentration of 3000 ng/L, with a flux rate of up to 70 L/m^2/h and an operating pressure in the range of 4–7 bars (58-101 psi) (Lipp et al., 2010).

Although there is limited information on full-scale RO and only bench-scale NF treatment information, both technologies are considered effective for PFOS removal from drinking water (Appleman et al., 2013; 2014). The results of the NF studies are promising since NF is a less energy intensive process than RO. Testing of the selected NF membrane for PFOS removal at both pilot- and full-scale is an important step for utilities when considering this treatment process. Since the size exclusion is an important mechanism for PFASs rejection by NF membranes, consideration should be taken to select membranes with MWCO smaller than the size of PFOS.

Considerations when using RO treatment include disposal of the reject water and the potential for increased corrosivity of the treated water. RO rejects a significant portion of the influent water as contaminant-rich brine, and the concentrate discharge must be disposed of appropriately. The removal of contaminants can cause mineral imbalances that could increase the corrosive nature of the treated water. In most cases, post-treatment corrosion control measures need to be taken.

7.1.4 Ion exchange

~~PFAAs~~PFAS are in an anionic form at ambient water pH values and therefore would be expected to be amenable to removal by anion exchange resins (Senevirathna, et al., 2010). Two primary mechanisms, hydrophobic and electrostatic interactions, were proposed for the removal of ~~PFAAs~~PFAS by ion exchange resins (Carter et al., 2010; Deng et al., 2010; Xiao et al., 2012).

Appleman et al. (2014) reported results for the only one known full scale application of ion exchange for the removal of PFASs. However, this system was not specifically designed for PFASs removal in drinking water. A 350 gpm full-scale ion exchange plant reduced the concentrations of PFOS in the range of 2.6–4.5 ng/L to below the detection level of 0.25 ng/L in groundwater. A strong base anion resin impregnated with iron oxide used for arsenic removal was assessed for PFOS removal after the resin had been in use for 5 and 9 months. The highly porous strong base anion exchange resin, achieved greater than 75% removal of PFOA, partial removal of perfluoroheptanoic acid (PFHpA) (46%), and high removal of PFOS (>92%) and perfluorohexanesulfonate (PFHxS) (97%). Shorter carbon chain compounds such as PFBA, and perfluorohexanoic acid (PFHxA) exhibited little to no removal. Results also indicated that perfluorosulfonic acids were preferably removed by anion exchange resin over the perfluorocarboxylic acids (Appleman et al., 2014).

Exchange resins exhibit a degree of selectivity for various ions, depending on the concentration of ions in solution and the type of resin selected. Laboratory-scale evaluations of different types of resins (i.e., ion exchange resins, non-ion exchange resins) for removal of PFASs

in water have been reported in the literature (Lampert et al., 2007; Carter et al., 2010; Deng et al., 2010; Senevirathna et al., 2011; Xiao et al., 2012; Chularueangaksorn et al., 2013). Batch kinetic tests conducted with a high initial PFOS concentration (mg/L) demonstrated a greater than 99% removal of PFOS in 25 hours of contact time using a commercial anion exchange resin, while another anion resin achieved only 32% removal. The study also observed that PFOS anions were preferably removed over PFOA anions in the ion exchange process (Lampert et al., 2007). In laboratory experiments, anion exchange resins demonstrated high capacity for PFOS removal in water (Senevirathna, et al., 2010; Chularueangaksorn et al., 2013; 2014). Laboratory-scale fix-bed columns with an EBCT of 1.3 minutes were evaluated for PFOS removal using five commercial anion exchange resins and GAC. The breakthrough goal was set at 90% removal efficiency and the tests conducted for 122 days. Most of the anion exchange resins demonstrated a higher capacity than GAC. One resin was capable of reducing an influent PFOS concentration of 5 µg/L to 0.05 µg/L (99% removal) achieving a run length of 56,000BVs (52 days) and demonstrated adsorption capacity of 455 mg/g. GAC reached the breakthrough concentration of 0.5 µg/L faster (40 days) than the anion exchange resins (Chularueangaksorn et al., 2014). Senevirathna et al. (2010) investigated the sorption behaviour of PFOS on two ion exchange polymers, three non-ion exchange polymers and GAC. Kinetic experiments demonstrated that the ion exchange polymers and GAC were capable of reaching an equilibrium concentration after 4 hours of operation, while non-ion exchange polymers needed 10 to 90 hours. At an equilibrium concentration of 1 µg/L PFOS, the sorption capacity of the tested material decreased in the following order: ion exchange polymer > non-ion exchange polymer > GAC. However at the lower equilibrium concentration of 0.1 µg/L the non-ion exchange polymers outperformed the ion exchange polymer and GAC (Senevirathna et al., 2010).

Anion exchange resins (in chloride form) with a different polymer matrix and porosity have also been tested for PFOS removal in water (Deng et al., 2010). The study was conducted with a high initial PFOS concentration (mg/L). The experiments demonstrated that the polymer matrix was a critical factor affecting the sorption rate of PFOS. Macroporous and gel-type polyacrylic resins exhibited faster sorption and higher capacity than macroporous polystyrene resins, followed by the gel-type polystyrene resins. Since the polyacrylic matrix is more hydrophilic than the polystyrene matrix, PFOS easily diffused into the polyacrylic resin pores. Both macroporous and gel-type polyacrylic resins demonstrated a similar kinetic profile and reached an equilibrium concentration after 48 hours. However, the macroporous and gel-type polystyrene resins required greater than 168 hours to reach the sorption equilibrium. While the porosity of polyacrylic resins had little influence on the sorption kinetic and capacity, the macroporous polystyrene resins demonstrated faster sorption and higher capacity than the gel-type polystyrene resins. The low sorption of PFOS on the gel-type polystyrene resins demonstrated a size exclusion effect. Since the amount of PFOS sorbed on both polyacrylic resins was greater than the chloride anions released from the resins, the authors concluded that interaction other than anion exchange were involved in the process (Deng et al., 2010). While findings showed that anionic resins had a higher capacity for PFOS than non-ion exchange resins (Deng et al., 2010; Senevirathna, et al., 2010; Chularueangaksorn et al., 2013, 2014), it was also observed that moderately polar non-ionic resins performed better than non-polar non-ionic resins for removal of PFOS from water (Xiao et al., 2012).

Studies indicate that the ion-exchange process is a promising technology (Dickenson and Higgins, 2013) for the removal of ~~PFAAs~~PFAS, including PFOS, from drinking water. However,

additional studies are needed on the selectivity of the resins, kinetic limitations, the impact of DOC, regeneration rates and the presence of competing ions such as sulfate and nitrate on removal efficiency (Dickenson and Higgins, 2013; Rahman et al., 2013).

7.1.5 Oxidation, UV irradiation and advanced oxidation processes

Advanced oxidation processes (AOPs) have been developed for removal of contaminants that are resistant to more typical chemical oxidation treatment processes. They include the use of appropriate combinations of ultraviolet (UV) light, chemical oxidants and catalysts (e.g., ozone, hydrogen peroxide, titanium dioxide,) to generate highly reactive radicals, such as hydroxyl radicals, which are strong oxidants and react rapidly and non-selectively with organic contaminants.

Rahman et al. (2014) summarized studies that have demonstrated that PFASs compounds like PFOS will likely be resistant to oxidation, even by molecular ozone and hydroxyl radicals. Due to the low reactivity of PFOS with ozone and AOPs, chlorine–based oxidation processes will likely not oxidize PFOS under typical drinking water conditions. The resistance of PFOS to oxidation is due to the shielding effect of the fluorine atoms and the strength of the carbon-fluorine bonds (3M Company, 1999; ATSDR, 2009).These conclusions have been confirmed in surveys of full-scale treatment plants (Quinones and Snyder, 2009; Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013) described below.

In a survey of several drinking water utilities, Quinones and Snyder (2009) observed that PFOS was resistant to chlorination, chloramination and ozonation even in a combination with other treatment processes such as coagulation/flocculation, deep bed filtration and UV irradiation. Results from drinking water treatment plants in Japan reported similar concentrations of PFOS in samples of water treated with an ozonation process and in the raw water samples (Shivakoti et al., 2010; Takagi et al., 2011). Ozone doses in the range 0.37–0.85 mg/L and contact time as high as 120 minutes showed that the ozonation process was ineffective to degrade PFOS concentrations at four utilities (Takagi et al., 2011). Thompson et al. (2011) observed that an ozone dose of 5 mg/L with a contact time of 15 minutes in reclaimed water was not effective at reducing PFOS concentrations in the range of 0.9-1.4 ng/L.

In a full scale 5 MGD water treatment plant that applied a UV dose of 500 MJ/cm^2 in combination with 4 mg/L of H_2O_2, no degradation of 11 ng/L PFOS in surface water was observed (Appleman et al., 2014). Only one utility reported a partial reduction (approximately 35 %) of an influent PFOS concentration in the range of 18–27 ng/L. The utility used two UV reactors each capable of treating 3 MGD groundwater with a UV dose of 80 mJ/cm^2 and UV transmittance of 95% (Appleman et al., 2014). Although the observed partial removal of PFOS in this water treatment plant, the oxidation/AOPs appear ineffective for PFOS removal in drinking water (Appleman et al., 2014). However, ozone or AOPs may be able to oxidize polyfluorinated precursor chemicals that may be present in raw water, resulting in the potential for increasing the concentration of PFOS and PFOA in the finished water (Rahman et al., 2014).

7.1.6 Aeration/air stripping

The removal of compounds using air stripping is based on the equilibrium partitioning of chemicals between air and water, which is affected by the contact surface area between the air and the water, as well as temperature, vapour pressure, ionic strength and the pH of the water.

Dickenson and Higgins (2013) evaluated 23 PFASs (including PFOS and PFOA) in raw and finished drinking water and at various steps along the treatment train. They found that aeration was ineffective at removing PFOS and PFOA (10% removal).

7.1.7 River bank filtration (soil aquifer treatment)

River bank filtration (RBF) is a drinking water treatment method where surface water flows through the subsurface sand and gravel layers of the bank or bed of a river to extraction wells and contaminants are removed through the processes of filtration, sorption, dilution and biodegradation.

A drinking water utility utilizing RBF with a hydraulic residence time of approximately 10 days observed approximately 20% removal for PFOS, variable removal of some PFASs, and increases in concentration for other PFASs (Appleman et al., 2014). The authors concluded that this variation was possibly due to the variability in the influent concentrations from wastewater effluents impacted the drinking water sources and/or due to breakdown of precursor compounds through the river bank. Dickenson and Higgins (2013) concluded that RBF was not likely to result in significant removal of PFASs.

7.1.8 Emerging technologies

Other potential treatment technologies for removal of PFOS and PFOA have promise, but are still being researched actively. They have not yet all been evaluated on drinking waters by laboratory, pilot, or full-scale studies, but have been mentioned in reviews of bench scale studies of some PFASs removal from drinking water and wastewater (Vecitis et al., 2009; Eschauzier et al., 2012).

Nanomaterials are being developed for drinking water treatment applications, including ion exchange, sorption and oxidation processes, and abiotic reduction (e.g., nanozerovalent iron) (Boyd et al., 2013). Different nanomaterials/nanotechnologies show promise for removal of PFOS including carbon nanotubes (CNTs), chitosan-based molecularly imprinted polymers (MIPs), electrospun nanofibrous membranes (ENFMs), and titanium dioxide (TiO_2) assisted photocatalysis (Yu et al., 2008; Deng et al., 2012; Dai et al., 2013). CNTs are carbon molecules composed of carbon lattices that can take the form of tubes. Chitosan is a natural polysaccharide based on the shells of crustaceans. It may be prepared as a nanoparticle or electrospun in nanofibers (Sonia and Sharma, 2011; Zhao et al., 2011; Boyd et al., 2013). Molecular imprinting is a technique where specific sites for target compounds are constructed on a polymer so that specific adsorbates are recognized in the sorption process. ENFMs are prepared by electrospinning nanofibers of polymer or polymer composite materials to create membranes of non-woven fibers with diameters ranging from several hundreds to tens of nanometers (Greiner and Wendorff, 2007; Dai et al., 2013; Boyd et al., 2013).

Deng et al. (2012) have demonstrated the effectiveness of CNTs for removal of perfluorinated contaminants, including PFOS, from aquatic environments when the hydrophobic interactions were involved in the sorption of perfluorinated contaminants onto the CNTs. The sorption of the perfluorinated contaminants was increased with increasing carbon-fluorine chain length with the same functional group. Yu et al. (2008) investigated a chitosan-based molecularly imprinted polymer (MIP) for sorption of PFOS and concluded that the MIP sorbent had a high sorption capacity and selectivity for PFOS and it could have application in both water and waste

water treatment for removal of PFOS. Electrostatic interaction played an important role in the adsorption process.

Dai et al. (2013) investigated the morphology, structure and physicochemical properties of the multi-walled carbon nanotube (MWCNT)-filled electrospun nanofibrous membranes (MWCNT-ENFMs) for sorption of PFOS. The authors concluded that these membranes showed promise as sorbents for removal of PFOS from aqueous solutions. The sorption kinetics and isotherm results showed faster sorption rates and higher sorption capacity onto the MWCNT-ENFMs than onto the pure ENFMs for PFOS removal. The authors also concluded that it would be possible to further optimize the MWCNT-ENFMs to increase their sorption capacities while also preventing the release of the MWCNTs into the water (Dai et al., 2013).

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to municipally treated water. In cases where an individual household obtains its drinking water from a private well, a private residential drinking water treatment device may be an option for reducing PFOS concentrations in drinking water.

Although there are no certified residential treatment devices for the reduction of PFOS from drinking water, available data suggests that residential activated carbon and reverse osmosis can achieve treated PFOS concentrations of 0.2 µg/L and below 0.05 µg/L, respectively. In addition, treatment devices using anion exchange may be effective for the reduction of PFOS.

The Minnesota Department of Health (MDH, 2008b) completed a study of the effectiveness of point-of-use (POU) water treatment devices for PFOA, PFOS and PFBA removal and demonstrated that RO and activated carbon filters were capable of reducing PFOS concentrations typically found in drinking water. Laboratory screening tests and field evaluation of devices installed in municipal water systems were undertaken. In the laboratory tests, the challenge waters had a PFOS concentration of 3.0 µg/L and the target goals for performance was reduction to 0.2 µg/L. The field testing involved monitoring and sampling of four activated carbon and seven RO point-of-use devices installed at two municipal wells. One of the wells had concentrations of 0.6 µg/L PFOA, 0.9 µg/L PFOS, and 1.4 µg/L PFBA, while only PFBA was present (1.5 µg/L) at the second well. All RO devices were equipped with an activated carbon pre-filter (before the RO membrane) and a post-treatment (after the RO membrane) activated carbon polishing filter. Results indicated that all activated carbon and RO devices were effective in removing PFOS to below the quantification limit of 0.2 µg/L and below the detection limit of 0.05 µg/L, respectively. Based on these results, activated carbon and RO are expected to be effective at reducing the level of PFOS in drinking water to levels below the ~~proposed~~ MAC of 0.6 µg/L.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2015):

- CSA Group (www.csagroup.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- UL LLC (www.ul.com);
- Bureau de normalisation du Québec (www.bnq.qc.ca); and
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

Activated carbon filtration systems may be installed at the faucet (POU) or at the location where water enters the home [point-of-entry (POE)]. RO systems are intended for POU installation, as larger quantities of influent (incoming) water are needed to obtain the required volume of treated water, which is generally not practical for residential-scale point-of-entry systems. RO systems should only be installed at POU as the water they have treated may be corrosive to internal plumbing components. A consumer may need to pre-treat the influent water to reduce fouling and extend the service life of the membrane.

Ion exchange treatment technology using anion exchange resins may also be a feasible for PFOS removal in residential scale applications. Ion exchange treatment devices is typically designed and constructed for residential use by drinking water treatment system providers or dealer. ~~Health Canada strongly recommends that homeowners ensure that these systems are constructed using materials certified to NSF/ANSI Standard 61 (NSF/ANSI, 2014).~~ If an ion exchange system is used, the water may need to be filtered through a GAC filter to remove any chlorine or chloramine (if connected to a treated water supply) from the water before it reaches the resin.

Health Canada strongly recommends that chemicals used in treatment systems be certified to NSF/ANSI Standard 60 – Drinking Water Treatment Chemicals Health Effects (NSF/ANSI, 2015a) and that materials and components be certified to NSF/ANSI Standard 61 – Drinking Water System Components Health Effects (NSF/ANSI, 2016a) and NSF/ANSI Standard 372 – Drinking Water System Components Lead Content (NSF/ANSI, 2016b). These standards ensure that these materials meet health-based leaching and lead content requirements and are safe for use in potable water applications. Activated carbon filters are covered in NSF/ANSI Standard 53: Drinking Water Treatment Units-Health Effect (NSF/ANSI, 2015b) and reverse osmosis systems are covered in NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems (NSF/ANSI, 2015c).

Before a treatment device is installed, the water should be tested to determine general water chemistry and verify the presence and concentration of PFOS. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Devices can lose removal capacity through use and time and need to be maintained and/or replaced.

8.0 Kinetics and metabolism

PFOS is considered chemically unreactive, and it is not metabolized. The oral absorption of PFOS is rapid and complete (Kemper, 2003; Hundley et al., 2006; Lau et al., 2007). Once absorbed, PFOS is primarily restricted to plasma and extracellular fluid (Chang et al., 2012) and excreted in urine.

8.1 Absorption

PFOS is rapidly and nearly completely absorbed through the GI tract. In rats, studies consistently estimated the oral absorption rates of PFOS at >95% after a single dose (4.2 to 20 mg/kg) by gavage (Johnson and Ober, 1979; 1999; Cui et al., 2010).

No controlled studies investigating the oral availability of PFOS have been conducted in humans, but there is evidence of oral absorption of PFOA from studies of residents living in areas with contaminated drinking water (Emmett et al., 2006; Hölzer et al., 2008; PFOS was not investigated in these studies). Emmett et al. (2006) correlated the number of glasses of tap water ingested per day with blood concentrations of PFOA, indicating this was the primary exposure route. Hölzer et al. (2008) correlated the litres of drinking water consumed per day with serum levels of PFOA; although there was no relationship noted with drinking water consumption and PFOS levels in either study, the main exposures in these communities were to PFOA.

No inhalation or dermal studies have reported PFOS kinetics; however, the physicochemical properties of the compound suggest that these routes of exposure are not important when PFOS is found in drinking water (see Section 5.7).

8.2 Distribution

The highest PFOS concentrations in rats were measured in the liver after a single oral gavage dose of 400 mg/kg (Benskin et al., 2009) and 2 weeks of dietary exposure to 400 mg/kg bw per day (De Silva et al., 2009). This might be due to the binding of PFOS to liver proteins in rat, including the liver fatty acid binding protein (L-FABP) (Luebeker et al., 2002). Similarly, the highest PFOS concentrations were found in liver and serum after intraperitoneal injection of PFOS in female rats (1 or 10 mg/kg bw per day for 2 weeks) (Austin et al., 2003). PFOS was also accumulated primarily in mouse livers after dietary exposure to 0.031 or 23 mg/kg bw per day for 1–5 days (Bogdanska et al., 2011) or a single oral dose of 1 or 20 mg/kg bw (Chang et al., 2012), with liver-to-blood ratios ranging from 2 to 6 (Bogdanska et al., 2011). One of the oral dosing mouse studies also identified storage of PFOS in lungs (lung-to-blood ratios of 1.5–2; Bogdanska et al., 2011). Average liver-to-serum PFOS concentration ratios in monkeys ranged from 0.9 to 2.7, after oral bolus administration of 0.03, 0.15, or 0.75 mg/kg bw per day for 183 days (Seacat et al., 2002). The average percent PFOS dose found in the livers of these monkeys ranged from 4.4 ± 1.6% to 8.7 ± 1.0%.

Few data have been gathered on the human tissues to which PFOS is typically distributed. In tissues taken from human cadavers in the U.S., the mean liver-to-serum concentration ratio was 1.3, suggesting there is no extensive binding to liver protein in humans as measured in the rat (Olsen et al., 2003a). Maestri et al. (2006) measured a lung to blood ratio of 1.5 from pooled human samples. Neither cerebrospinal fluid (Harada et al., 2007) nor thyroid (Pirali et al., 2009) have been observed to be relevant partitioning sites for PFOS.

PFOS, as with other perfluoroalkyls, binds to serum albumin and, to a lesser extent, to plasma γ-globulin, α-globulin, α-2-macroglobulin, transferrin and β-lipoproteins (ATSDR, 2009; Butenhoff et al., 2012a). Binding of PFOS to the plasma lipoprotein-containing fractions appears to be limited (≤ 9%) in human, as shown *in vitro* with the plasma of a human donor (Butenhoff et al., 2012a). Linear PFOS isomer preparations bind more tightly with human serum albumin than branched PFOS isomers (Beesoon and Martin, 2015). PFOS has also been shown to competitively

bind to the human thyroid hormone transport protein transthyretin (TTR), with less than one-tenth of the T4 affinity (Weiss et al., 2009).

Sex and age have been demonstrated to influence PFOS distribution in rodents and humans. Sex-related differences were observed in maximal serum concentrations of PFOS measured in Sprague-Dawley rats (single oral dose of 2 mg/kg) with females having a 2.5 times higher level than males. At 15 mg/kg, however, the differences were not seen. Chang et al. (2012) also reported slightly slower elimination for PFOS in female rats. After dietary exposure ranging from 4 to 14 weeks (0.5, 2.0, 5.0 and 20 ppm in food), PFOS levels increased proportionally with cumulative dose in both sexes (Seacat et al., 2003). Average serum levels in females were approximately 31–42% higher than in males with liver concentrations reported as being equal. Liu et al. (2011) reported varying distributions of PFOS with age in mice administered a single subcutaneous dose (50 mg/kg) on postnatal day (PND) 7, 14, 21, 28 or 35. The levels of PFOS in the liver increased with age at exposure, whereas the PFOS levels in brain decreased with levels at PND 7 two times that at PND 35. In contrast, the blood PFOS levels did not vary with postnatal age. As previously described in Section 5.6, serum PFOS levels in humans appeared to be influenced by age and gender in CHMS. The effect was also observed in U.S. studies. In the general U.S. population (NHANES data for 1999–2008), the serum PFOS levels were reported to be significantly higher in males than in females, regardless of age. As age increased, PFOS concentration increased in both sexes and the increase was more pronounced in females than in males (Kato et al., 2011). PFOS blood levels were shown to be influenced by age and gender, with lower PFOS serum in females than in males in the age group 20–50 years; a plausible explanation is menstrual bleeding, as well as gestation and lactation transfer (Harada et al., 2004; Ingelido et al., 2010). The analysis of mother–children data indicated that PFOS levels were on average 42% higher in children than in their mothers, and that this trend persisted until at least 19 years of age. The PFOS child:mother ratios were higher in boys aged 5 years than in girls (Mondal et al., 2012).

PFOS exposure can occur transplacentally and lactationally. Fetal and pup PFOS concentrations in serum and brain were higher than corresponding maternal concentrations in rats exposed to 0.1–1.0 mg/kg bw per day from gestational day (GD) 20 to PND 21 (Chang et al., 2009). Serum concentrations in newborn rats exposed *in utero* to 1–10 mg/kg bw per day on GD 2–21 mirrored the maternal administered dose and were similar to those in the maternal circulation at GD 21 (Lau et al., 2003). Serum PFOS concentration in mouse pups administered a daily oral bolus from GD 1 to 17 (1, 5, 10, 15 or 20 mg/kg/day) were consistent with the rat data (Thibodeaux et al., 2003). In humans, PFOS cord blood levels have been shown to correlate with maternal serum concentrations (Inoue et al., 2004; Midasch et al., 2007; Needham et al., 2011; Gützkow et al., 2012a); moreover, maternal serum PFOS concentrations have been observed to decrease throughout pregnancy (Fei et al. 2007). PFOS has been measured in breastmilk samples collected worldwide (So et al., 2006; Kärrman et al., 2010; Roosens et al., 2010; Kadar et al., 2011; Sundström et al., 2011). A correlation has been reported for PFOS levels in human milk and maternal serum with average milk to maternal serum concentration ratios ranging from of 0.01 to 0.03 (Liu et al., 2011). PFOS breastmilk concentrations were shown to decrease as the number of infants breast-fed by a mother increased (Tao et al., 2008; Kadar et al., 2011). Most studies reported decreases in PFOS breastmilk (Thomsen et al., 2010) or maternal serum (von Ehrenstein et al., 2009; Monroy et al., 2008) throughout the lactation period; however, Tao et al. (2008) reported an upward trend for PFOS levels in milk through 6 months of lactation.

Similarly, infants breastfed for > 12 months had significantly higher serum PFOS concentrations compared to infants who were not breastfed in a community with PFAS-contaminated water (Mondal et al., 2014); however, the authors noted that the estimates may be imprecise as they are based on only 8 infants in the long-duration group. Similarly, a study of Faroese infants with serum PFOS data at birth and at 11, 18, and 60 months estimated an increase in serum PFOS concentrations of about 29% per month during the period of exclusive breastfeeding and of about 4% per month during periods of partial breastfeeding (Mogensen et al., 2015a). In this study, serum PFOA levels measured up to five years of age did not decline to serum PFOA levels at birth, which the authors attributed to ongoing dietary exposure to PFOA (in particular through traditional intake of pilot whale meat).

8.3 Metabolism

The available data indicate that PFOS is not metabolized. Based on the available evidence for PFOA, metabolism is not expected to play a role in the clearance of PFOS (Kemper and Nabb, 2005; EFSA, 2008; ATSDR, 2009).

8.4 Excretion

Remarkable species-dependent differences in elimination half-life have been observed, with PFOS remaining in human bodies for a much longer duration than in other species, including non-human primates, rats and mice. Species- and sex-related differences are primarily attributed to elimination kinetics where, at higher doses, the kinetics of PFOS in rodents and primates do not follow one-compartment or simple first-order models (Andersen et al., 2006). The arithmetic mean half-life value for serum elimination of PFOS in humans was calculated as 5.4 years (95% CI = 3.9–6.9 years; range = 2.4–21.7 years) based on data obtained in retired workers ~~(Olsen et al. 2007); no half-life could be found from general population studies.~~from a 3M Company factory in Alabama, USA (Olsen et al., 2007) and a geometric mean half-life value estimated through daily elimination of PFOS in occupational workers in a fluorochemical plant in China was calculated as 32.6 years (range = 0.76–30475 years; Fu et al., 2016). Fu et al. (2016) suggest that the ongoing high exposure to PFOS could explain the longer half-lives reported in the Chinese study compared to Olsen et al. (2007). In a study of Faroese children followed from birth to 5 years the biological half-life of the serum-PFOS concentration was estimated as over 4.3 years (Mogensen et al., 2015a). The arithmetic mean elimination half-life value was estimated as 6.2 years (95% CI = 5.7–6.7 years; range = 3.2–10 years) in young females and 27 years (95% CI = 23.9–30.1 years; range = 1.6–121 years) in males and older females in healthy adult volunteers in China (Zhang et al., 2013a). No half-life could be found from general population studies in North America. The half-life of PFOS in animals varies depending on experimental protocols, including the duration animals are followed, but is on the order of days to weeks in rodents and months in monkeys (see Table 1).

Table 1: Serum half-life estimates in experimental animals

Species	Dosing regime	Mean half-life (days)	Reference
Rat	Single oral dose of 2 mg/kg-bw; followed for 24 hours	3.10[a] (M) 1.94 ± 0.13[b] (F)	Chang et al., 2012
	Single oral dose of 4.2 mg/kg-bw; followed for 144 hours	8.23[a] (M)	
	Single i.v. dose of 2 mg/kg-bw; followed for 24 hours	7.99 ± 4.94 [b] (M) 5.62[a] (F)	
	Single oral dose of 2 mg/kg-bw; followed for ≥10 weeks	38.31 ± 2.32 [b] (M) 62.30 ± 2.09 [b] (F)	
Mouse	Single oral dose of 1 mg/kg-bw; followed for 20 weeks	42.81[c] (M) 37.80[c] (F)	Chang et al., 2012
	Single oral dose of 20 mg/kg-bw; followed for 20 weeks	36.42[c] (M) 30.45[c] (F)	
Monkey	Single i.v. dose of 2 mg/kg-bw; followed for up to 161 days	132 ± 7 [b] (M) 110 ± 15 [b] (F)	Chang et al., 2012
	Oral dose of 0.15 or 0.75 mg/kg-bw per day for 182 days	~200[c] (M & F)	Seacat et al., 2002
Human	26 former workers with an average of 31 years of work and 2.6 years retired; external exposure data not provided	1971 (1424–2517)[d]	Olsen et al., 2007
	86 adults; external exposure data not provided	2263(2081-2446)[d] (F) 9855 (8724-10987)[d] (M & F)	Zhang et al., 2013a
	81 children; prenatal exposure assessed from mother's serum-PFOS at pregnancy week 32; external exposure data not provided	1606[c] (M & F)	Mogensen et al., 2015a
	302 workers before and after PFOS was restricted in 2009; years of service not reported; external exposure data not provided	11899[e] (M & F) 22229[e] (M) 2920[e] (F)	Fu et al., 2016

[a]No standard error was calculated because value was based on a sample size of 1
[b]± Standard error
[c]Authors did not provide standard error
[d]95% confidence interval
[e]Geometric mean since authors did not provide arithmetic mean

Urinary and fecal excretion are the primary routes of PFOS elimination in rats (Cui et al., 2010; Chang et al., 2012) and mice (Chang et al., 2012), with most data indicating that urine is a more important route of excretion than feces. One exception was the measurement of slightly higher excretion by fecal than urinary route in rats in the 48 hours after exposure to a single oral

dose of 4.2 mg/kg bw; however, excretion was almost 3 times higher in urine in the 89 days after single i.v. dose of 4.2 mg/kg bw in the same study (Chang et al., 2012). PFOS might be subject to extensive enterohepatic recirculation prior to biliary and fecal excretion (Harada et al., 2007; Chang et al., 2012). The relevance of urinary clearance in humans has been questioned, as renal clearance of PFOS was substantially lower than in animals (Harada et al., 2005). Because of the possibility of excretion pathways other than urine, Zhang et al. (2013a) cautioned that the elimination half-lives reported above may be viewed as "upper limits".

In humans, the loss of blood during menstruation may contribute significantly to excretion in women (Harada et al., 2005).~~2005).~~ Pharmacokinetic modeling by Wong et al. (2014) predicted that menstruation accounts for 30% of the discrepancy in elimination of PFOS between men and women. Lactation can also be a significant route of excretion in women (von Ehrenstein, 2009; Kim et al., 2011a; Mondal et al., 2014; Mogensen et al., 2015a).

8.5 Physiologically-based pharmacokinetic (PBPK) models

Several models with varying complexities have been developed to describe the kinetics of PFOS in both experimental animals and humans (Andersen et al., 2006; Tan et al., 2008; Loccisano et al., 2011; 2012a; 2012b; 2013). Due to the non-linear nature of PFOS pharmacokinetics, where faster clearance is seen with high bolus dosing, physiological models can provide an improved means of assessing cross-route and cross-species dosimetry for risk assessment.

The first model developed for PFOS was a biologically-motivated compartmental pharmacokinetic (PK) model for monkeys, which included saturable renal resorption of filtered PFOS (Andersen et al., 2006). Subsequent work to refine the model included the addition of a liver compartment and of time-dependent functions for protein binding and volume of distribution to fit high-dose monkey and rat oral and intravenous plasma, urine and feces kinetic data (Tan et al., 2008). PFOS PBPK models for adult rats (Loccisano et al., 2012a), monkeys (Loccisano et al., 2011) and humans (Loccisano et al., 2011) were built upon the compartmental models; however, the time-dependency function for volume of distribution was removed. Further models for lactation and pregnancy were developed for rats (Loccisano et al., 2012b) and humans (Loccisano et al., 2013). No models have been developed for mice, and no pregnancy and lactation models have been developed for monkeys. The basic structure of the PBPK model was the same for all three species, with only time-dependent changes in physiology included to describe pregnancy and lactation along with the time-dependency for plasma and tissue binding. The models included tissue compartments for gut (for oral/dietary dosing), skin (human and monkey model only; for dermal dosing), liver, fat, and kidney, with remaining body tissues grouped together (and not divided into richly and poorly perfused compartments). Biliary excretion and fecal elimination of the unabsorbed bolus oral dose or dietary exposure was added to the rat model; moreover, the rat version did not include a fat compartment (which became lumped with the rest of the body) or physiological gut, which was described as a one compartment non-physiological compartment. The PBPK model assumes only the plasma free fraction of PFOS is available for uptake into tissue, excretion or resorption. Elimination from plasma is described as glomerular filtration of the free fraction into a filtrate compartment. The filtered PFOS can either be eliminated in urine or resorbed into the kidney where it can return to systemic circulation. Finally, the rat PFOS model included protein binding in the liver, which was described as being saturable. The models were relatively good at reproducing controlled dosing data for rats (dietary, oral gavage, and IV

routes of exposure; Loccisano et al., 2012a), and monkeys (IV and oral gavage routes of exposure; Loccisano et al., 2011). Although no controlled dosing data were available for humans, biomonitoring data (for typically only a single timepoint) were within similar ranges as model simulations (using measured water concentrations for the biomonitored populations, along with assumptions on ingestion patterns; Loccisano et al., 2011).

The Loccisano models for humans (2011), monkeys (2011) and rats (2012a) were considered for use in the current assessment (see Section 10); moreover, a mouse model (that was scaled from the rat model, but that could not be validated) was used. Further specifics of the models used for this assessment, including the values used for each of the physiological and chemical-specific parameters, are described in Campbell and Clewell (2013). Exposure was described as a constant intake of PFOS in humans (ingesting 1.5 L of water per day) and the model was allowed to reach steady state conditions prior to determining the predicted drinking water concentration consistent with the internal dose metric. The human was simulated as a 70 kg adult.

The Andersen et al. (2006) pharmacokinetic model was modified by Wambaugh and colleagues (2013) by adding a gut compartment for oral absorption and specifying an upper limit on tissue distribution. The authors used the model to translate dose regimes and available LOEL, NOEL, and benchmark dose (BMD) values from 13 *in vivo* studies of PFOS into internal dose metrics (area under the curve, average, and maximum serum concentrations). The data were modelled for cynomolgus monkeys, Sprague-Dawley rats, and CD-1 mice. A Bayesian approach was employed to model ranges of various physiological parameters. Wambaugh et al. (2013) identified relatively good concordance between predicted and measured (at study termination) serum concentrations, with few outliers, and identified that no single dose metric appeared to be best for all adverse endpoints. Dose metrics for points-of-departure (PODs) tended to be similar (with the exception of immune studies, which had lower PODs than other endpoints), indicating consistency between species and most adverse outcomes.

Dermal and inhalation routes from contact with drinking water were not included in as potential routes of exposure in this effort, as their contribution to exposure is considered to be negligible (see Section 5.7).

8.6 Animal-to-human extrapolation

Although animal-to-human extrapolations are typically discussed after the selection of potential PODs, consideration has been given to this extrapolation earlier in the PFOS assessment, as the large variability between species can affect POD selection. The large differences in PFOS clearance between humans and other species must be accounted for when using animal studies as a basis for human risk assessments. The application of default approaches for animal-to-human extrapolation—such as the use of an interspecies uncertainty factor of 10 or allometric scaling—might not be sufficiently protective of humans, who receive longer internal exposures to target tissues. For this reason, chemical-specific approaches that can account for pharmacokinetic differences between species and nonlinear behavior of PFOS were considered for the risk assessment. These approaches include the application of chemical-specific adjustment factors (CSAFs) and PBPK modelling. A discussion and application of each of these approaches is outlined below, and further details can be found in a report prepared for Health Canada by Summit Toxicology (2015).

8.6.1 Derivation of CSAFs

A major advantage of the application of CSAFs over default uncertainty or allometric scaling factors is that the approach incorporates both species- and chemical-specific data. Despite this strength, the approach relies on single values representative of pharmacokinetics in species, and does not necessarily account for non-linear pharmacokinetics.

IPCS guidelines on calculating CSAFs (IPCS, 2005) were applied to derive the toxicokinetic portion of the interspecies uncertainty factor (AK_{UF}). IPCS recommends that the default interspecies uncertainty factor of 10 be divided into values of 4.0 ($10^{0.6}$) for the toxicokinetic portion (AK_{UF}) and 2.5 ($10^{0.4}$) for the toxicodynamic component (AD_{UF}). The default AK_{UF} of 4.0 becomes replaced with any AK_{UF} values calculated based on chemical-specific data (IPCS, 2005). As data were not available to quantitatively evaluate toxicodynamic differences between species, no AD_{UF} was calculated.

To calculate the AK_{UF} (i.e., reflecting interspecies toxicokinetic differences), the following equation was used:

$$AK_{UF} = \frac{CL_{animal}}{CL_{human}}$$

where:

- AK_{UF} is the toxicokinetic component of the interspecies uncertainty factor; and
- CL is clearance in animals and humans (e.g., mL/kg bw per day).

All clearance values in animals were obtained from a study by Chang et al. (2012). In this study, Sprague-Dawley rats, CD-1 mice, and cynomolgus monkeys (3–5 per sex) were provided a single dose of 1–2 mg/kg bw (oral for rats and mice, and IV for monkeys) and followed for ≥70 days. Clearance was much higher in male than female rats (and differs from sex-related variability for PFOA, where females consistently have increased clearance and lower half-life than males); therefore, clearance levels are presented separately for each sex. Clearance rates for monkeys, mice, and male, and female rats were 1.38, 4.72, 22.24, and 5.39 mL/~~d~~-kg bw per day, respectively.

Clearance was not measured directly in humans, and must be calculated based on half-life estimates using the following equation:

$$CL = \frac{Ln\ 2 \times V_d}{T_{½}}$$

where:

- CL is clearance in animals and humans (L/kg bw per day);
- ln 2 is the natural log of 2;
- V_d is the volume of distribution, which is the theoretical volume of blood in which the amount of a chemical would need to be uniformly distributed to produce the observed blood concentration; and
- $T_{½}$ is the half-life of a compound.

A half-life of 1971 days (5.4 years) was calculated from decreases in serum concentrations of 26 workers previously occupationally exposed to PFOS, with an average of 31 years of work and 2.6 years retired (Olsen et al., 2007). ~~No~~Higher half-life values ~~could be found~~were reported in the general population from China. However, due to lifestyle and environmental differences between the Canadian and Chinese populations and to the absence of half-life values for the exposure of the general population exposed environmentally to PFOS in North America, the half-life of 1971 days from retired workers was employed. Volume of distribution values for PFOS are typically relatively consistent among species (Thompson et al., 2010), and a value of 200 mL/kg bw was used to represent a chemical that is mostly distributed extracellularly. The resulting clearance in humans, using the above equation, is 0.07 mL/~~d~~-kg bw per day. Using the human:animal ratios of clearance values described above, the calculated AK_{UF} values for PFOS for monkeys, mice, male rats and female rats were 19, 67, 318, and 77, respectively. Clearance was selected as the dose metric for the derivation of AK_{UF} values because data for this metric were readily available in most species, and could be calculated from half-life data in humans. Moreover, the use of clearance as a dose metric is a reasonable assumption for chemicals with long half-lives. Preliminary analyses have suggested that peak concentrations might be more predictive of toxicity for certain adverse endpoints (Haber et al., 2013). Although this hypothesis was not further explored for the present analysis, using clearance is considered to be a more conservative alternative to using peak concentrations as the dose metric for AK_{UF} derivation. Finally, ratios of clearance levels are considered an appropriate basis for AK_{UF} derivation typically only if first-order kinetics are assumed to apply; however, as urinary clearance of PFOS is complex, this assumption might not be appropriate.

8.6.2 PBPK modelling

A typical approach for PBPK modelling is to use the model to calculate human-relevant PODs, which are derived by applying a human PBPK model to internal dose metrics (e.g., concentrations of PFOS in plasma) that were either calculated or measured in animals. With sufficiently validated models, this approach is considered to be the most robust approach for performing animal-to-human extrapolations. However, there is only medium confidence in human, monkey, and rat models, because different model codes were used for different species, and model fits to some datasets were not optimal. Moreover, the limited understanding of reasons for the observed sex differences in clearance in rats means there are weaknesses in how this could be addressed in the model. Finally, a major drawback in using the standard PBPK modelling approach is that human models have not been fully verified. Human data available for verification are limited to biomonitoring studies that allow for only rough estimates of exposure scenarios, and for which serum concentration measurements were typically only performed once (with a few populations with measurements at two timepoints). Loccisano and colleagues did not develop PBPK models for mice, but Health Canada modelling approaches using mouse studies scaled the rat models using mouse data. As insufficient toxicokinetic data exist to verify whether the mouse model is appropriate, confidence in the mouse model is low. Therefore, there is insufficient confidence to use precise PBPK model results as PODs for the risk assessments.

As an alternative approach to using the PBPK model for POD calculations, ratios of PBPK model-predicted dose metrics were used to calculate AK_{UF} values for relevant doses. This approach is thought to provide more robust estimates of the AK_{UF} than the traditional calculations described in Section 8.6.1, as it can address the non-linear kinetics of PFOS, identifying different

values at steady state for different oral dose levels. In contrast, the AK_{UF} values calculated above are dependent on the specific doses and dose regimes used in the pharmacokinetic studies; uncertainties arise in the values obtained from these studies, as the animals were provided only single doses, and the human data were not obtained from controlled dosing studies. Furthermore, clearance-based AK_{UF}s are ratios of low doses in humans to high doses in animals, and therefore exposures between the species are not of the same magnitude; using the PBPK model to derive the AK_{UF} allows for a more appropriate comparison of doses of the same magnitude.

The selected dose metric for the PBPK-derived AK_{UF} values was steady-state concentrations of PFOS. Steady-state concentration was selected as it is typically relevant for chemicals with long half-lives, and is a conservative assumption. Although alternative dose metrics—including peak concentrations (Haber et al., 2013)—might be more predictive of PFOS toxicity for certain adverse endpoints, additional work was not performed to further investigate the most appropriate dose metric. Plasma was selected as the relevant tissue for steady-state concentrations, as it is a metric that can act as a relevant proxy for a wide variety of organs, because blood flows to these different organs. Liver steady state concentrations were also incorporated into the assessment for comparison with plasma-based AK_{UF} values, as the liver has been identified as a primary organ for PFOS distribution in pharmacokinetic studies, and is also a potential target organ for toxicity. However, there is lower confidence in liver-based values than plasma values, as very little pharmacokinetic data exists to be able to perform verification of the PBPK model for liver concentrations. Liver concentrations could not be verified for humans, mice, and monkeys; for rats, minimal verification could be performed, but as data were available for only one to two timepoints in each study, the comparisons are not robust. Moreover, the use of plasma concentrations as a proxy for a variety of organs simplifies the application of AK_{UF} values in the assessment, which is already complex due to the use of AK_{UF} values that are species- and dose-specific.

Using the Loccisano PBPK models described in Section 8.5, steady-state plasma and liver concentrations were calculated at various doses in each of the species. The same doses were used for each of the species. For each dose run in the PBPK model, ratios of steady-state PFOS concentrations in humans vs. other species were calculated to obtain dose- and species-specific AK_{UF} values (Summit Toxicology, 2015). Steady-state concentrations and AK_{UF} values for plasma and liver at potentially relevant doses are listed in Table 2.

Table 2: PBPK dose metrics and PBPK-derived AK_{UF} values at relevant doses

Metric	Species	Oral dose (mg/kg bw per day)			
		0.001	0.01	0.1	1
Steady-state plasma PFOS predictions (µg/mL)	Human	5.40	53.0	360	530
	Monkey	2.85	26.6	140	239
	Mouse	NC[a]	NC	17.1	170
	Rat	0.349	3.69	36.9	368
Steady-state liver PFOS predictions (µg/mL)	Human	20.1	197	1340	1977
	Monkey	10.6	98.8	521	894
	Mouse	NC	NC	NC	NC
	Rat	4.45	20.7	195	1935
AK_{UF} derived based	Monkey[b]	2	2	3	2

on plasma predictions	Mouse[c]	NC	NC	21	3
	Rat	16	14	10	1
AK_{UF} derived based on liver predictions	Monkey[b]	2	2	3	2
	Mouse[c]	NC	NC	NC	NC
	Rat	5	10	7	1

[a]NC = could not be calculated due to limitations in the PBPK model
[b]Default AK_{UF} values of 4 will be applied for monkeys due to insufficient confidence in the models to apply value lower than default
[c]AK_{UF} values for rats will be applied due to low confidence in the PBPK model

To select the appropriate AK_{UF} for each POD, the POD is rounded down to the nearest value in the oral dose column (i.e., values within the same order of magnitude are used). As discussed above, low confidence is placed on the mouse PBPK model. Until a PBPK model has been developed based on mouse data, the use of rat AK_{UF} values for mice is recommended (Summit Toxicology, 2015).

8.6.3 Recommended interspecies extrapolation approach

The recommended approach for interspecies extrapolation is the use of a PBPK model for the calculation of the AK_{UF} component of the CSAF, using steady-state plasma concentrations as the dose metric. The use of plasma concentrations ensures the relevance of the dose metric to adverse effects that occur in a variety of organs. Organ-specific dose metrics are typically preferred over blood-based values, whenever available; however, using the plasma metrics for this assessment provides consistency in the application of the AK_{UF} over a wide variety of adverse endpoints. AK_{UF} values were calculated for liver metrics for comparison with plasma values; the behaviour of PFOS in the liver was similar to that in the plasma, and AK_{UF} estimates were on the same order in both compartments. These results indicate that plasma values are appropriate proxies to be used for adverse hepatic effects. The liver-based values in rats were slightly lower than plasma-based values; however, greater confidence is placed in the plasma values because more data were available to verify this compartment of the PBPK model. The dose- and species-specific AK_{UF} values (for steady-state plasma concentrations) in Table ~~3~~2 are applied in Sections 10.1 and 10.2.

Although PBPK-derived AK_{UF} values were selected as the recommended approach for this assessment, several weaknesses have been identified. As described above, the AK_{UF} was plasma based rather than being organ specific. Steady state concentrations were also selected as the dose metric, as a conservative assumption relevant to the nature of the compound; detailed work was not performed to identify whether other dose metrics (e.g. peak concentrations) would be more appropriate for the various adverse endpoints. Steady state was also not reached in the human model at doses below 0.1 mg/kg bw per day. Furthermore, PBPK models have not been developed specifically for the mouse, and have been scaled instead from the rat, without further pharmacokinetic data for mice to be used for verification; the application of AK_{UF} values for rats is therefore recommended for use in mice in the absence of robust data in the species. AK_{UF} values for rats ~~are also~~were derived based on male rats ~~only, despite sex,~~ which experience slower clearance of PFOS than female rats, in order to minimize the interspecies differences ~~in the species~~.

Despite these weaknesses, using the PBPK model to derive the AK_{UF} was thought to be of equal or greater robustness to other potential interspecies extrapolation approaches. The selected approach quantitatively incorporates pharmacokinetic differences among species, in a manner that addresses the non-linear kinetics of PFOS, which cannot be done using the default AK_{UF}-derivation approach. Moreover, the PBPK-derived AK_{UF} values do not rely on individual pharmacokinetic studies that are often single-dose studies and not easily comparable among species. An ideal approach to address species differences would be to use blood concentrations of PFOS—either by using pharmacokinetic models to estimate the concentrations, as employed by Wambaugh et al. (2013), or using the values specifically measured in individual studies—as PODs for the assessment. However, the human PBPK models that would be used to extrapolate from this serum concentration cannot be fully verified based on existing human pharmacokinetic data, which decreases the level of comfort of using this approach to estimate precise PODs. The recommended approach was selected as a means of quantifying interspecies differences while addressing the non-linear kinetics of PFOS, without relying on precise PBPK-derived estimates of PODs.

9.0 Health effects

Many studies have been conducted to investigate the effects of PFOS on health. The summary of literature on health effects for PFOS is largely based on a comprehensive review conducted by a consultant (Sanexen Environmental Services Inc., 2013), and includes only the studies of direct relevance to the derivation of the health-based value. More specifically, this summary includes reports, reviews, and original papers published concerning PFOS in order to understand toxicity in humans exposed to PFOS via drinking water.

9.1 Effects in humans

9.1.1 Acute toxicity

No epidemiological data regarding acute or short-term toxicity of PFOS were located.

9.1.2 Subchronic and chronic toxicity

Many quality epidemiological studies have been conducted. Large cohorts of workers and environmentally exposed populations have been followed, with observations of significant relationships between exposure to PFOS and lipid levels, liver and thyroid functions, and reproductive (fecundity, age of puberty, and sperm quality), immunological, and developmental (birth weight) outcomes. Although all of these studies present limitations to some extent, including in terms of study design, bias and confounders, the human weight of evidence provides a strong argument in favor of detrimental health effects of the compound. This information should support the choice of a health endpoint; however, deriving a safe exposure dose based on studies in humans remains a challenge because of the difficulty in characterizing a dose–response pattern with current studies. Their use in the present assessment is important to verify the relevance of animal to human extrapolation, and the monitoring of future studies will help in determining the accuracy of the observed associations.

Most environmental studies among PFAA-exposed populations were conducted in the Mid-Ohio Valley within the C8 Science Project. The C8 Science Panel was convened as a result of a class action settlement against DuPont, and is composed of independent epidemiologists

jointly selected by lawyers for the community and DuPont. The C8 Health Project is the largest study of a population exposed to ~~PFAAs~~PFAS in drinking water, containing residents of Ohio and West Virginia communities surrounding the DuPont Washington Works plant. The health survey was conducted in 2005–2006 on approximately 69,000 individuals, including children and adults. The main PFAA exposures in the community were to PFOA—the median PFOS serum concentrations in this population were 20.2 ng/mL, compared to 17.5 ng/mL in the general American population during the same period (Frisbee et al., 2009). Some longitudinal/prospective studies were also conducted among this population after a follow-up period. Some recent data in the project have not yet been published in peer reviewed literature; summaries of these studies—as well as panel conclusions and further information on the members of the panel—are available on the C8 Science Panel website (www.c8sciencepanel.org/panel.html).

9.1.2.1 Liver effects

Some level of association between exposure to PFOS and alteration in liver enzymes has been observed, but no clear trend has been defined. A cross-sectional study found no association between PFOS serum levels (range = 20–2,110 ng/mL) of 3M Cottage Grove employees (Minnesota) participating in the medical surveillance exam (70% of them eligible for the study) and hepatic parameters (data were not shown in the report; Olsen et al., 2003b). In another cross-sectional study, a small linear association between levels of PFOS and of Alanine transaminase (ALT) was reported in participants of the C8 project (Gallo et al., 2012). However, the clinical significance of the low magnitude in ALT increase is unknown. An occupational study compared hepatic enzymes before and after the demolition of manufacturing facilities. A significant association was found between PFOS and decreased ALT among workers with baseline PFOS levels similar to the general population. No association was found between PFOS and total bilirubin, AP or AST (Olsen et al., 2012). Overall, no definitive conclusion on liver toxicity can be drawn due to study limitations and low magnitude of enzymatic changes.

9.1.2.2 Immune suppression

Studies in environmentally-exposed populations have identified associations between PFOS levels and decreased antibodies against various illnesses, but the influence of PFOS exposure on clinical immunosuppression (i.e., incidence of illnesses) appears to be more tenuous. A study in children found an inverse relationship in immune response with PFAA exposure (Grandjean et al., 2012; Grandjean and Budtz-Jørgensen, 2013), with maternal cord PFOS levels negatively correlated with anti-diphtheria antibody concentration at 5 years. Moreover, children in this population demonstrated increased odds of not reaching protective antibody levels for diphtheria after vaccination at 7 years old (Grandjean et al., 2012). The prospective nature, sample size, low risk of selection bias and defined objectives make the results relevant to the studied population; however, relevance to other populations is questionable, as increased exposure to other potential immunosuppressants occurring in this region (Faroe Islands) was not accounted for in the study. Additionally, a portion of the 13-year old cohort had received booster vaccinations during emergency room visits, which could add variance to the study design (Grandjean et al., 2017). Increased PFOS exposure was also associated with decreased antibodies against rubella in children from a prospective birth cohort of pregnant women from Norway (2007–2008; Granum et al., 2013). In contrast, prenatal exposure to PFOS was not associated with hospitalizations for infections in a Danish Cohort (1996–2002; Fei et al., 2010a), nor with

episodes of common cold, gastroenteritis, eczema or asthma in the aforementioned Norwegian cohort (Granum et al., 2013). In a Taiwanese cohort study, the median serum PFOS concentration was significantly higher in asthmatic children (Dong et al., 2013), and prenatal exposure to PFOS was positively correlated with cord blood IgE levels, particularly in male children; however, there was no association with atopic dermatitis (Wang et al., 2011b). Cord blood IgE levels, food allergy, eczema, wheezing, or otitis media were not associated with maternal PFOS in female infants in a prospective cohort study of pregnant women from 2002 to 2005 in Japan (Okada et al., 2012).

Although some effects on the antibody response have been observed, conflicting results were common in the dataset, which remains relatively small. A low level of consistency was observed across studies, with variations between genders, specific microbial immunoglobins, infections, mother vs. child exposure, and child years, amongst other characteristics. Moreover, the risk of residual confounding, bias, and chance cannot be discarded. These flaws impede concluding on a causative mechanism, and the nature of the association remains unclear.

The U.S. National Toxicology Program (NTP) conducted a systematic review of the literature related to PFOS-induced immunotoxicity and concluded that PFOS is presumed to be an immune hazard to humans based on a moderate level of evidence in humans and a high level of evidence that PFOS suppresses the antibody response in experimental animals (see Section 9.2.2.1), and after considering biological plausibility (NTP, 2016).

9.1.2.3 Lipidemia

Significant associations between PFOS and increased total cholesterol and alteration of other lipid parameters have been reported. A cross-sectional study found no association between PFOS serum levels (range 20–2,110 ng/mL) of 3M Cottage Grove employees (Minnesota) participating in the medical surveillance exam (70% of them eligible for the study) and lipid parameters (data were not shown in the report) (Olsen et al., 2003b). Careful interpretation is required because the data for these results were not published. A longitudinal study conducted in workers involved in the demolition of perfluoroalkyl manufacturing facilities found no clear association between PFOS levels and serum lipids, although some level of association was found between PFOS and increased HDL (Olsen et al., 2012). Some limitations include the self-reporting of employees' characteristics, low participation rate, the possibility of exposure to other contaminants, and relatively short follow-up times. In contrast, an unpublished cross-sectional study found lower HDL values in male employees with the highest serum PFOS levels.

Another longitudinal study conducted in 560 adults (2005–2006 with follow-up in 2010) found a decrease in LDL and total cholesterol with decreased serum PFOS level (no changes for HDL or TG) (Fitz-Simon et al., 2013). The clinical significance is uncertain, given the low number of participants changing from the high to the normal level of cholesterol categories, the unknown mechanism of action, and the low magnitude of the changes. Cross-sectional studies within the C8 Health Project found increasing trends for total cholesterol, LDL, triglycerides, and the total cholesterol (TC)/HDL ratio with increasing PFOS (Steenland et al., 2009; Frisbee et al., 2010). A cross-sectional study of the general U.S. population indicated that adults in the highest serum PFOS quartile had higher TC levels than those in the lowest quartile (no association for serum LDL) (Nelson et al., 2010). In another cross-sectional study conducted in Inuits from Nunavik, a negative association was found between plasma PFOS level and triglycerides and the total cholesterol/HDL ratio, and a positive association was found with HDL levels (Château-

Degat et al., 2010). The clinical relevance of very small alterations in cholesterol levels is unclear. Increased PFOS exposure also resulted in increased uric acid in two occupational and one general population studies (reviewed by Steenland et al., 2010). Finally, no association between serum PFOS levels and metabolic function (i.e., insulin and glucose levels) or plasma lipids (measured as triglycerides, HDL, LDL, and total cholesterol) was found as measured in a subsample of Canadians as part of the CHMS (Cycle 1 2007 – 2009) (Fisher et al., 2013). Overall, associations between PFOS and alterations in lipid parameters have been observed; however, the conclusions are limited by the lack of consistency across studies, the study designs, the possibility of selection bias, and chance finding from the high number of testing conducted.

9.1.2.4 Thyroid disruption

Inconsistent effects on thyroid hormone levels were observed in PFOS-exposed populations. A cross-sectional study found no association between PFOS serum levels (range 20–2,110 ng/mL) of 3M Cottage Grove employees (Minnesota) participating in the medical surveillance exam (70% of them eligible for the study) and thyroid parameters (data were not shown in the report) (Olsen et al., 2003b). A cross-sectional study of the general population (C8 Health Project) indicated that PFOS was associated with an increase of serum total T4 (TT4) and a decrease of T3 uptake in both genders (Knox et al., 2011a). The association with PFOS and serum TT4 and T3 uptake was stronger in women, but lower than men for serum albumin. Another cross-sectional study conducted in the children enrolled in the C8 Health Project indicated a positive association between serum PFOS levels and increased TT4 levels (Lopez-Espinosa et al., 2012). Serum PFOS levels were not associated with prevalence of thyroid disease in a cross-sectional analysis of the general U.S. population (Melzer et al., 2010). However, men from the highest serum PFOS quartile were more likely to report current (treated) thyroid disease. A cross-sectional study conducted in the Inuit population of Nunavik found negative associations between serum PFOS and serum TSH, T3, and thyroxin-binding globulin, and a positive association between serum PFOS and serum free T4 (fT4) (Dallaire et al., 2009). A matched-case control study found no association between environmental exposure to PFOS and hypothyroidism (TSH and fT4 levels) in pregnant women from Edmonton, Canada (Chan et al., 2011). A negative correlation was found between PFOS levels in fetal and maternal serum and T3 in the general population in South Korea (Kim et al., 2011a). No association was found between PFOS and TSH in a small population of anglers in New York (Bloom et al., 2010).

Although associations between serum PFOS and TT4, fT4, T3 and TSH were observed, no clear trend for thyroid hormone changes related to PFOS exposure can be established because results were equivocal, it was not possible to calculate cumulative exposure, individuals with thyroid diseases were excluded, possibly biasing the results, and temporality cannot be established with the cross-sectional study design.

9.1.2.5 Kidney effects

An increased risk of chronic kidney disease (reduced estimated glomerular filtration rate) was reported in a cross-sectional study of the general U.S. population (Shankar et al., 2011). Causality will be difficult to be established for adverse kidney effects, as altered kidney function could cause an increase in serum PFOS levels.

9.1.3 Carcinogenicity

Some associations between PFOS and risk of cancer of the bladder, breast, male reproductive organs, and overall cancers were observed; however, the evidence does not support the carcinogenicity of PFOS. In an occupational study, PFAA workers (n = 2,083) were found to have an elevated risk for bladder cancer mortality in the City of Decatur, Alabama (Alexander et al., 2003). However, the authors reported that it was difficult to draw any definite conclusions because there were only 3 cases of bladder cancer and the workers were exposed to several compounds concurrently (all 3 cases were production workers considered at high PFOS exposure, and had also worked at the plant incinerator or wastewater treatment plant). Moreover, no adjustment was conducted for race, smoking or other contaminants; the exposure was based on job categories; the cases with bladder cancer were not the ones with the highest exposure; and there was a risk of selection bias, lowering the credibility of the results. In a follow-up study, there was no association between PFOS exposure and an increased risk of bladder cancer (Alexander and Olsen, 2007). In an earlier analysis of the same cohort, the risks for episodes of medical care for overall and male reproductive cancers were greatest in the group of employees with the highest and longest exposures to fluorochemicals (Olsen et al., 2001). A prospective cohort study was conducted in the general population of Denmark to investigate the possible association between PFOS exposure and cancer risk (Eriksen et al., 2009). No significant correlation was found between PFOS serum concentrations and the incidence of prostate, bladder, pancreas and liver cancer across quartiles of serum PFOS. Evidence of a relationship between PFOS and breast cancer was found in a small case–control study conducted in Greenlandic Inuit women. However, considering that the risk of breast cancer was increased in relation with several chemicals, confounding by other compounds or chemical groups may have played a role in the observed association (Bonefeld-Jorgensen et al., 2011).

~~Although~~ A systematic and critical review of epidemiological studies on the association between cancer risk in humans and PFOA and PFOS exposure concluded that the evidence does not support a causal association between cancer in humans and exposure to PFOA and PFOS (Chang et al., 2014). Thus, although some evidence of an association between PFOS and the risk of cancer has been observed, the effects were equivocal, and no clear trend could be determined due to limitations in the studies (small number of cases, confounding, and participant selection bias).

9.1.4 Developmental and reproductive toxicity

Recent epidemiological studies have observed effects on birth weight, developmental milestones, thyroid hormones, immune system, fecundity, and age of puberty, indicating that the fetus, neonate and young children may be considered as vulnerable sub-populations to prenatal and early life PFOS exposure (Apelberg et al., 2007; Stein et al., 2009; Washino et al., 2009; Andersen et al., 2010; Hoffman et al., 2010; Gump et al., 2011; Stein and Savitz, 2011; Maisonet et al., 2012).

9.1.4.1 Developmental toxicity

Inverse associations between PFOS at early pregnancy and birth weight have been reported in different general population studies. A cross-sectional study conducted by the C8 Science Panel found an association between serum PFOS levels and low birth weight at PFOS levels above the median (Stein et al., 2009). Lower birth weight and higher weight at 20 months

were observed in girls born from mothers with higher prenatal concentration of PFOS (who were previously selected for a nested case-control study of pubertal development among mothers enrolled in the Avon Longitudinal study of Parents and Children in Great Britain [ALSPAC]) (Maisonet et al., 2012). However, the results were of poor precision (–140 g, 95% CI: –238 to –42). Also, the analysis of a prospective cohort study in Japan (n = 230) indicated that birth weight of female neonates was negatively correlated with prenatal exposure to PFOS after adjustment for multiple covariates (Washino et al., 2009). Again, the results were of poor precision due to high variability in the dataset (infants were estimated to be 269 g lighter, with 95% CI ranging from 73 to 466), low participation rate (29%), and the possibility of measurement errors (as suggested by the authors). Small but significant negative associations were observed with head circumference, ponderal index, and birth weight in a cross-sectional study of the general population in Baltimore, Maryland (Apelberg et al., 2007). In contrast, no association between maternal levels of PFOS and any of the measured fetal growth indicators (placental weight, birth length and head and abdominal circumferences) was found in a random sample of women and their offspring in the Danish National Birth Cohort (Fei et al., 2008b). Other general population studies in Canada and Denmark found no associations between maternal serum PFOS levels and birth weight (Fei et al., 2007; Monroy et al., 2008; Hamm et al., 2010~~). PFAAs (including PFOS) were not associated with BMI and waist circumference in a prospective cohort study with long-term follow-up (20 years) among pregnant women recruited within the Danish National Birth Cohort and their male or female children (Halldorsson et al., 2012).~~; Ashley-Martin et al., 2017)). PFAS (including PFOS) were not associated with BMI and waist circumference in a prospective cohort study with long-term follow-up (20 years) among pregnant women recruited within the Danish National Birth Cohort and their male or female children (Halldorsson et al., 2012). Similarly, a systematic review of the epidemiological data conducted by Bach et al. (2015) concluded that the existing data are insufficient to confirm or reject an association between PFAS exposure and fetal growth.

In a trans-Canada cohort study, an inverse association between first-trimester maternal PFOS concentrations and cord blood concentrations of leptin and adiponectin was found using data on 1705 mother-infant pairs recruited as part of the Maternal Infant Research on Environmental Chemicals (MIREC) Study (Ashley-Martin et al., 2017). However, the study authors cautioned against generalizing these findings to other Canadian populations because the study participants were on average older, more educated, had higher incomes, and were less likely to smoke than other women giving birth in Canada.

PFOS-induced developmental health effects on thyroid and neurobehaviour have also been investigated. A negative correlation between maternal serum PFOS levels and fetal T3 levels was found in a small South Korean cross-sectional study (but not with TSH and TT4 levels or with birth weight) (Kim et al., 2011a). In the U.S. general population, a higher risk of parental report of diagnosis of attention deficit/hyperactivity disorder (ADHD) with higher levels of PFOS was found in children aged 12–15 years (Hoffman et al., 2010). In a cross-sectional study conducted within the C8 Health Project, no association was found between PFOS and the prevalence of parents who reported that a doctor diagnosed their child with ADHD or a teacher told them their child had a learning disorder (Stein and Savitz, 2011). No association was found between maternal serum PFOS and motor or developmental milestones (fine/gross motor, attention, cognition and language) in children aged 18 months (Fei et al., 2008a), or behavioral or motor coordination problems in children aged 7 years old (Fei and Olsen, 2011).

Although some effects on development have been observed in population studies, the evidence supporting a link between early-life exposure to PFOS and developmental toxicity is equivocal because most studies were not designed to allow causal inference. The most preoccupying evidence come from the prospective studies showing an increased risk of altered birth weight in Britain and Japan; however, the clinical significance of these findings is unclear, and other larger studies would be needed to support the results considering the poor precision of the point estimate, the relatively small size of the studies and the risk of confounding and bias.

9.1.4.2 Reproductive toxicity

The main findings suggest a possible link between PFOS exposure and reduced fecundity in cohort and case–control studies and delayed puberty; however, the quality of the evidence is limited and not sufficient to define the nature of the relationship.

A delay in the median age of puberty in both sexes was associated with PFOS concentrations in a cross-sectional study of individuals aged 8–18 years within the C8 Health Project (Lopez-Espinosa et al., 2011). The authors questioned the clinical significance of the results because the median age at puberty in this study was similar to the median age reported in the general U.S. population (12.5 vs 12.9 years), and the mechanisms behind the delayed onset of puberty are unclear. In another cross-sectional study on the same population, Lopez-Espinosa et al. (2016) reported significant inverse associations between PFOS serum concentrations and estradiol and testosterone in boys and testosterone in girls. PFOS exposure *in utero* was found to be slightly (but not significantly) associated with an increased odds of earlier puberty in girls participating in the aforementioned ALSPAC cohort (Christensen et al., 2011). The authors mentioned the results could be biased by the misclassification of exposure and selection of participants.

The influence of PFOS exposures on sperm parameter observations is inconsistent. Serum levels of PFOS were associated with a decreased number of normal sperm in young Danish men aged 18.2–25.2 years in a cross-sectional study (Joensen et al., 2009). A tendency toward reduced levels of all semen parameters (testosterone, free androgen, etc.) was also found in the highest quartile. However, there was a high risk of selection bias and chance findings. A positive association between serum PFOS and a lower proportion of morphologically normal sperm of pregnant partners was identified in the combined groups of three populations from Greenland, Poland, and Ukraine (Toft et al., 2012). A few significant associations with sperm concentration and total sperm count were found in the analyses based on single countries; however, there was no overall dose-response, the results are subject to the ecological fallacy, and the authors mentioned the results were likely due to chance findings. In a cross-sectional study conducted in men from Durham, NC, a positive correlation between plasma PFOS and serum LH levels was found, but there was no association with altered semen quality (Raymer et al., 2012). Maternal PFOS at pregnancy week 30 (*in utero* exposure) was not associated with sperm quality and serum reproductive hormones in male offspring at age 19–21 years in a pregnancy cohort in Denmark (Vested et al., 2013). In conclusion, no clear pattern of association between maternal PFOS levels and sperm quality can be established because of studies' inconsistencies, design limitations, and high risk of selection bias.

An association between PFOS exposure and a reduction in fecundity has been observed; however, the studies were not robust and the results are inconclusive. A reduction in fecundity (increased time to pregnancy and irregular menstrual periods) was found to be associated with the

plasma PFOS levels in 1,240 parous/nulliparous women from the Danish National Birth Cohort; however, the information for multiple confounders was omitted from the analysis (sperm quality, frequency of intercourse, etc.) (Fei et al., 2009). Increased relative odds of subfecundity (time to pregnancy greater than 12 months) was also reported in a case–control study on parous women enrolled in the Norwegian Mother and Child Cohort Study (no association in nulliparous women) (Whitworth et al., 2012). The lack of adjustment for confounders generates doubt on the validity of their observation. No association between serum PFOS and time to pregnancy or fecundity was found in nulliparous women in a longitudinal cohort study in Denmark (Vestergaard et al., 2012). In an Italian case–control study, couples affected by infertility tend to have higher PFOS levels and to have a higher gene expression of nuclear receptors involved in steroid and xenobiotics metabolism; however, the mechanism of action remains unclear (La Rocca et al., 2012).
The occurrence of self-reported preeclampsia in the Mid-Ohio Valley was associated with PFOS for exposure above the median; however, the results were of poor precision (Stein et al., 2009). A significant inverse association was found between PFOS and serum estradiol levels in perimenopausal and menopausal age groups of women from the C8 Health Project; however, temporality cannot be established with the study design (Knox et al., 2011b).

A prospective cohort study recruited 1,400 pregnant women (randomly out of 43,045) within the Danish National Birth Cohort (DNBC, 1988–1989) and measured PFOS concentration in their plasma (Fei et al., 2010b). Duration of breastfeeding was reported 6 and 18 months after birth by phone interviews. The risk of breastfeeding for a shorter period was higher with increasing plasma PFOS concentrations. For example, the risk (adjusted hazard ratio) of shorter breastfeeding duration (weeks) for women with plasma PFOS > 43.3 ng/mL was 1.4 (95% CI 1.2-1.6) times higher than for those with plasma PFOS 6.4-26.6 ng/mL, after adjusting for maternal age at delivery, pre-pregnancy BMI, maternal socioeconomic status, alcohol consumption and smoking (the trend for an increase in risk with increasing four-quartile comparison was also significant). Also, the odds (adjusted odds ratio) of weaning before 6 months of age was 1.20 (95% CI: 1.1–1.4) times higher for each 10 ng/mL increase in plasma PFOS when restricting the model to multiparous women (not significant in primiparous women), after statistical adjustments. A similar association was observed with weaning before 3 months of age. However, more studies would be needed to support these results, since PFOS plasma concentration was measured only one time, only 18% of eligible women participated in the DNBC study, there is a risk of outcome recall bias (mothers might not report accurately the date of weaning), and the authors did not rule out the possibility that reverse causation could explain the association (considering that women that have breastfed longer can be more likely to breastfed longer their next infants, and that PFOS is excreted in breast-milk, lowering the plasma concentration).

Correlations and associations have been observed between PFOS and altered birth weight, fecundity, fertility, sperm quality, preeclampsia, shorter duration of breastfeeding, and thyroid hormones. However, the evidence remains insufficient to clarify the nature of the relationship due to the lack of consistency across studies, important limitations in study design, and risk of bias and confounding.

9.2 Effects on experimental animals

The vast majority of animal studies stated that PFOS exposure was performed using the potassium salt of PFOS (K^+PFOS), with the exception of studies by Qazi et al., which used the tetraethylammonium salt (Qazi et al., 2010b) or tetrabutylammonium salt (Qazi et al., 2009b,

2010a) of PFOS. Studies that did not state the specific salt used in their study were assumed to have used the potassium salt, as this was the most common compound used. Most of the studies did not state whether the administered dose referred to the K^+PFOS compound, or specifically to the PFOS ion; only one study (Peden-Adams et al., 2008) stated that the doses reflect the concentration of PFOS ion, separate from the potassium salt. The summaries described herein use the concentrations and doses stated by authors. This approach is also used for quantitative assessments; however, as the PFOS ion contributes to 93% of the molar weight of K^+PFOS and is released from the compound upon exposure, only minor quantitative differences would result from using K^+PFOS and PFOS doses interchangeably.

9.2.1 Acute toxicity

A mean oral LD_{50} value of 251 mg/kg bw was calculated for male and female CD rats based on a single administration of PFOS (100–1,000 mg/kg bw) by gavage (5/sex/group) (Dean and Jessup, 1978). An inhalation LC_{50} of 5,200 mg/m^3 was determined in Sprague-Dawley rats (5/sex/group) exposed to PFOS dust in air (1,890–45,970 mg/m^3) for one hour (Bio/Dynamics, 1979; Rusch, 1979).

Single oral exposure of rodents (rats and mice) to PFOS at ≥ 250 mg/kg bw was shown to cause tonic convulsions when ultrasonic stimulus was applied to the animals (Sato et al., 2009). PFOS alone did not cause neurotoxic symptoms, morphological changes or physiological alteration (hormone concentration). Although the convulsive effect was observed at very high doses, it is considered as neurotoxicity induced by PFOS because the same ultrasonic stimulus did not cause convulsions in control animals or in animals treated with PFOA.

Skin irritation was not observed in albino New Zealand White rabbits dermally exposed to PFOS (Biesemeier and Harris, 1974). Severe eye irritation was reported in rabbits (0.1 mL ocular application, washout after 5 or 30 seconds) (Riker Laboratories Inc., 1981). Additional studies reported mild to moderate eye irritation after ocular PFOS exposure (Biesemeier and Harris, 1974; Warf Institute Inc., 1975; Hazleton Laboratories America Inc., 1987; Hazleton Wisconsin Inc., 1994; Corning Hazleton Inc., 1997).

Acute developmental neurobehaviour studies are discussed in Section 9.2.5.

9.2.2 Short-term exposure

Studies documenting the toxicity of PFOS after short-term oral exposure identified four main targets, namely the immune system, the liver, serum lipids and thyroid. The immune system appears to be the most sensitive target, with a LOAEL of 0.00166 mg/kg bw per day and a NOAEL of 0.000166 mg/kg bw per day in mice (Peden-Adams et al., 2008). The lowest LOAELs for hepatic, lipid, and thyroid effects were 0.024 mg/kg bw per day (Butenhoff et al., 2012b), 0.03 mg/kg bw per day (Seacat et al., 2002), and 0.15 mg/kg bw per day (Seacat et al., 2002), respectively. This section will focus primarily on these key effects observed at the lowest levels, and will only briefly discuss other types of changes observed in animals.

9.2.2.1 Immune system effects

Immune system effects observed at the lowest levels tend to indicate that immunosuppression is the effect of greatest concern. Studies designed to identify the effects of PFOS on the immune system measured mortality from infection, changes in levels of immunoglobulins and cytokines, activity levels of immune cells, and lymphocyte phenotype and

proliferation. In studies that were not designed to specifically study immunological effects (i.e. higher dose bioassays), more general immune system toxicity was measured as decreases in white blood cell counts, and organ weight and histological changes in the spleen and thymus. The various immune system effects were reported only in mice and rats, with no immunotoxicity studies designed for other species.

The IPCS (2012) has presented a continuum of the strength of evidence provided for various types of data that could suggest the occurrence of immunosuppression. In animal studies, host resistance data and immune function data (including antibody production and NK cell function) provide the strongest weight of evidence for immunotoxicity. Data from observational immune assays (including lymphocyte phenotype and proliferation, and changes in cytokine levels), as well as evidence of changes in haematology and organ histopathology and weight, are all classified as providing equivocal evidence of immunosuppression. This section will discuss the effects in order from strongest to weakest weight of evidence for immunosuppression. Because several studies for PFOS provide evidence of decreased host resistance and immune function, these studies will form the greater focus of this section.

Only one study investigated the effect of PFOS on host resistance (i.e. the top tier in the IPCS framework) to infections. In the study, female B6C3F1 mice were exposed to PFOS at gavage doses of 0, 0.005 or 0.025 mg/kg bw per day for 21 days, and subsequently innoculated with Influenza A virus (Guruge et al., 2009). Increased mortality from Influenza A infection was observed in mice exposed to 0.025 mg/kg bw per day. Although B6C3F1 appears to be a strain of mice that is sensitive to PFOS effects, female mice have been demonstrated to be less sensitive than males to other immune outcomes arising from PFOS exposure.

The U.S. NTP (2016) concluded that there is high confidence that exposure to PFOS is associated with antibody response suppression in animals based on consistent suppression of primary antibody response in mice. The most sensitive effect observed in animal studies in the IPCS category of immune function data was the suppression of T-dependent antigen response (TDAR) for IgM, using sheep red blood cell (SRBC) as an antigen. The lowest LOAEL on this effect was 0.00166 mg/kg bw per day (NOAEL of 0.000166 mg/kg bw per day; Peden-Adams et al., 2008), and decreases tended to have clear dose dependence in most studies. The effect was observed at the lowest levels in adult mice in three studies described below:

- At ≥0.00166 mg/kg bw per day in male and ≥0.0166 mg/kg bw per day in female B6C3F1 mice (n = 5/dose) exposed through oral gavage (doses of K^+PFOS: 0, 0.000166, 0.00166, 0.00331, 0.0166, 0.0331 or 0.166 mg/kg bw per day) for 28 days (Peden-Adams et al., 2008).
- At ≥0.083 mg/kg bw per day in male C57BL/6 mice (n = 10/dose) exposed by oral gavage (to doses of 0, 0.00833, 0.0833, 0.417, 0.833, and 2.083 mg/kg bw per day) for 60 days (Dong et al., 2009).
- At ≥0.083 mg/kg bw per day in male C57BL/6 mice (n = 6/dose) exposed by oral gavage (to doses of 0, 0.00833, 0.0167, 0.0833, 0.417, and 0.833 mg/kg bw per day) for 60 days (Dong et al., 2011).

SRBC-specific IgM decreases were also observed at 5 mg/kg bw per day (but not 1 mg/kg bw per day) in male B6C3F1 mice exposed prenatally to PFOS on GD 1–17 (Keil et al., 2008). Moreover, decreases in non-specific serum IgM were observed at ≥5 mg/kg bw per day in male C57BL/6 mice exposed to 5 or 20 mg/kg bw per day for 7 days (Zheng et al., 2011).

In contrast, a study exposing male C57BL/6 mice to 0.25 mg/kg bw per day (as the tetraethylammonium salt of PFOS; no other dose levels were used in the study) for 28 days did not find any change in serum levels of anti-SRBC or anti-TNP–LPS IgM, nor in the number of splenic cells secreting anti-SRBC IgM (Qazi et al., 2010b).

PFOS-induced changes in serum levels of other immunoglobulins—which also fall under the IPCS category of immune function data—were observed at higher exposure levels. In contrast with IgM levels, IgG and IgE levels tended to be increased after PFOS exposure. In male C57BL/6 mice, increased SRBC-specific IgE and IgG were observed at the highest dose (0.833 mg/kg bw per day; see more detailed study description above) (Dong et al., 2011). Increases in non-specific serum total IgG were observed at 5 mg/kg bw per day—but not 20 mg/kg bw per day—in male C57BL/6 mice exposed to PFOS for 7 days (Zheng et al., 2011). A study of male rats exposed to 0.14–6.34 mg/kg bw per day (Lefebvre et al., 2008) explored the effects of PFOS on various IgG subtypes; the study found a significant trend for increased total serum IgG2a and IgG2c and secondary T-dependent IgG response (using KLH as an antigen). Total serum IgG1 was decreased in male rats exposed only to the two lowest doses (0.14 and 1.33 mg/kg bw per day).

The final effect in the IPCS category of immune function data was altered splenic natural killer (NK) cell activity, which was observed to be altered in mice in studies previously described above; activity tended to be increased at the lowest doses and decreased at higher doses. Decreased splenic NK cell activity was observed in male B6C3F1 mice exposed to 0.0166–0.166 mg/kg bw per day (Peden-Adams et al., 2008). In Dong et al. (2009), non-monotonic changes in the activity were observed in male C57BL/6 mice, with increases at 0.083 mg/kg bw per day, no effects at 0.417 mg/kg bw per day, and decreases at 0.833 and 2.083 mg/kg bw per day. Splenic NK cell activity was decreased in male mice exposed prenatally to ≥1 mg/kg bw per day (Keil et al., 2008) and adult male mice exposed to ≥20 mg/kg bw per day for 7 days (Zheng et al., 2009). In female mice, no changes in activity were observed at doses up to 0.166 mg/kg bw per day (Peden-Adams et al., 2008), but decreased NK cell activity was observed in those exposed prenatally to 5 mg/kg bw per day (Keil et al., 2008).

Additional immunological effects observed in studies of PFOS exposure were described by IPCS as types of data that provide only equivocal evidence of immunosuppression. Although the data support the PFOS-induced immune suppression described above, they are described only briefly as they are not robust enough to be used as a basis for a drinking water quality guideline. The observed effects were as follows (with IPCS classifications indicated in brackets):

- Alterations in subpopulations of B-cell, T-cell, and presenting antigen cells in the spleen and thymus in male and female mice, with a lowest LOAEL of 0.00331 mg/kg bw per day (Keil et al., 2008; Peden-Adams et al., 2008; Dong et al., 2009; Qazi et al., 2009b; Zheng et al., 2009). No effects on blood lymphocyte phenotype were observed in rats exposed to ≤7.58 mg/kg bw per day (Lefebvre et al., 2008) [observational immune assays].
- Alterations in levels of various cytokines in male and female mice, with a lowest LOAEL of 0.0031 mg/kg bw per day (Qazi et al., 2010a; Dong et al., 2011, 2012b; Fair et al., 2011; Mollenhauer et al., 2011; Zheng et al., 2011). The nature of effects was described by Zheng et al. (2011) and Dong et al. (2011) as appearing to create an excessive Type 1 response and deficient Type 2 response (i.e. a predominance in humoral immunity and deficiency in cell-mediated immunity, which can lead to a decreased ability to fight intracellular pathogens and cancerous cells [Guruge et al., 2009; Zheng et al., 2011]) [observational immune assays].

- Decreased cellularity and lymphocyte proliferation in male mice, with a lowest LOAEL of 0.417 mg/kg bw per day (Dong et al., 2009, 2012b; Qazi et al., 2009b) [observational immune assays].
- Reduced leukocyte counts in rats at ≥6 mg/kg bw per day (Goldenthal et al., 1978a) [haematological data].
- Evidence of increased apoptosis in spleen and thymus, at ≥0.0833 mg/kg bw per day in mice (Wang et al., 2011b; Dong et al., 2012a; Zhang et al., ~~2013~~2013b) and ≥3.21 mg/kg bw per day in rats (Lefebvre et al., 2008) [histopathological data].
- Histological effects in thymus and spleen at ≥5 mg/kg bw per day in mice (Qazi et al., 2009b; Wang et al., 2011b; Zhang et al., ~~2013~~2013b) and ≥18 mg/kg bw per day in rats (Goldenthal et al., 1978a; Cui et al., 2009) [histopathological data].
- Decreased absolute and/or relative weight of thymus and spleen at ≥0.417 mg/kg bw per day in male mice (Dong et al., 2009, 2012a; Qazi et al., 2009b; Zheng et al., 2009, 2011) and at 0.984 mg/kg bw per day in male rats (Butenhoff et al., 2012b) [organ weight data].
- Increased serum corticosterone in male mice at 0.25 mg/kg bw per day (Qazi et al., 2010b) and ≥20 mg/kg bw per day (Zheng et al., 2009, 2011), but not at ≤0.833 mg/kg bw per day (Dong et al., 2011) [not classified by IPCS, but supportive data].

Sensitivity to immunological effects appears to be dependent on several factors. The influence of species on effects is difficult to ascertain, as only one rat study was specifically designed to measure immune effects (Lefebvre et al., 2008); however, the NOAEL in the study was several orders of magnitude higher than some of the LOAELs from mouse studies (Peden-Adams et al., 2008; Dong et al., 2009, 2011). Even within a single species, differences in sensitivity might occur among strains—effects on SRBC-specific IgM levels and splenic NK cell activity have been observed at lower levels in B6C3F1 mice (Peden-Adams et al., 2008) than in C57BL/6 mice (Dong et al., 2009, 2011), even after a shorter duration of exposure (28 days vs. 60 days). Moreover, these effects were observed at lower levels in males than in females (Peden-Adams et al., 2008). However, there are no indications that pre-natally exposed mice are more sensitive to immunological effects than adults, as changes in SRBC-specific IgM response and splenic NK cell activity were not observed at ≤1 mg/kg bw per day in male mice exposed *in utero* on GD 1–17 (Keil et al., 2008), whereas LOAELs for these effects were <0.1 mg/kg bw per day in adult mice (Peden-Adams et al., 2008; Dong et al., 2009, 2011).

9.2.2.2 Hepatic effects

The hepatic effects occurring at the lowest levels in short-term studies were increases in liver weight. Histological changes in the liver and increases in serum enzymes that are indicators of adverse hepatic effects were also observed at higher levels.

Increased liver weight (absolute or relative) was observed in studies of varying durations, with lowest LOAELs at:

- 0.0833 mg/kg bw per day in C57BL/6 mice (10/dose) exposed via gavage for 60 days to 0.00833, 0.0833, 0.417, 0.833, and 2.083 mg/kg bw per day (Dong et al., 2009). The effect was also observed at higher doses in many other mouse studies (Thibodeaux et al., 2003; Yahia et al, 2008; Era et al., 2009; Qazi et al., 2009b, 2010a, 2010b; Zheng et al., 2009, 2011; Dong et al., 2011, 2012a; Wan et al., 2011; Wang et al,. 2011b; Zhang et al., ~~2013~~2013b). Conversely, no increase in liver weight was observed in mice exposed up to

0.166 mg/kg bw per day for 28 days (Fair et al., 2011), 10 mg/kg bw per day for 7 days (Wan et al., 2011), or 10.5 mg/kg bw per day for 4 days (Abbott et al., 2009);

- 0.15 mg/kg bw per day in female and 1.33 mg/kg bw per day in male Sprague-Dawley rats (15/group) with exposure to 2, 20, 50, or 100 ppm PFOS in feed (0.14, 1.33, 3.21, and 6.34 mg/kg bw per day in males and 0.15, 1.43, 3.73, and 7.58 mg/kg bw per day in females) for 28 days (Lefebvre et al., 2008). The effect was also observed at higher doses in many other rat studies (Goldenthal et al., 1978a; NOTOX, 1999; Seacat et al., 2003; Thibodeaux et al., 2003; Cui et al., 2009; Yu et al., 2009a; Elcombe et al., 2012a);
- 0.75 mg/kg bw per day in monkeys (n=6) with exposure to 0.03, 0.15, and 0.75 mg/kg bw per day by oral bolus dose (Seacat et al., 2002).

Increased fetal liver weight was also observed in developmental studies; this effect is described in Section 9.2.5.

Increases in histological effects were observed in short-term studies. The study in which the effects were observed at the lowest levels (Seacat et al., 2003) was of rats in 4- and 14-week early sacrifice groups of a 2-year dietary study (Butenhoff et al., 2012b; histological effects in the liver in this study are summarized in Section 9.2.3). The LOAELs in the 4-week study were 0.37 mg/kg bw per day in males and 1.77 mg/kg bw per day in females; in the 14-week study, the values were 0.34 mg/kg bw per day in males and 1.56 mg/kg bw per day in females. Hepatic hypertrophy and cytoplasmic vacuolation were observed in these dose groups. Similar effects were observed at higher doses in other rat studies (Elcombe et al., 2012a; Goldenthal et al., 1978a; NOTOX, 1999; Cui et al., 2009), and in studies of monkeys (Seacat et al., 2002). Additional hepatic gross and histological effects observed at higher doses included:

- Brown liver in male rats exposed to 3.2 mg/kg bw per day (Christian et al., 1999);
- Fatty changes in male rats exposed to ≥5 mg/kg bw per day (Kim et al., 2011b); and
- Focal or flakelike necrosis at ≥5 mg/kg bw per day and focal hemorrhage, erythrocytic transudation, and focal hepatocytic degeneration accompanied by inflammatory cellular infiltration at 20 mg/kg bw per day in male rats (Cui et al., 2009).

Serum enzymes that are potential indicators of adverse liver effects were increased in several studies. ALT was increased in male rats exposed to 1.33 mg/kg bw per day for 14 weeks in diet (Seacat et al., 2003). Increased AST and ALT was also observed in rats exposed to 6 mg/kg bw per day (Goldenthal et al., 1978a). Conversely, no significant increases in serum ALT or AST were observed in rats exposed up to 9.65 mg/kg bw per day for 7 days (Elcombe et al., 2012a). Decreased serum bilirubin and increased serum bile acids were also observed in male monkeys exposed to 0.75 mg/kg bw per day (Seacat et al., 2002). Increased serum alkaline phosphatase was observed in male mice exposed to 0.005% PFOS in feed (approximately 6.5 mg/kg bw per day, using Health Canada's default assumption that 1 ppm in feed is equivalent to 0.13 mg/kg bw per day in mice [Health Canada, 1994]) (Qazi et al., 2010a). A slight decrease in serum alkaline phosphatase was observed in male monkeys exposed to 0.5 mg/kg bw per day (but not 1.5 or 4.5 mg/kg bw per day) for 90 days (Goldenthal et al., 1978b).

9.2.2.3 Serum lipid effects

Decreased total cholesterol and HDL cholesterol were the serum lipid effects observed at the lowest levels in short-term studies; the various serum lipid measurements were decreased in

monkeys, mice, and rats in the vast majority of studies that considered these endpoints. Decreased LDL and triglycerides were also measured in various studies. The lowest LOAEL for this endpoint was 0.03 mg/kg bw per day.

The LOAEL of 0.03 mg/kg bw per day for this endpoint was observed in a longer duration (26 week) study conducted in male and female Cynomolgus monkeys (4-6 animals per group) administered PFOS (0, 0.03, 0.15, or 0.75 mg/kg bw per day) by oral intubation of PFOS in a capsule (Seacat et al., 2002). Serum concentrations of cholesterol and triglycerides were measured before treatment and at several time points during treatment (Day 37, 62, 91, 153 and 182); HDL cholesterol was only analyzed on days 153 and 182. The changes considered consistent and statistically/biologically significant by the authors were decreased total cholesterol in both sexes at 0.75 mg/kg bw per day and decreased HDL (at 0.03 and 0.75 mg/kg bw per day in males, 0.15 and 0.75 mg/kg bw per day in females). At various time points following treatment at the lowest dose level (0.03 mg/kg bw per day), cholesterol levels were statistically significantly decreased compared to controls in male and female monkeys, and HDL levels were decreased in male monkeys, with no clear dose or time relationship. Lower levels of HDL (females) were observed at 0.15 mg/kg bw per day. Based on their statistical analyses, the investigators concluded that the NOAEL in this study was 0.15 mg/kg bw per day (LOAEL of 0.75 mg/kg bw per day) (Seacat et al., 2002).

However, both EFSA and Health Canada proposed different interpretations of the findings by Seacat et al. (2002). EFSA (2008) considered that the changes in HDL observed at this dose level were treatment-related and therefore concluded that it was justified to consider 0.03 mg/kg bw per day as a NOAEL (LOAEL of 0.15 mg/kg bw per day). Health Canada (2013c) considered that the statistical approach used in the original study (Seacat et al., 2002) was inadequate to interpret measures carried out repeatedly throughout the study and instead used linear mixed models to assess the effects of dose on these endpoints (TG, HDL, and cholesterol). Based on these models, Health Canada assessed the effect of dose and days on each endpoint and found a significant effect ($p = 0.0003$ to $p < 0.0001$) of dose on cholesterol and HDL in both sexes. There was no dose effect on the TG endpoint among both males and females, although when one outlier point for TG in males was removed, an overall significance between dose groups was observed ($p = 0.0213$). Differences between days were generally observed in all endpoints in both males and females. Results from Dunnett's pair wise test comparing treatment groups to control group indicate a statistically significant difference at ≥0.03 mg/kg bw per day for HDL in males, at ≥0.15 mg/kg bw per day for decreased cholesterol (females) and at 0.75 mg/kg bw per day for decreased cholesterol in males (for TG, only the lowest group was different from control when the outsider data point was removed). The time–dose interaction was significant for cholesterol in females (Health Canada, 2013c). Based on this statistical analysis, the LOAEL should be 0.03 mg/kg bw per day for decreased HDL in males (no NOAEL) and 0.15 mg/kg bw per day for decreased total cholesterol (NOAEL: 0.03 mg/kg bw per day).

The other monkey study for PFOS (Goldenthal et al., 1978b) also observed a significant reduction in serum cholesterol, at 4.5 mg/kg bw per day after 90 days of exposure. In a lower dose group (1.5 mg/kg bw per day), one of the female monkeys (i.e., half of the females in the dose group) had very low serum cholesterol.

Decreases in serum lipid parameters were also observed in other species. The LOAEL in mice was 0.166 mg/kg bw per day for total cholesterol in animals exposed for 28 days, with a NOAEL of 0.0331 mg/kg bw per day (Fair et al., 2011). Decreased triglycerides were observed at

≥5 mg/kg bw per day in mouse dams exposed to PFOS on GD 1–17 (Thibodeaux et al., 2003). Total cholesterol and triglycerides were also decreased in mice exposed to 0.005% PFOS in feed (sole treatment group; approximately 6.5 mg/kg bw per day, using Health Canada's default assumption that 1 ppm in feed is equivalent to 0.13 mg/kg bw per day in mice [Health Canada, 1994]) (Qazi et al., 2010a). Bijland et al. (2011) attributed PFOS-induced reductions in plasma triglycerides and total cholesterol to PFOS's ability to both (i) lower VLDL as a result of decreased hepatic VLDL-triglycerides production and increased VLDL-triglycerides clearance, and (ii) lower HDL as a result of decreased production and maturation in APOE*3-Leiden.CETP mice, which exhibit human-like lipoprotein metabolism and attenuated clearance of apopliprotein B containing lipoproteins.

In rats, the lowest LOAEL of 0.4 mg/kg bw per day was observed in dams exposed beginning 42 days prior to mating, until either gestational day 20 (for rats delivering by Caesarean section) or lactation day 4 (for rats delivering naturally; Luebker et al., 2005b). At this dose, total serum cholesterol was decreased; serum triglycerides were decreased only at ≥1.6 mg/kg bw per day. These effects were supported by decreased serum cholesterol (Seacat et al., 2003; Thibodeaux et al., 2003; Elcombe et al., 2012a) and decreased triglycerides (Thibodeaux et al., 2003; Elcombe et al., 2012a) in rats exposed to higher doses of PFOS.

Decreased liver cholesterol and triglycerides were also observed at the lowest dose in which this endpoint was studied (1.6 mg/kg bw per day, in rats dams in a developmental study; Luebker et al., 2005b).

9.2.2.4 Thyroid effects

A LOAEL of 0.15 mg/kg bw per day for altered thyroid hormone levels was observed in male and female Cynomolgus monkeys (4–6 animals per group) administered potassium PFOS (0, 0.03, 0.15, or 0.75 mg/kg bw per day) for 26 weeks by oral intubation of PFOS in a capsule (Seacat et al., 2002). Serum concentrations of TSH and free and total T3 and T4 were measured before treatment and at several time points during treatment (Day 37, 62, 91, and 182). The thyroid hormone changes considered consistent and statistically/biologically significant by the authors were increased TSH and decreased TT3 in males and females at 0.75 mg/kg bw per day. At 0.15 mg/kg bw per day, the changes observed included increased levels of TSH (males) and lower T3 concentrations (males and females). Some changes in T4 were also observed, but they were not consistent (including inconsistencies in direction). Based on the authors' statistical analysis, they stated that the LOAEL for thyroid hormone changes was 0.75 mg/kg bw per day (NOAEL = 0.15 mg/kg bw per day).

However, as was described for serum lipid effects, Health Canada & EFSA performed reinterpretations of the Seacat et al. (2002) results. EFSA considered that the changes in thyroid hormones observed at 0.15 mg/kg bw per day were treatment-related and therefore concluded that it was justified to consider 0.03 mg/kg bw per day as a NOAEL (LOAEL of 0.15 mg/kg bw per day) (EFSA, 2008). Health Canada's reanalysis (2013c) was similar to that described for the serum lipid parameters (Section 9.2.2.3). Results from Dunnett's pair wise test comparing treatment groups to control group indicate a statistically significant difference at ≥ 0.15 mg/kg bw per day for decreased TT3 (both sexes) and decreased TT4 (females only). The time–dose interaction was significant for T3, T4 and TSH in males and for T4 in females (Health Canada, 2013c). Based on this statistical analysis, the LOAEL is considered to be 0.15 mg/kg bw per day for decreased TT3 and TT4 (NOAEL: 0.03 mg/kg bw per day).

The LOAEL for changes in thyroid hormones in rats was similar to that for monkeys. In a developmental study (Wang et al., 2011a), the effects were observed in rat dams exposed from GD 1 to PND 14 to 3.2 ppm of PFOS in feed (0.16 mg/kg bw per day using Health Canada's default assumption that 1 ppm in feed is equivalent to 0.05 mg/kg bw per day in rats [Health Canada, 1994], an assumption that might not be relevant in pregnant rats). The LOAEL was for dose-dependent decreases in T4; T3 was observed to be reduced only at a higher dose. In other rat studies of 5–91 days, decreases in T4 and T3 were observed, with the former effect being more sensitive (Yu et al., 2009a, 2011; Luebker et al., 2005b; Thibodeaux et al., 2003~~)~~.; Martin et al., 2007). The effects were primarily measured on total levels of the hormones, with some studies also measuring effects on levels of free T4 and T3. No effects on TSH were observed in rat studies. In investigating the mechanisms underlying these changes to thyroid hormones in rats following oral exposure to PFOS. Chang et al. (2008) showed that PFOS transiently increases tissue availability of the thyroid hormones and turnover of T4 with a resulting reduction in serum tetraiodothyronine but concluded that PFOS does not induce a hypothyroid state or alter the function of the hypothalamic-pituitary-thyroid axis.

Few mouse studies measured changes in thyroid hormones. A dose-dependent, but transient, decrease in total T4 was observed to be significant at 20 mg/kg bw per day in dams exposed GD 1–17 (Thibodeaux et al., 2003), but no effect on serum T3 or T4 levels was measured in mice exposed to up to 0.166 mg/kg bw per day for 28 days (Fair et al., 2011).

Changes in thyroid hormone levels were observed in rat and mouse pups exposed *in utero* to PFOS; these effects are described in Section 9.2.5.

No changes in thyroid follicular cell proliferation index was observed in male Sprague-Dawley rats exposed to K^+PFOS (20 or 100 ppm in diet) for 7 days (1.9 or 9.6 mg/kg bw per day), when measured at various timepoints (1 day after cessation of exposure or after recovery periods of 28, 56, or 84 days (Elcombe et al., 2012a).

9.2.2.5 Other short-term effects

A wide variety of other short-term effects were observed for PFOS. These effects are described below, albeit only briefly as they occurred at higher levels than immune, hepatic, serum lipid, or thyroid effects.

Decreased body weight (or body weight gain) was a common observation in a wide variety of studies. The effect was observed in rats at ≥0.4 mg/kg bw per day (Goldenthal et al., 1978a; Gortner, 1980; Wetzel, 1983; Christian et al., 1999; NOTOX, 1999; Grasty et al., 2003; Thibodeaux et al., 2003; Luebker et al., 2005a; Butenhoff et al., 2009; Cui et al., 2009; Kawamoto et al., 2011; Xia et al., 2011; Elcombe et al., 2012a); in mice at ≥0.4167 mg/kg bw per day (Yahia et al., 2008; Dong et al., 2009, 2011, 2012b; Era et al., 2009; Wan et al., 2011); and in rabbits at ≥1 mg/kg bw per day (Case et al., 2001). Contributing to this effect might be decreased food consumption, which was observed at ≥0.4 mg/kg bw per day in rats (Goldenthal et al., 1978a; Wetzel, 1983; Christian et al., 1999; Thibodeaux et al., 2003; Cui et al., 2009), ≥0.4167 mg/kg bw per day in mice (Yahia et al., 2008; Dong et al., 2011, 2012b), and ≥5 mg/kg bw per day in rabbits (Case et al., 2001).

Few studies demonstrated increases in mortality in adult animals. In monkeys, deaths were observed in all males in the 4.5 mg/kg bw per day group in a 90 day study (Goldenthal et al., 1978b), and in 2 (out of 6) males exposed to 0.75 mg/kg bw per day for 6 months (Seacat et al., 2002). Increased mortality was also observed in rats at ≥6 mg/kg bw per day (Goldenthal et al.,

1978a; Wetzel, 1983; Grasty et al., 2005b; Cui et al., 2009), and in rabbits at ≥20 mg/kg bw per day (Case et al., 2001).

Other general effects observed included localized alopecia in rats (Christian et al., 1999) and soft stool, diarrhea, anorexia, emesis, and twitching, trembling and convulsions in monkeys (Goldenthal et al., 1978b).

A few neurotoxicity endpoints were observed in PFOS-exposed mice. Worsened performance was observed in neurobehavioural tests, including the water maze (at ≥2.15 mg/kg bw per day [Long et al., 2013], and 3 mg/kg bw per day, but not 6 mg/kg bw per day [Fuentes et al., 2007c]), and transient effects in the open field test (3 mg/kg bw per day) and number of rearings (6 mg/kg bw per day) (Fuentes et al., 2007c). However, the transient effects were both observed only on the same day, leading authors to conclude that the effects might be related to increased anxiety. Increased apoptosis (at ≥2.15 mg/kg bw per day) and glutamate levels (at 10.75 mg/kg bw per day) were observed in the hippocampus (Long et al., 2013). Increased expression of CaM-KIIα, pCREB, c-fos and c-jun was also observed in rat cortex and hippocampus at ≥1.7 mg/L in drinking water (0.238 mg/kg bw per day using Health Canada's default assumption that 1 ppm in water is equivalent to 0.14 mg/kg bw per day in rats [Health Canada, 1994]) (Liu et al., 2010a).

Neurotoxicity was also observed in rats. Reductions in activity and lethargy were observed at ≥5 mg/kg bw per day (Cui et al., 2009). Histological effects in the brain were also observed at ≥20 mg/kg bw per day (Cui et al., 2009), but not at levels of up to approximately 7 mg/kg bw per day (Kawamoto et al., 2011). Co-exposure with ultrasonic stimulation induced tonic convulsion (no tonic convulsion was induced by PFOS alone) after exposure to approximately 7 mg/kg bw per day (Kawamoto et al., 2011).

Renal effects from PFOS exposure were limited to increased BUN in male and female rats (with a LOAEL of 1.33 mg/kg bw per day; Seacat et al., 2003) and increased relative kidney weight at (at ≥5 mg/kg bw per day) in rats (Goldenthal et al., 1978a; Cui et al., 2009).

Respiratory tract effects—including pulmonary congestion, thickened epithelial walls, cell infiltration, and vasodilation—were observed at 5 and 20 mg/kg bw per day, with worsened severity at the high dose (Cui et al., 2009). Laboured breathing and bloodstains around the nose were also reported for the high dose in the study.

9.2.3 Long-term exposure and carcinogenicity

Only one chronic bioassay has been performed for PFOS. The study exposed Sprague-Dawley rats to dietary K^+PFOS (0, 0.5, 2, 5 and 20 ppm in feed) for 2 years (mean daily doses: 0, 0.024, 0.098, 0.242 and 0.984 mg/kg bw per day for males; 0, 0.029, 0.120, 0.299 and 1.251 mg/kg bw per day for females) (Butenhoff et al., 2012b). A recovery group (20 ppm Rec.) was also exposed to the high dose diet for the first 52 weeks and then fed with control diet (mean daily doses: 1.144 and 1.385 mg/kg bw per day for male and female respectively). Early sacrifice was also performed at weeks 4 and 14; the observations at these time points are presented throughout Section 9.2 (as Seacat et al., 2003).

Liver was identified as the principal target site in males (a LOAEL of 0.5 ppm or 0.024 mg/kg bw per day was identified by the study authors; no NOAEL was identified). The suggested LOAEL was based on significant increased incidence of cystic degeneration in the liver in all dose groups. However, the incidence of cystic degeneration was similar among exposed groups (ranging from 27-38%) with no dose-related increases, and generally fell within the range of

spontaneous development of cystic degeneration in male rats, which is as high as 34% (Karbe and Kerlin, 2002). Other effects in the liver of males at higher doses (≥ 0.098 mg/kg bw per day) include significant increased incidence and severity of centrilobular hepatocytic hypertrophy, eosinophilic hepatocytic granule, centrilobular hepatocytic pigment, hepatocyte necrosis, and midzonal/centrilobular hepatocytic vacuolation. Most effects were observed to be reversible, as they were observed at levels similar to controls in the recovery group; however, incidence of cystic degeneration and hepatocyte necrosis were similar in the recovery group, indicating that the effect persisted even after exposures had been ceased for one year. Decreased mortality (statistically significant at 5 and 20 ppm) and changes in absolute and relative organ weights in the high dose group (increased in liver and decreased in spleen and left thyroid/parathyroid) were also observed. An increased incidence of interstitial fat infiltration was reported in males at 0.098 mg/kg bw per day (no data available for other doses). Given the shortcomings of the cystic degeneration endpoint described above (and described in more detail in section 10.2), we determined that the study LOAEL and NOAEL are 0.098 and 0.024 mg/kg bw per day, respectively, based on increased incidence of centrilobular hepatocytic hypertrophy and other histological effects.

In female rats, no consistent dose–response relationship was observed for non-neoplastic lesions in the liver; a statistically significant increased incidence of several liver lesions was observed at ≥0.120 mg/kg bw per day for lymphohistiocytic infiltrate, centrilobular hepatocytic hypertrophy, eosinophilic hepatocytic granule, centrilobular hepatocytic pigment, hepatocyte necrosis, periportal hepatocyte vacuolation, and macrophage pigmented infiltrate and decreased periportal hepatocyte hypertrophy. Increased relative (to body weight) brain, kidney, liver and spleen weight were also observed as well as decreased absolute left adrenal weight and relative (to brain weight) left and right adrenal weight.

Decreased serum total cholesterol was observed at several different timepoints in males (14, 17, and 53 weeks), with significance observed only at the high dose (NOAEL of 0.242 mg/kg bw per day, and LOAEL of 0.984 mg/kg bw per day). The effect in females was limited to a transient decrease, with decreases in the three highest dose groups at week 27 only.

Macroscopic observations of livers at the end of the study exhibited enlarged, mottled, diffusely darkened or focally lightened livers in male and female rats given 5 or 20 ppm. No data were available for the other groups (Butenhoff et al., 2012b).

Carcinogenic effects in the study included tumours in the liver, thyroid, and mammary gland. An increased incidence of total hepatocellular adenoma, statistically significant at 20 ppm, was observed in both sexes in rats exposed for 2 years, but not 52 weeks. Thyroid follicular cell tumours (adenomas in males, and adenomas/carcinomas combined in females) were significantly increased in recovery group males and in the second highest exposure group in females (5 ppm or 0.299 mg/kg bw per day). In females, mammary fibroadenoma and fibroadenoma/adenoma combined were increased over controls only in the lowest dose group, and showed a significant negative trend.

The authors noted that serum and liver PFOS levels at the end of study were dramatically lower than after 14 weeks exposure in both sexes. In males, serum levels at terminal sacrifice were 33%, 44%, 51%, and 47% of those measured on Week 14 in the 0.5, 2, 5, and 20 ppm groups, and liver levels were 33%, 36%, 19%, and 33% of Week 14 values in the same dose groups, respectively. The authors suggested that this decline was likely due to chronic progressive nephritis leading to increased urinary excretion of PFOS across all treatment groups.

Data on nephritis were not provided by authors, who described the effect as occurring across all treatment groups; however, they stated significant associations were observed between incidence and severity of nephritis in males (but only at one dose in females). Serum PFOS concentrations also increased in approximate proportion to length of dosing between Weeks 4 and 14; however, Week 53 concentrations in the 20 ppm group were similar to those measured on Week 14, suggesting that steady state may have been approached after 14 weeks in the 20 ppm dose group. The serum PFOS levels corresponding to the LOAEL (0.5 ppm in diet) were 4,040 ng/mL at 14 weeks and 1,310 ng/mL at 105 weeks (Butenhoff et al., 2012b).

9.2.4 Genotoxicity

Based on negative results of a large series of *in vitro* and *in vivo* short-term tests of genes, chromosomes, or DNA repair, EFSA (2008) and Health Canada (2006) concluded that PFOS and its salts are not genotoxic. More recently published data (see the following subsections) are in agreement with this conclusion.

9.2.4.1 In vitro findings

Negative results were obtained in various in vitro assays conducted for PFOS on prokaryotes, namely the reverse gene mutation assay in Salmonella typhimurium (TA100, TA1535, TA1537, TA1538 and TA09 strains; 2 studies) and Escherichia coli (WP2uvrA, one study) conducted with/without metabolic activation (S9) and the mitotic recombination test in Saccharomyces cerevisiae (D4 strain, 1 study) (as reviewed by EFSA, 2008). PFOS (tested up to 1,000 µM) had no mutagenic activity in the *umu* test (Oda et al., 2007).

In human hepatoma HepG2 cells, PFOS (up to 400 µM for 24 h) did not induce ROS generation, DNA single strand breaks or micronuclei (Florentin et al., 2011). In another study of human HepG2 cells, PFOS induced slight ROS generation (0.4–2,000 µM) without generating detectable DNA damage (200 µM) (Eriksen et al., 2010).

PFOS did not induce chromosomal aberrations in cultured human lymphocytes with or without metabolic activation and did not induce unscheduled DNA synthesis (UDS) in primary cultured rat liver cells (as reviewed by EFSA, 2008).

In Syrian hamster embryo (SHE) cells, PFOS induced cell transformation at non-cytotoxic concentrations (0.2–2 µg/mL) and increased the expression of PPARβ/δ (0.2 µg/mL for 1 and 7 days; 2 µg/mL for 7 days), PPARγ (0.02–2 µg/mL for 7 days) and PPARα (20 µg/mL for 7 days). PFOS did not induce DNA damage in the comet assay (Jacquet et al., 2012).

Negative results were also found in different *in vitro* tests conducted with several PFOS precursors (as reviewed by EFSA, 2008).

9.2.4.2 In vivo findings

PFOS was negative in the *in vivo* bone marrow mouse micronucleus assay at single oral doses of 237.5, 450 and 950 mg/kg bw (with sampling at 24, 48 and 72 hours), and several PFOS precursors were found negative in different *in vivo* tests (as reviewed by EFSA, 2008).
A comet assay conducted in Paramecium caudatum was negative (Kawamoto et al., 2010).

9.2.5 Reproductive and developmental toxicity

The reproductive and developmental database for PFOS is robust. A 2-generational study has been developed in rats (Christian et al., 1999; Luebker et al., 2005a), and reproductive and

developmental parameters have been investigated in many one-generation studies in rats, mice, and rabbits. Effects that occurred at the lowest levels in animals exposed *in utero* included changes in brain structure (≥0.1 mg/kg bw per day), neurobehaviour (≥0.3 mg/kg bw per day), thyroid hormone levels (≥0.16 mg/kg bw per day), and fetal body weight (≥0.1 mg/kg bw per day). The majority of the other effects were observed at ≥1 mg/kg bw per day. Doses described throughout this section refer to maternal doses for animals exposed *in utero*, unless otherwise specified.

Changes in structure and in levels of various proteins and neurotransmitters in the brain were observed in mice and rats. In Sprague-Dawley rats exposed on GD0–20 to 0, 0.1, 0.6, and 2 mg/kg bw per day by gavage, structural modification of synapses in the hippocampus was observed in all doses (Zeng et al., 2011b). This study also identified decreased mRNA levels of synapsin1, synapsin2, and synaptophysin in the brain at all doses. Brain transcriptional changes—with multiple genes related to long-term potentiation/depression, synaptic transmission, calcium-dependent signal transduction, and phosphatidylinositol signalling pathways—were also observed in rats exposed to 3.2 ppm of PFOS in feed (equivalent to approximately 0.16 mg/kg bw per day using the Health Canada default assumption of 1 ppm in food = 0.05 mg/kg bw per day in rats [Health Canada, 1994]) (Wang et al., 2010, 2012). A companion study exposing rats to the same doses on GD2–21 also noted increases in GFAP in the hippocampus and cortex (at ≥0.1 mg/kg bw per day) and IL-1β and TNF-α in the hippocampus (at ≥0.6 mg/kg bw per day)(Zeng et al., 2011a). Changes were observed in the levels of proteins that are important in brain development (CamKII, GAP-43, synaptophysin, and tau, in cerebral cortex and/or hippocampus), in mice exposed to a single dose of 8.7 mg/kg (Johansson et al., 2009). At higher doses (>1 mg/kg bw per day) in rats, changes were observed in choline acetyltransferase activity in prefrontal cortex (Lau et al., 2003) and calcium related signalling molecules (Liu et al., 2010b).

In addition to changes in the brain, adverse effects from PFOS manifested as neurobehavioural changes at ≥0.3 mg/kg bw per day. The most common effect observed was changes in activity levels in mice (Onishchenko et al., 2011; Johansson et al., 2008; Fuentes et al., 2007a) and rats (Butenhoff et al., 2009), with some evidence that the effect was more pronounced in males (Onishchenko et al., 2011). Other effects observed were neuromotor decrements (worsened screen climb and pull and diminished forelimb grip strength in mice [Fuentes et al., 2007b] and decreased hindlimb strength in rats [Butenhoff et al., 2009]), delayed reflex in rats (Christian et al., 1999; Luebker et al., 2005a), and decrements in spatial learning and memory in the water maze test (Liu et al., 2009b) and hidden platform test (Wang et al., 2015) in rats.

Developmental exposure to PFOS resulted in changes to thyroid hormones at similar exposure levels to adult animals. Rat neonates whose mothers were exposed during gestation and lactation to ≥3.2 ppm in food (equivalent to ≥0.16 mg/kg bw per day using Health Canada's default assumption that 1 ppm in food = 0.05 mg/kg bw per day [Health Canada, 1994], an assumption that might not be relevant in pregnant or newborn rats) had dose-dependent decreases in total T4 (Wang et al., 2011a; Yu et al., 2009b; Lau et al., 2003). No changes in T3 levels were observed in two rat studies (Yu et al., 2009; Lau et al., 2003), but they occurred at high levels in another (Wang et al., 2011a). An additional neonatal study describing thyroid effects did not see any change in serum TSH in rat offspring, but increases in thyroid follicular epithelial cell proliferation were observed at 1 mg/kg bw per day (Chang et al., 2009). The only effect observed in developmental studies in mice was a decrease in total T4 at ≥5 mg/kg bw per day, but the effect was less consistent than in rats (Lau et al., 2003).

Although effects on the immune system and serum lipid levels were key effects that were well studied in adult mice, rats, and monkeys, very few studies investigated these effects during prenatal exposure. Adult mice exposed *in utero* to PFOS at 0, 0.1, 1, or 5 mg/kg bw per day had decreases in NK cell activity (at ≥1 mg/kg bw per day in males and 5 mg/kg bw per day in females), decreases in SRBC-IgM response (in males at 5 mg/kg bw per day), and changes in thymic lymphocytic subpopulations (at 5 mg/kg bw per day)(Keil et al., 2008). Increased serum cholesterol and LDL were increased on GD21 in rat fetuses exposed *in utero* to ≥1.6 mg/kg bw per day, the lowest dose at which this effect was studied (Luebker et al., 2005b). At LD5, the same study found no effects on serum lipid parameters in pups, but did observe a decrease in liver triglyceride levels.

Increased absolute or relative fetal liver weight was increased in mice at ≥5 mg/kg bw per day (Keil et al., 2008; Lau et al., 2003; Abbott et al., 2009). The effect was also observed in rats (Lau et al., 2003), but the species was less sensitive than mice (effects were only observed at 20 mg/kg bw per day.

Cardiac mitochondrial injury and increased relative heart weight were observed at 2 mg/kg bw per day in rats exposed *in utero* (Xia et al., 2011). These effects were not accompanied by changes in heart rate or blood pressure; however, systolic blood pressure was increased in rats exposed prenatally to 18.75 mg/kg bw per day (Rogers et al., 2014). The blood pressure effect in Rogers et al. (2014) was correlated with decreased nephron endowment. The only other effect that was noted in kidney development was decreased kidney weight in mice exposed to 5 mg/kg bw per day (Keil et al., 2008).

Changes suggesting immaturity of lungs were noted in rats exposed *in utero* to PFOS at ≥2 mg/kg bw per day. Observed histological changes included hemorrhage, thickened interalveolar septum and alveolar walls, focal lung consolidation, inflammatory cell infiltration, and apoptotic cells (Chen et al., 2012; Grasty et al., 2003, 2005). Atelectasis and abnormal expansion of lungs was also observed (Grasty et al., 2003, 2005). Because the pulmonary surfactant profile in offspring was normal and rescue agents (accelerators of pulmonary maturation) did not improve laboured respiration and mortality, the authors thought the latter effects were not due to lung immaturity (Grasty et al., 2005). The only evidence of potential adverse lung effects in mice pups was the observation of post-delivery cyanosis in some pups exposed to 12.5 mg/kg bw per day (Borg et al., 2010).

A variety of adverse effects were noted on the general health status of animals exposed prenatally to PFOS. Decreased survival or viability, or increased mortality were observed in foetuses or pups at ≥1.6 mg/kg bw per day in rats (Christian et al., 1999; Lau et al., 2003; Luebker et al., 2005a, 2005b; Xia et al., 2011) and at ≥4.5 mg/kg bw per day in mice (Lau et al., 2003; Yahia et al., 2008; Abbott et al., 2009). Decreased pup body weight or fetal weight was observed at the lowest levels at ≥0.1 mg/kg bw per day in a study of rats (Christian et al., 1999; Luebker et al., 2005a, 2005b). Other studies noted effects at higher levels in rats (at ≥1.6 mg/kg bw per day; Wetzel, 1983; Lau et al., 2003; Wang et al., 2011a; Xia et al., 2011; Chen et al., 2012; Rogers et al., 2014), mice (at 6 mg/kg bw per day; Fuentes et al., 2007b; Era et al., 2009), and rabbits (at ≥2.5 mg/kg bw per day; Case et al., 2001). Non-significant growth deficit was also observed in mice at 10 mg/kg bw per day (Lau et al., 2003). Rat pups also appeared pale and delicate at 1.6 mg/kg bw per day (Wang et al., 2011a).

Prenatal PFOS exposure caused developmental landmark delays and structural abnormalities. Delayed eye opening was observed at ≥1 mg/kg bw per day in mice (Lau et al.,

2003; Fuentes et al., 2007b; Abbott et al., 2009) and ≥1.6 mg/kg bw per day in rats (Christian et al., 1999; Lau et al., 2003; Luebker et al., 2005a); moreover, abnormalities were observed in the eye lens of rats at ≥1 mg/kg bw per day (Gortner, 1980). Other developmental landmark delays occurred in pinna unfolding in rats (Christian et al., 1999; Luebker et al., 2005a) and mice (Fuentes et al., 2007b), and incisor eruption in mice (Fuentes et al., 2007b; Yahia et al., 2008;). Skeletal abnormalities were also observed at ≥1 mg/kg bw per day. The effects observed at the lowest levels were sternal defects in mice (Lau et al., 2003; Yahia et al., 2008;) and rats (Wetzel, 1983; Lau et al., 2003;) and incomplete skull closure in rats (Wetzel, 1983). Other effects observed included: cleft palate in mice (Lau et al., 2003; Yahia et al., 2008; Era et al., 2009) and rats (Wetzel, 1983; Lau et al., 2003); rib abnormalities in mice (Yahia et al., 2008) and rats (Wetzel, 1983); delayed ossification in mice (Yahia et al., 2008), rats (Wetzel, 1983), and rabbits (Case et al., 2001); curved fetus, spina bifida occulta, and tail abnormalities in mice (Yahia et al., 2008); and subcutaneous edema and cryptorchism in rats (Wetzel, 1983).

Decreases in reproductive organ weights were observed in animals. A dose-related trend in decreased uterus weight was observed in mice, and was significant at ≥0.166 mg/kg bw per day (Fair et al., 2011). Reduced mean gravid uterine weight was also observed at 10 mg/kg bw per day in rats (Wetzel, 1983). These effects occurred in the absence of histological effects. Other reproductive organ weight decreases that were observed were in male rats, affecting absolute seminal vesicle weight (Christian et al., 1999) and relative gonad weight (Cui et al., 2009).

Reproductive effects also resulted from PFOS exposure. The effect at the lowest level was decreased gestation length at ≥0.8 mg/kg bw per day in rats (Christian et al., 1999; Luebker et al., 2005a, 2005b). Other effects observed at higher levels were fewer implantation sites in rats (Luebker et al., 2005a; Christian et al., 1999), reduced litter size in rats (Christian et al., 1999; Xia et al., 2011) and rabbits (Case et al., 2001), and increase in fetal resorptions, dead foetuses, and stillbirths in rats (Luebker et al., 2005a; Wetzel, 1983), rabbits (Case et al., 2001), and mice (Lau et al., 2003; Yahia et al., 2008). A significantly reduced lactation index was also observed in rat pups exposed to 1.6 mg/kg bw per day (Christian et al., 1999; Luebker et al., 2005a).

Reproductive effects observed in males were limited to decreased estradiol in male monkeys at 0.75 mg/kg bw per day (Seacat et al., 2002), and decreased serum testosterone levels and epididymal sperm count in male rats exposed to 10 mg/kg bw per day (Wan et al., 2011).

Comparing observations across generations in two-generation studies can help to identify emerging patterns in developmental and reproductive effects. Effects in rat pups from the two-generation study (Christian et al., 1999; Luebker et al., 2005a) that were described throughout this section occurred primarily in the F_1 offspring. The F_0 dams were exposed to four different doses of PFOS—0.1, 0.4, 1.6, or 3.2 mg/kg bw per day—for 42 days prior to mating, through the mating period (maximum of 14 days), and to day 9 of gestation for rats with C-section delivery, or lactation day 20 for rats with natural delivery. Significantly decreased viability of F_1 pups was observed at the two higher doses. At 3.2 mg/kg bw per day, fewer pups were liveborn and more were stillborn. Moreover, the numbers of pups that survived in the first few days of life was lower in the 1.6 mg/kg bw per day group. At the high dose, 0% of pups survived, and at 1.6 mg/kg bw per day, survival was only 66.1% (compared with >98% in controls and lower dose groups). Delays in developmental landmarks—eye opening, pinna unfolding, surface righting, and air righting—were also observed at 1.6 mg/kg bw per day in F_1 pups. Maternal toxicity had been apparent in these dose groups, as F_0 dams displayed decreases in food consumption and bodyweight gain at ≥0.4 mg/kg bw per day. Due to significant decreases in survival at the two

highest doses, exposure to F_1 dams was limited to 0.1 and 0.4 mg/kg bw per day. No effects on reproductive outcome (including number of live births and pup survival) were observed in F_1 dams/F_2 pups; moreover, no maternal toxicity was observed. The only effect observed in the F_2 generation was a decrease in pup weight and weight change at 0.4 mg/kg bw per day, for 2 timepoints only (days 7 and 14). Therefore, decreased pup weight was first observed at a lower level in F_2 pups (0.4 mg/kg bw per day) than F_1 pups (1.6 mg/kg bw per day); however, the effect was less severe and/or more transient than in F_1 pups, where the effect was observed consistently at all time points (days 1–21). Mating and fertility appeared to be unaffected in both generations.

9.3 Mode of action

Mode of action (MOA) analysis was considered for effects occurring at the lowest PFOS levels (i.e. immune effects in mice, lipid effects in monkeys and mice, liver weight increase in rats and mice, liver histological changes in rats, hepatocellular tumours in rats, and thyroid hormone changes in monkeys, rats, and mice). Only a preliminary evaluation of data could be performed for most of the MOAs; a MOA analysis using recent guidance (Meek et al., 2014) could only be performed for peroxisome proliferation effects on liver endpoints. Based on the MOA analysis, no endpoints were considered to be irrelevant to humans~~, and the results suggest that the TDI approach is the most appropriate method for cancer risk assessment~~. Results of the MOA evaluations are summarized in this section.

9.3.1 Direct-acting mutagenicity

Direct-acting mutagenicity was considered as a potential MOA for the development of hepatocellular tumours in rats. As discussed in Section 9.2.4, evidence strongly indicates that PFOS is not mutagenic, with or without metabolic activation. PFOS was negative for genotoxicity in a wide variety of *in vitro* and *in vivo* assays. The pattern of PFOS-induced tumours also did not follow that of typical mutagens. For example, mutagens are typically expected to cause tumours in many different organs, but PFOS only induced tumours in the thyroid and liver of rats (Butenhoff et al., 2012b), which were organs that also demonstrated adverse non-cancer effects in rats and other species. Furthermore, mutagens often produce a high incidence of tumours, which occur at early timepoints. In PFOS-exposed animals, hepatocellular tumours were only observed after lifetime duration (and not in rats exposed for 1 year and kept alive for an additional 1 year), and at low incidences (8–12%) (Butenhoff et al., 2012b). Thyroid tumours in the study demonstrated inconsistencies in time–dose relationships and dose–response relationships (with a significant increase only in the high-dose group exposed for 1 year and not 2 years in males, and a significant increase in a middle dose group in females). The incidence of tumours was still relatively low in most groups, ranging from 7–10% when observed in rats exposed for two years (6–10%), and slightly higher in the male recovery group (23%). These data suggest that low-dose linear extrapolation is not appropriate for PFOS-induced tumours. No further MOA analysis is required for direct-acting mutagenicity, unless contradictory data are published.

9.3.2 Peroxisome proliferation

Peroxisome proliferation was considered as a potential MOA for hepatocellular tumours in rats, hepatic cystic degeneration in rats, liver weight increase in mice, and increase in serum lipids in monkeys and mice. Some data exist for hepatic PPAR activity in rats; however, no studies directly measured PPAR impact on other outcomes. As insufficient data were available to fully

apply the evolved Bradford-Hill considerations to evaluate the MOA, the weight of evidence analysis is limited to the evaluation of the dose–response of key events for peroxisome proliferation in rat liver.

Three main key events in the peroxisome proliferation MOA are considered to lead to liver histological effects and hepatocellular tumours. These key events are 1) the activation of hepatic PPARα receptors, which leads to 2) altered cell growth pathways that inhibit apoptosis and/or promote cell replication, eventually leading to 3) hepatocyte proliferation (Corton et al., 2014).

9.3.2.1 Key event 1 – PPARα activation

The lowest doses at which PPARα activation was investigated were 0.024–1.25 mg/kg-bw per day, in rats exposed for 4, 14, or 104 weeks (Seacat et al., 2003; Butenhoff et al., 2012b). PPARα activation was not observed to occur at any dose, based on the absence of increase in palmitoyl CoA oxidase activity. Increased PPARα activity was measured after 1 week of exposure at higher doses in rats, with a dose-dependent upregulation of PPARα target genes after exposure to 5 or 20 mg/kg-bw per day (Ye et al., 2012), and an increase in ACOX and 12-OH LAH at 9.65 mg/kg-bw per day (Elcombe et al., 2012b). However, the latter effects were not observed after 1 week of exposure to 1.93 mg/kg-bw per day (Elcombe et al., 2012b). PPAR-activation only occurs at higher concentrations for PFOS than PFOA in *in vitro* (Takacs and Abbott, 2007; Rosen et al., 2013) and *in vivo* (Rosen et al., 2010) gene expression studies. Furthermore, studies with PPAR-null mice indicated histological effects and hepatic gene expression changes that were similar to mice with active PPAR activity, indicating PPAR-independent effects (Rosen et al., 2010).

9.3.2.2 Key event 2 – altered cell growth

No studies of markers of altered cell growth pathways could be found.

9.3.2.3 Key event 3 – hepatocyte proliferation

Hepatocyte proliferation was not observed at the lowest doses studied (0.024–1.25 mg/kg bw per day, for 4, 14, or 104 weeks; Seacat et al., 2003; Butenhoff et al., 2012b). The liver proliferative index was increased, but was not sustained, after exposure to 1.93 or 9.65 mg/kg bw per day for 1 week (Elcombe et al., 2012b).

9.3.2.4 Comparison of dose–response of key events and outcomes

For modes of action to be deemed as relevant for an adverse outcome, dose–response concordance—i.e., the observation of early key events at doses that are lower than or equal to later key events and the adverse outcome—is required. For PFOS, however, the lowest observed doses associated with the adverse outcomes in rats (cystic degeneration: 0.024 mg/kg bw per day, hepatocellular adenomas: 0.984 and 1.251 mg/kg bw per day in male and females, respectively) were lower than those at which hepatocyte proliferation was observed (≥1.93 mg/kg bw per day). This hepatocyte proliferation also might not be associated with PPARα activation, which was only observed at ≥5 mg/kg bw per day. Finally, PPARα activation and hepatocyte proliferation were not observed concurrently with cystic degeneration and hepatocellular adenoma in the study where these effects were observed. Because it appears that liver proliferation, hepatocellular adenomas, and cystic degeneration precede PPARα activation, adverse hepatic effects observed in

rats exposed for 2 years to PFOS do not appear to be driven by a peroxisome proliferation MOA. For this reason, human relevance of PFOS-induced hepatic effects cannot be discarded. Moreover, hepatic effects do not appear to be specific to rodents—the LOAEL for hepatocellular hypertrophy accompanied by cytoplasmic vacuolation in monkeys (0.75 mg/kg bw per day; Seacat et al., 2002) is on the same order of magnitude as in rats (0.242 mg/kg bw per day; Butenhoff et al., 2012b).

Although insufficient data exist to examine the impact of PPAR activation on changes in serum lipid, thyroid, and immune parameters, peroxisome proliferation is plausible for all endpoints. PPAR activators are known to produce hypolipidemic effects (Corton et al., 2014), and PFOS is similar in structure to fatty acids. In rats, PFOS-induced alterations in gene expression related to fatty acid metabolism and thyroid hormone synthesis and release were of a similar pattern to known PPARα activators (Martin et al., 2007). Some immune effects (weight and cellularity changes in spleen and thymus) were muted in PPAR-null mice (vs. wild-type mice) exposed to PFOA; however, no similar data exist for PFOS, which does not appear to be as strong of a PPAR activator as PFOA. The peroxisome proliferation MOA for these endpoints cannot be fully examined until further data are produced on the impacts of PFOS-induced PPAR activation on immune and serum lipid pathways.

9.3.3 *Sex hormone disruption*

Sex differences were observed in immune response, with males more sensitive than females. However, no studies have been developed to identify whether this effect is associated with sex hormones; therefore, there are insufficient data to evaluate the MOA. PFOS does, however, appear to have some impact on sex hormone disruption—in a variety of *in vitro* assays of estrogenicity, PFOS did not display direct estrogenic activity, but enhanced the effects of 17β-estradiol in several assays (Sonthithai et al., 2015). If more in-depth studies on the effect of PFOS on sex hormone disruption are performed, this potential MOA could be further investigated.

9.3.4 *Immune suppression*

Immune suppression in rats (decrease in IgM and NK cell levels) has been observed at lower doses than those that were tumorigenic. Although NK cells are involved in eliminating cancer cells, no studies investigating the role of PFOS-induced immunosuppression in tumour development have been performed. No detailed analysis for this potential MOA can be performed using current data. If more in-depth studies on the association between PFOS-induced immunosuppression and tumour development are performed, this potential MOA could be further investigated.

9.3.5 *Other MOAs*

Insufficient data exist to allow for the assessment of other potential MOAs considered in the MOA analysis. Some data—particularly in regards to PPAR activation/peroxisome proliferation—exist for other endpoints that were not included in the MOA analysis (i.e. effects that were observed only at higher PFOS exposure levels).

9.4 Additivity

The application of an additive approach for PFAS was considered using the World Health Organization /International Programme on Chemical Safety (WHO/IPCS) framework for risk assessment of combined exposure to multiple chemicals (Meek et al., 2011). This section focuses on the evaluation of additivity for PFOS and PFOA, which are the predominant PFAS detected in Canadian water samples.

Considerations relevant to the additivity analysis are addressed within four over-arching questions (Meek et al., 2011):

1. What is the nature of exposure?
2. Is co-exposure likely, taking into account the context?
3. Is there a likelihood of co-exposure within a relevant time-frame?
4. What is the rationale for considering compounds in an assessment group?

Additionally, evidence demonstrating the toxic effects of mixture exposure can be used as supporting information in an additivity analysis (Meek et al., 2011). Based on analysis of these considerations, the application of an additive approach for PFOS and PFOA in drinking water is the most appropriate method for the protection of human health. The results are summarized below.

What is the nature of exposure?

PFOS and PFOA are highly fluorinated synthetic organic chemicals that consist of a straight-chain hydrocarbon backbone with a carbon chain length of eight. Structurally, they differ only in their terminal functional groups (i.e., PFOS has a sulfonic acid moiety and PFOA has a single carboxylate moiety). This class of chemicals has numerous uses, including stain/water resistant coatings and in fire-fighting foams, which is of particular concern for water (see section 4.1). Their elevated water solubility and the negligible volatility of ionized species suggest that PFOS and PFOA will partition primarily to the aquatic environment, supporting their occurrence in water. Additionally, they are persistent compounds that do not undergo biodegradation and are thus stable in water. Many studies have confirmed the presence of PFAS in drinking water sources and tap water (see Sections 4.1, 5.1, and 5.1.1).

Is co-exposure likely, taking into account the context?

Yes. Routine monitoring programmes to test drinking water for PFOS and PFOA have not been implemented; however, available studies have reported co-exposure in Canadian drinking water sources and tap water (see Section 5.1.1). As discussed in Section 5.1.1, PFOS and PFOA are the predominant PFAS detected in Canadian water samples.

Is there a likelihood of co-exposure within a relevant time-frame?

Yes. Co-exposure to PFOS and PFOA is likely – through ingestion of contaminated food and water, inhalation of dust, and use of consumer products. PFOS and PFOA are persistent compounds that do not undergo biodegradation, thus they compartmentalize into similar media, making the temporal aspects of external co-exposure likely. Additionally, they do not undergo biotransformation and have relatively long half-lives in humans (i.e., 3.9-6.9 years for PFOS and 2.5-4.4 years for PFOA (Olsen et al., 2007; Brede et al., 2010; Bartell et al., 2010)), thus their toxicokinetics make internal co-exposure likely. Additionally, biomonitoring data indicate co-occurrence of PFOS and PFOA in human serum in Canadian studies, as well as International studies.

What is the rationale for considering compounds in an assessment group?

Grouping of PFOS and PFOA is appropriate at the level of structure, application/use (as described above), and toxicology. The human health and toxicological effects, and modes/mechanisms of action induced by PFOS and PFOA are discussed below.

Human health and/or toxicological effects are similar. The available information on PFOS and PFOA toxicokinetics indicates a high degree of similarity (reviewed in section 8 of both documents). Oral uptake of PFOS and PFOA results in rapid and almost complete resorption (>90%) within 24 hours in male rats (Gibson and Johnson, 1979). PFOS and PFOA are weakly lipophilic, very water soluble, and bind preferentially to proteins, such as serum albumin. However, differences in their tissue distribution have been reported - whereas PFOA is mainly present in the serum/plasma (Johnson and Ober, 1999; Han et al., 2003; Kudo et al., 2007), PFOS is primarily distributed to the liver (Beskin et al., 2009; De Silva et al., 2009). Both PFOS and PFOA are highly resistant to biotransformation and are not metabolized in mammals, which accounts for their relatively long half-lives. Additionally, because of their resistance to biotransformation, the toxicity of the parent compound and not that of a metabolite is of concern for both PFOS and PFOA.

As reviewed in section 9.1 of this document and the PFOS document, studies in humans (including the general population and workers) have demonstrated similarities in health outcomes associated with elevated levels of serum PFOS and PFOA, including liver effects, immune suppression, lipidemia, thyroid effects, kidney effects, cancer, and some reproductive and developmental toxicities (i.e., reduced fecundity, reduced birth weight, changes in the onset of puberty). However, elevated serum PFOS is additionally associated with delays in developmental milestones, thyroid hormone levels, and immune system effects in offspring, while elevated serum PFOA is associated with decreased duration of breastfeeding.

Similarities and dissimilarities in health outcomes in experimental animals have also been demonstrated. Studies in experimental animals have demonstrated similarities in adverse effects of treatment with PFOS and PFOA on the liver (including increased liver weight, hepatocellular hypertrophy, changes in serum enzymes), immune system effects, serum lipids, thyroid effects, neurotoxicity, reduced body weight, and tumor formation (i.e., liver), and the induction of reproductive and developmental toxicities (including neurobehaviour, liver weight changes and histopathology, reduced survival/viability of pups, and increased mortality in pups). Additionally, neither PFOS nor PFOA are considered to be direct-acting genotoxic chemicals. However, discordant results are observed in some outcomes following treatment with PFOS and PFOA. For

example, chronic administration of PFOA causes hepatocellular adenomas and Leydig cell adenomas in rats; yet while an increase in the incidence of hepatocellular adenomas is observed following chronic administration of PFOS, no significant dose-responsive changes in the incidence of Leydig cell tumours were found. Furthermore, the most sensitive developmental effects observed following exposures to PFOA (i.e., delayed mammary gland development in the offspring of mice, uterine effects in immature female mice, and obesity in female offspring in mice at adulthood) are not observed following exposure to PFOS. Collectively, although some toxic effects appear to be compound-specific, there is a large degree of concordance in adverse toxicological effects induced by PFOS and PFOA in experimental animals.

There is similarity in their modes of action. The modes of action for PFOS and PFOA are not fully understood and it is likely that multiple pathways are involved in their toxic effects. The largest body of evidence points to PPARα ligand-dependent activation by PFOS and PFOA as a key initiating event in the development of liver toxicities (described in section 9.3 of each document). However, although some toxicity by PFOS and PFOA is attributable to PPARα activation, PPARα-independence has also been proposed. For example, PFOS-induced hypertrophy and lipid vacuolization occurred in the absence of peroxisome proliferation or increase in palmitoyl-CoA-oxidase activity in monkeys (Seacat et al., 2002) and transmission electron microscopy of liver sections with hepatocellular hypertrophy and hepatic inflammation observed in pups exposed to PFOA *in utero* revealed cellular damage and mitochondrial abnormalities with no evidence of peroxisome proliferation (Quist et al., 2015). Additionally, PFOS and PFOA have been shown to alter fatty acid metabolism, lipid transport, cholesterol synthesis, proteasomal activation and proteolysis, cell communication, and inflammation processes in experimental animals. Thus, although the mode of action for PFOS and PFOA-induced toxicities has yet to be elucidated, the similarity in the mechanisms activated by each compound is sufficient to suggest similar modes of action are at play.

In addition to the evaluation of data for additivity using the WHO/IPCS framework (Meek et al., 2011), evidence demonstrating the toxic effects of combined exposures were evaluated to strengthen support for the use of an additive approach for PFOS and PFOA. Only one *in vivo* mammalian study was found. Tatum et al. (2010) reported in a conference proceeding that a binary mixture of PFOS and PFOA (6 mg/kg bw per day and 4 mg/kg bw per day, respectively) behaves additively by dose addition (also known as concentration addition) on reproductive and developmental toxicity endpoints (i.e., maternal weight gain, pup body weight, maternal and neonatal liver weight) in CD-1 mice exposed to the mixture and to PFOS and PFOA individually by oral gavage on gestational days 1-17. The authors additionally reported less than additive behaviour for neonatal mortality (i.e., the mixture of PFOS and PFOA caused less neonatal mortality compared to PFOS and PFOA alone).

This finding is in general agreement with *in vitro* studies on the combined action of PFOS and PFOA (and other PFAS). In studies of binary mixtures of PFOS and PFOA, additivity has been observed at the level of apoptotic potential in mouse HEPG2 liver cells (Hu and Hu, 2009), mortality in zebrafish embyros (Ding et al., 2013), and PPARα activation in Cos-1 cells (Wolf et al., 2014). The additive effects reported by Wolf et al. (2014) and Ding et al. (2013) were observed at low exposure concentrations but deviations from additivity were observed at higher doses. Similarly, deviations from additivity showing less than additive effects (i.e., the mixture response is less than would be expected under conditions of additivity) have been observed at the level of PPARα activation in Cos-1 cells (Carr et al., 2013) and toxicity in cyanobacteria (Rodeo-

Palomares et al., 2012) in studies of binary mixtures of PFOS and PFOA, as well as on cellular viability in human liver HL-7702 cells exposed to a simple mixture of 11 PFAS, including PFOS and PFOA. Greater than additive effects on cellular viability have also been reported in human liver HL-7702 cells (Hu et al., 2014) and in rare minnow hepatocytes (Wei et al., 2009) in studies of binary mixtures of PFOS and PFOA, and in human U2OS bone osteosarcoma cells exposed to a simple mixture of five PFAS, including PFOS and PFOA (Wilson et al., 2016). Wilson et al. (2016) further investigated glucocorticoid receptor transactivation but the mixture responses were too weak to report, as were the estrogen receptor and androgen receptor activities in human MVLN breast cancer cells and hamster CHO-K1 ovary cells, respectively, exposed to a mixture of seven PFAS including PFOS and PFOA (Kjeldsen and Bonefeld-Jorgensen, 2013). Gene expression changes measured following exposure to PFOS and PFOA alone or in a binary mixture demonstrated that mechanisms activated following exposure to mixtures and individual chemicals are complex and can differ depending on the treatment (Wei et al., 2009). The differences reported among studies are largely attributable to the biological model, the concentrations used, and the particular composition/complexity of the mixtures.

The absence of *in vivo* studies investigating the additivity of PFAS was identified as a major data gap. However, based on the evaluation of the exposure and toxicological data for PFOS and PFOA in consideration of the WHO / IPCS framework for the risk assessment of combined exposures (Meek et al., 2011), an additive approach for PFOS and PFOA is the most appropriate in the interest of human health protection.

10.0 Classification and assessment

The benchmark dose (BMD) approach was used wherever possible to calculate potential points-of-departure, because it is derived on the basis of data from the entire dose-response curve for the critical effect rather than from the single dose group at the NOAEL (IPCS, 1994). A lower confidence limit of the benchmark dose (BMDL) has been suggested as an appropriate replacement of the NOAEL (Crump, 1984). More specifically, a suitable BMDL is defined as a lower 95% confidence limit estimate of dose corresponding to a 1–10% level of risk over background levels. Definition of the BMD as a lower confidence limit accounts for the statistical power and quality of the data (IPCS, 1994). For dichotomous data (i.e. presence vs. absence of effect), benchmark dose values representing a 10% increase in adverse effect over background rates (BMD_{10}) and their lower 95% confidence limits ($BMDL_{10}$) were calculated using the U.S. EPA Benchmark Dose Software (BMDS Version 2.6.0.86~~)~~(; U.S. EPA, 2015).

Large pharmacokinetic differences exist between animals and humans, with lower clearance (i.e., higher half-life values) in humans than in rats, mice, and monkeys. These differences result in higher target tissue doses in humans when exposed to the same external doses as animals. Default approaches for interspecies extrapolation (e.g., using an interspecies uncertainty factor of 10 or allometric scaling) are therefore not considered to be sufficiently protective of humans. As described in Section 8.6, AK_{UF} values (i.e., the component of the CSAF reflecting interspecies toxicokinetic differences) were calculated with a PBPK model to address pharmacokinetic differences between animals and humans. As different AK_{UF} values were calculated for various doses, the values can also address non-linearities in pharmacokinetics. Weaknesses still exist with this approach, as outlined in detail in Section 8.6, including the use of the steady-state plasma concentration as a dose metric, rather than selecting organ-based values or

exploring whether other dose metrics (e.g., peak concentrations) are more appropriate. However, despite the weaknesses, the approach was determined to be the best of the available options. This approach was selected over the use of serum concentrations as PODs, because human PBPK models were determined to not be sufficiently robust for precise estimates of human exposure levels corresponding to serum-based PODs.

10.1 Cancer risk assessment

The carcinogenicity of PFOS has not been evaluated by IARC. Consistent observations of associations between PFOS exposure and cancers have not been identified in epidemiological studies. Some associations between PFOS and risk of cancer of the bladder, breast, male reproductive organs, and overall cancers were observed; however, the evidence does not support the carcinogenicity of PFOS. The association for bladder cancer was lost after further follow-up, the population demonstrating associations for breast cancer were also exposed to several other chemicals, and associations for male reproductive cancers were not supported by studies of other populations. Therefore, although some evidence of an association between PFOS and the risk of cancer has been observed, the effects were equivocal, and no clear trend could be determined due to limitations in the studies (including small number of cases, confounding, and participant selection bias).

In the sole chronic bioassay performed for PFOS, tumours were observed in the liver, thyroid, and mammary gland of Sprague-Dawley rats (Butenhoff et al., 2012b). Hepatocellular adenoma was observed to be significantly increased in high dose males and females (0.984 and 1.251 mg/kg bw per day, respectively) after 2 years of exposure. Dose–response and temporal patterns for thyroid and mammary gland tumours were less consistent. Thyroid follicular cell adenomas were increased in recovery group males (exposed to 1.144 mg/kg bw per day for 52 weeks), but not those exposed for the duration of the study. Combined thyroid follicular cell adenomas and carcinomas were increased only in females in the second-highest exposure group (0.299 mg/kg bw per day), but not in high-dose females. Finally, incidence of mammary fibroadenoma and combined fibroadenoma/adenoma was increased only in the lowest dose of females (0.029 mg/kg bw per day), but no other groups.

Although the mode of action for PFOS-induced tumours has not yet been elucidated, the weight of evidence more strongly suggests that PFOS is a non-mutagenic compound (see Sections 9.2.4 and 9.3). For this reason, a non-linear low-dose extrapolation approach (i.e., the tolerable daily intake (TDI) approach) is the most appropriate method for deriving a health-based value (HBV) for cancer.

Hepatocellular tumours were selected as the critical effect for the cancer risk assessment, as it is the cancer endpoint with the most consistent dose–response relationship. In males, tumours were only classified as hepatocellular adenomas; in females, the majority of tumours were hepatocellular adenomas, with one incidence of hepatocellular carcinoma in the 2-year high-dose group. Incidence of these tumours in male and female rats is presented in Table 3.

Table 3: Incidence of hepatocellular tumours in Butenhoff et al. (2012b)

Treatment group (ppm)	Males – hepatocellular adenomas only		Females – hepatocellular adenoma & carcinoma combined	
	Dose (mg/kg bw per day)	Incidence (%)	Dose (mg/kg bw per day)	Incidence (%)
0	0	0/60 (0%)	0	0/60 (0%)
0.5	0.024	3/50 (6%)	0.029	1/50 (2%)
2	0.098	3/50 (6%)	0.12	1/49 (2%)
5	0.242	1/50 (2%)	0.299	1/50 (2%)
20	0.984	7/60 (12%)*	1.251	5/60 (8%)*
20 ppm recovery	1.144	0/40 (0%)	1.385	2/40 (5%)

*$p \leq 0.05$

Benchmark dose (BMD) modelling was performed separately for males and females. The Log Logistic model provided the best fit (i.e., lowest Akaike information criterion [AIC]) for both males and females. Estimated BMD values in males were BMD_{10} of 2.25 mg/kg bw per day and $BMDL_{10}$ of 0.318 mg/kg bw per day; in females, the values were BMD_{10} of 1.81 mg/kg bw per day and $BMDL_{10}$ of 0.732 mg/kg bw per day. Due to dose–response curves that were less than ideal (i.e. incidence did not increase progressively as dose increased), model fits were somewhat weak, particularly in males (p-values for Log Logistic models were 0.44 in males and 0.77 in females). However, the model fit was considered to be sufficient based on recommended criteria (i.e. p-value >0.10) (U.S. EPA, 2012a). As the $BMDL_{10}$ of 0.318 mg/kg bw per day for males is more conservative than the corresponding value in females, this has been selected as the point-of-departure for the calculation of the HBV for cancer. Because the test material used in the study was only 86.9% pure, the adjusted $BMDL_{10}$ to account for actual PFOS concentration is 0.276 mg/kg bw per day.

To reflect the large interspecies differences in pharmacokinetics, the human-equivalent point-of-departure (POD_{HEQ}) can be calculated by dividing the $BMDL_{10}$ by the AK_{UF}, as follows:

$$POD_{HEQ} = \frac{0.276 \text{ mg/kg bw per day}}{10}$$

$$= 0.028 \text{ mg/kg bw per day}$$

where:

- 0.276 mg/kg bw per day is the $BMDL_{10}$ for hepatocellular tumours in male rats (Butenhoff et al., 2012b); and
- 10 is the dose-specific AK_{UF} for rats in the 0.1 mg/kg bw per day range (see Section 8.6.2).

Using the calculated POD_{HEQ}, the cancer TDI was calculated as follows:

$$TDI = \frac{0.028 \text{ mg/kg bw per day}}{}$$

$$= \frac{}{25}$$

$$= 0.0011 \text{ mg/kg bw per day}$$

where:

- 0.028 mg/kg bw per day is the POD_{HEQ} calculated above; and
- 25 is the composite uncertainty factor, as described below.

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (×2.5) and intraspecies uncertainty factor (×10). A value of 2.5 is used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. A default value of 10 was applied for the intraspecies uncertainty factor. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOS excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. In the one study of human half-life of PFOS, the range between the lowest and highest values is 10-fold. If further studies of PFOS consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies uncertainty might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed.

Using this TDI, the HBV for drinking water can be calculated as follows:

$$\text{HBV} = \frac{0.0011 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= 0.010 \text{ mg/L (10 µg/L)}$$

where:

- 0.0011 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7).

10.2 Non-cancer risk assessment

Although epidemiological evidence has shown an association between the exposure to PFOS and an increased risk of multiple health outcomes, such as reproductive, developmental, and immunological effects (see Section 9.1.~~3~~2 and 9.1.4), a point-of-departure (POD) cannot be derived from the studies due to their limitations, including in terms of study design, bias and confounders.

The effect observed at the lowest exposure levels was immune system suppression in mice. The lowest LOAEL for immunosuppression data classified by IPCS (2012) as providing the strongest weight of evidence for immunotoxicity was suppression of SRBC-specific IgM in mice at ≥0.00166 mg/kg bw per day (Peden-Adams et al., 2008). Immune system effects were excluded from the quantitative risk assessment due to inconsistencies in NOAELs and LOAELs among studies and uncertainty of the importance of observed effects to human health, both of which will be expanded upon in this section. Inconsistencies were observed in the effective PFOS doses for immune function endpoints: the suppression of SRBC-specific IgM in B6C3F1 mice in Peden-Adams et al. (2008) was observed at ≥0.00166 mg/kg bw per day, whereas the LOAEL in C57Bl/6 mice was 0.0833 mg/kg bw per day, with no significant changes observed at 0.0083 mg/kg bw per day (Dong et al., 2009) or 0.0167 mg/kg bw per day (Dong et al., 2011). Moreover, NK cell activity was actually increased at 0.0166 mg/kg bw per day in B6C3F1 mice (Peden-Adams et al., 2008); in C57Bl/6 mice, the effect was non-monotonic, with increased activity at low doses (significant at 0.0833 mg/kg bw per day), and significant decreases at higher doses (0.833 and 2.083 mg/kg bw per day) (Dong et al., 2009). An additional study identified increased mortality from influenza A infection in mice at 0.025 mg/kg bw per day (Guruge et al., 2009); however, this effect was not studied in other species. The adversity of IgM suppression and changes in NK cell activity is also debatable—although these effects indicate immune system changes, it is unclear whether small variations in these measures are sufficient to result in adverse health effects in humans. Of note for discussion of clinical importance in humans is the Grandjean et al. (2012) study, which demonstrated that despite decreased vaccine-specific immunoglobulin response in PFOS-exposed children, the number of children with immunoglobulin levels below the clinically-protective level was low. Moreover, mice appear to be more sensitive than other species, as the LOAEL for immunosuppression was several orders of magnitude higher in the lone rat study, at 3.21 mg/kg bw per day (Lefebvre et al., 2008). In humans, evidence of immunosuppression is inconsistent—associations are observed between PFOS levels and decreases in antibodies against some (but not all) illnesses, and the influence of PFOS exposure on clinical immunosuppression (i.e. incidence of illnesses) appears to be more tenuous. Therefore, although low PFOS doses appear to be associated with immunosuppression, the data are not considered to be presently reliable for use as a key study for the PFOS assessment. Further explorations should be performed to address the nearly two orders of magnitude difference in LOAELs in the studies before these endpoints can be reliably considered as a basis for a risk assessment.

The adverse effect observed at the lowest level (other than the IgM and NK-cell effects in Peden-Adams et al., 2008) was liver cystic degeneration observed in male Crl:CD(SD)IGS BR rats exposed for 104 weeks in feed (Butenhoff et al., 2012b). This effect was observed in a robust study, with 4 treatment groups ($n \geq 55$) and an additional high-dose recovery group ($n = 40$); however, it is not proposed as critical effect for the risk assessment. The endpoint is a common benign, spontaneous lesion in aging rats, particularly males (Bannasch and Zerban, 1997; Karbe and Kerlin, 2002), which has been classified by some pathologists as a benign neoplasm (Bannasch, 2003). Cystic degeneration only rarely occurs in other mammals, including humans (Bannasch and Zerban, 1997; Karbe and Kerlin, 2002). Although cystic degeneration can be associated with foci of cellular alteration or tumours (Karbe and Kerlin, 2002), the progression in PFOS-exposed animals does not follow that of the more serious histological changes. Moreover, the incidence of cystic degeneration was similar among exposure groups, ranging from 27–38%

with no dose–related increases, and occurring in similar levels in high-dose rats exposed for 2 years versus recovery rats (33 vs. 38%). The frequency of cystic degeneration in most groups is within the range of spontaneous development in male rats, which is as high as 34% (Karbe and Kerlin, 2002).

Hepatocellular hypertrophy was first observed at one dose higher than the LOAEL for cystic degeneration (0.098 mg/kg bw per day) in the Butenhoff study, and incidence increases in a dose-related manner. Although hepatocellular hypertrophy can sometimes be considered an effect that is adaptive rather than adverse in its own right, evidence of other histological effects in the liver at higher concentrations provide an indication of their progression upon continued exposure (ECETOC, 2002; Hall et al., 2012). Clearly adverse histological effects (including cytoplasmic vacuolation) were observed in livers of male rats beginning at the next dose level (0.242 mg/kg bw per day) in the study. Although hepatocellular hypertrophy occurs at one dose level lower than the clearly adverse histological effects, the effect is proposed as a critical effect for this assessment, as it might be a sensitive indicator of the potential for the progression of adverse histological effects. Moreover, the LOAELs were the same for both hepatocellular hypertrophy and cytoplasmic vacuolation in rats from the Butenhoff study that were sacrificed early (after 4 or 14 weeks, with LOAELs of 0.34–0.37 mg/kg bw per day; Seacat et al., 2003) and female rats exposed for 2 years (0.299 mg/kg bw per day; Butenhoff et al., 2012b). Hepatocellular hypertrophy accompanied by cytoplasmic vacuolation was also observed in monkeys, with a NOAEL and LOAEL of 0.15 and 0.75 mg/kg bw per day, respectively. Therefore, increased liver weight and hepatocellular hypertrophy are considered in the dose–response assessment—despite their potential to be adaptive, rather than adverse, effects—as a means of preventing the more serious histological effects observed in other studies or at higher doses. The NOAEL of 0.024 mg/kg bw per day was adjusted to a value of 0.021 mg/kg bw per day to account for decreased purity of the test material, which was only 86.9%.

The use of conservative endpoints for liver effects is not contradicted by epidemiology studies. Human studies demonstrated weak and inconsistent evidence of alterations of hepatic enzymes due to PFOS exposure, with positive, negative, and absent associations for hepatic parameters, depending on the study. Associations between changes in ALT levels of former perfluoroalkyl workers (3M plant) and geographically exposed individuals (included in the C8 project) and median PFOS serum levels ranging from 18 to 366 ng/mL have been reported (Gallo et al., 2012; Olsen et al., 2012); the ALT levels were increased in the environmentally-exposed population and decreased in the occupationally-exposed. No effect on liver enzyme levels was observed in a cross-sectional study of PFOS workers with serum levels in the range of 20–2,110 ng/mL (Olsen et al., 2003b).The serum values in the study with positive results are one to two orders of magnitude lower than the serum NOAEL and LOAEL values for the Butenhoff study (1,310 and 7,600 ng/mL, respectively).

Changes in thyroid hormone levels—which were observed in monkeys, rats, and mice—are also proposed as a critical effect for this analysis. The observed effects were typically decreases in T3 and T4 that were often observed at the lowest doses in studies. Corresponding increases in TSH were observed in a 26-week study of cynomolgus monkeys, but not in the rodent studies. Authors of a 26-week study of cynomolgus monkeys (Seacat et al., 2002) concluded that a LOAEL for thyroid hormone changes was 0.75 mg/kg bw per day; however, Health Canada (2013c) performed a statistical reanalysis of the data from Seacat et al. (2002) that allowed for improved interpretation of measures at multiple timepoints. The reanalysis identified

dose effects for decreases in total T3 in both sexes and total T4 in females only, and dose–time effects for total T3, total T4, and TSH. The LOAEL and NOAEL values for changes in thyroid hormone levels as identified by the reanalysis were 0.15 and 0.03 mg/kg bw per day, respectively. Most rat studies had no NOAEL; the lowest LOAELs were in a similar range to the monkeys, as outlined in Section 9.2.2.4. As the NOAEL of 0.03 mg/kg bw per day from the 26-week monkey study is ~~lower than~~similar to the NOAEL for hepatocellular hypertrophy, thyroid hormone changes are considered as a potential critical effect for this assessment. Effects on thyroid hormone levels were not studied in many mouse studies, but decreases in T4 were observed only at higher levels (with the lowest LOAEL of 5 mg/kg bw per day in pups exposed *in utero* [Lau et al., 2003]). The chronic study of rats (Butenhoff et al., 2012b) did not identify any histological changes to the thyroid; however, the study did not explore changes in thyroid hormone levels, which can impact various systems in the body even in absence of structural changes to the thyroid. Epidemiology studies do not indicate any clear trends in PFOS-induced thyroid hormone changes—although some decreases in T3 and T4 were observed in association with increased PFOS levels, other studies indicated positive or absent associations.

Several of the studies identifying decreases in T3 and T4 levels were one-generation studies (primarily in rats), with observations of thyroid hormone level changes in both dams and pups. These thyroid hormones play an important role in development of fetal organs, including that of the central nervous system, with deficiencies observed to result in worsened neurobehavioural outcomes in animals and humans (Pop et al., 1999; Koibuchi and Chen, 2000; Morreale de Escobar, 2004; Williams, 2008; Delahunty et al., 2010; Gilbert et al., 2012; Schroeder and Privalsky, 2014). Several studies have provided some evidence of neurodevelopmental effects resulting from PFOS exposure (including changes in the brain ultrastructure, gene and protein expression, and learning abilities in rats, and motor behaviour in both rats and mice), with many LOAELs in a similar range to those observed for thyroid effects (see Section 9.2.5). In the one study (in rats) that investigated both thyroid and neurodevelopmental effects (Lau et al., 2003), lower T4 levels were observed in conjunction with small decreases in prefrontal cortex choline acetyltransferase levels (which is sensitive to thyroid hormone status), but no changes in learning and memory behaviours were noted. Although several studies indicate changes in motor behaviour in rats and mice at doses of 0.3–0.75 mg/kg bw per day (Johansson et al., 2008; Butenhoff et al., 2009; Onishchenko et al., 2011; Wang et al., 2015), weaknesses in each of the studies preclude their use as critical studies for these low doses. Study design affected the mouse studies, as Johansson et al. (2008) only provided the dose on a single day, and Onischenko et al. (2011) only contained a single dose group. The rat studies had inconsistent results. In Butenhoff et al. (2009), changes in motor activity were only observed on a single day, which was different in males and females (only at PND 17 in males exposed to 0.3 and 1 mg/kg bw per day, and only at PND 21 in females exposed to 1 mg/kg bw per day, with no effects in either sex at PND 13 or 61). In the Wang et al. (2015) study, rat pups were exposed *in utero*, lactationally, or both to 5 and 15 mg/L in drinking water (equivalent to 0.7 and 2.1 mg/kg bw per day using Health Canada's [1994] assumption of 1 ppm in water = 0.14 mg/kg bw per day in rats, which might not be relevant for pregnant or lactating dams). Effects on learning ability were observed in both dose groups, but more consistently at the high dose; at the low dose, changes were observed at fewer measurement days and were observed in the groups exposed only *in utero* or lactationally, and not in the group exposed over both periods. In cross-sectional epidemiological studies, although one study reported a positive association between increased

PFOS levels and neurodevelopmental effects (reported ADHD), no clear relationships were observed for this endpoint in limited and equivoqual epidemiological evidence; no associations were observed for other neurodevelopmental milestones. If further studies demonstrate consistency of effects at low levels, the endpoint could be considered as a potential critical effect for PFOS exposures; in the absence of consistent effects at low levels, a TDI based on liver or thyroid effects is assumed to be sufficiently protective of neurobehavioural changes.

Changes in serum lipid levels were also observed around the levels at which liver and thyroid effects occur. Typical observed changes were decreases in total cholesterol, HDL, and triglycerides. The lowest dose at which serum lipid changes were observed was in the 26-week study of Cynomolgus monkeys, where decreases in HDL were observed at 0.03 mg/kg bw per day (i.e., the NOAEL for the previously-described thyroid effects). The lowest LOAEL for mice was 0.166 mg/kg bw per day (Fair et al., 2011), and for rats was 0.4 mg/kg bw per day (Luebker et al., 2005b). These effects are important for consideration during the assessment of PFOS risks, as epidemiology studies tend to demonstrate minor positive (albeit inconsistent, and of questionable clinical importance) associations between PFOS and serum cholesterol levels. Because inconsistencies in effect were observed between the two databases, and within the epidemiology database, and clear dose–response relationships were absent in the animal studies, quantitative assessments were not performed for serum lipid effects. Based on the present database, a TDI based on liver or serum effects is assumed to be sufficiently protective of lipid changes.

To reflect the large interspecies differences in pharmacokinetics, POD_{HEQ} are calculated for both of the proposed critical effects, as follows:

$$POD_{HEQ} = \frac{\text{X mg/kg bw per day}}{AK_{UF}}$$

where:

- X mg/kg bw per day is the point-of-departure associated with the NOAEL for hepatocellular hypertrophy or thyroid hormone changes described above; and
- AK_{UF} is the appropriate dose- and species-specific adjustment factor (as described in Section 8.6.2).

Two different AK_{UF} values were applied for the assessments. Both of the LOAELs were <0.1 mg/kg bw per day; therefore, the corresponding AK_{UF} was applied for each species. An AK_{UF} value of 14 was used for rats, and a value of 4 was used for monkeys, as described in Section 8.6.

Using the calculated POD_{HEQ}, the non-cancer TDIs are calculated as follows:

$$TDI = \frac{\text{X mg/kg bw per day}}{UF}$$

where:

- X mg/kg bw per day is the POD_{HEQ} calculated for each critical effect, as described above; and
- UF is the composite uncertainty factor, as described below.

The composite UF varied based on the effect. For all PODs, an interspecies uncertainty factor of 2.5 was used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between animals and humans were already incorporated when calculating the POD_{HEQ}. Likewise, default values of 10 were applied for the intraspecies uncertainty factor for all PODs. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOS excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. In the one study of human half-life of PFOS, the range between the lowest and highest values is 10-fold. If further studies of PFOS consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed. An uncertainty factor of 3 was also applied to reflect that the longest duration at which effects on thyroid hormone levels were explored was a 26-week study in monkeys (Seacat et al., 2002), which is only a fraction of the animal's lifetime. A value of 3 was selected rather than the full value of 10 because the LOAELs for shorter duration studies in rats were similar to those in subchronic studies; however, a subchronic-to-chronic uncertainty factor was still necessitated, despite this observation, as the Health Canada (2013c) reanalysis of data identified a statistically significant time–dose effect for thyroid endpoints. The uncertainty factor was not required for hepatocellular hypertrophy, which was observed in a chronic study.

The POD_{HEQ} and TDIs for each critical health effect are calculated and presented in Table 4 below:

Table 4: Calculation of non-cancer POD_{HEQ} and TDI for each critical health effect

Study	Hepatocellular hypertrophy Butenhoff et al., 2012b	Thyroid hormone changes Seacat et al., 2002
NOAEL (mg/kg bw per day)	0.021	0.03
AK_{UF}	14	4
POD_{HEQ} (mg/kg bw per day)	**0.0015**	**0.0075**
Composite UF	25	75
TDI (mg/kg bw per day)	**0.00006**	**0.0001**

The TDIs calculated for the two critical effects are similar, with a slightly lower value for hepatocellular hypertrophy in rats. For this reason, hepatocellular hypertrophy is used as the basis of the TDI, but is further quantitatively supported by the TDI for thyroid effects in monkeys. ~~Using this TDI~~ Please note that a NOAEL approach was employed following consideration of a BMD approach for hepatocellular hypertrophy only since data on thyroid hormone changes were not amenable to BMD modeling. Briefly, BMD_{10} and $BMDL_{10}$ were calculated for hepatocellular hypertrophy in male rats. Of the models that provided a reasonable fit, the lowest $BMDL_{10}$ was 0.044 mg/kg bw per day, which is two-fold the NOAEL. In the interest of being protective of human health and due to the uncertainty surrounding PFOS's human half-life, we determined that the BMD approach did not provide a secure basis for risk assessment purposes. Therefore, using the NOAEL for hepatocellular hypertrophy, the HBV for drinking water can be calculated as follows:

$$\text{HBV} = \frac{0.00006 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= 0.00056 \text{ mg/L}$$

$$\approx 0.0006 \text{ mg/L } (0.6 \text{ µg/L})$$

where:

- 0.00006 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7).

10.3 Comparison of cancer and non-cancer risk assessment

The HBV for the non-cancer assessment, which was 0.0006 mg/L using data of histological changes in rat liver, is more conservative than the HBV for hepatocellular tumours of 0.01 mg/L. The ~~proposed~~ HBV of 0.0006 mg/L that was derived for non-cancer effects is therefore considered to be sufficiently protective of the carcinogenic effects of PFOS.

10.4 Application of additive approach

In keeping with a precautionary approach, the currently available data support the implementation of an additive approach for PFOS and PFOA when evaluating situations where PFOS and PFOA co-occur in drinking water. Given that PFOS and PFOA are the predominant PFAS detected in Canadian water samples and the lack of toxicological data on PFAS besides PFOS and PFOA, the additive approach was not extended to other PFAS. Of the existing additivity approaches for risk assessment (i.e. hazard index, point of departure index, combined margin of exposure index, toxic unit summation, and relative potency factors/toxic equivalency factors; Meek et al., 2011; SCHER, 2012), the hazard index approach was deemed to be the best choice for PFOS and PFOA that is health protective. The hazard index is the sum of the hazard quotients (i.e., the ratios between exposure and the reference value) for each component to be evaluated (SCHER, 2012). When the hazard index is less than 1, the combined risk is considered acceptable; values greater than 1 indicate potential health concern. This approach is the preferred approach for chemicals with high quality toxicology data (e.g., dose-response data, health hazard information), reflecting the scientific knowledge and toxicity associated with each chemical, and it is transparent and easy to apply (Meek et al., 2011; SCHER, 2012), although it is likely to overestimate risk (Boobis, 2009; Meek et al., 2011). Additionally, the value of this approach has been demonstrated for the combined risk assessment of PFOS and PFOA (Ludwicki et al., 2015) and for 17 perfluoroalkylated substances (Borg et al., 2013). Borg et al. (2013) noted that their assessment of 17 perfluoroalkylated congeners should be looked upon as conservative, given that

the use of the hazard index approach is likely to overestimate risk (Boobis, 2009; Meek et al., 2011) and that the majority of congeners lack toxicological data, requiring the use of read-across extrapolations to the closest congeners with longer carbon chain lengths (assuming that potency is proportional to carbon chain length). Similarly, Ludwicki et al. (2015) cited the lack of toxicological data on other congeners besides PFOS and PFOA as a reason for not including them in any cumulative risk assessments of perfluoroalkylated substances. The differences between PFOS and PFOA described above (in section 9.4), in particular the lack of evidence demonstrating that a single receptor is required to mediate the toxicities of PFOS and PFOA and the ability of PFOS and PFOA to induce a multitude of toxicities, preclude the use of a scaling system analogous to the toxicity equivalence factor system used for polychlorinated biphenyls and polycyclic aromatic hydrocarbons (Scialli et al., 2007; Peters and Gonzalez, 2011). Therefore, in employing the additive approach for PFOS and PFOA, the addition of the observed concentration to MAC ratios for PFOS and PFOA should be kept below the value of 1. This approach can be expressed as:

$$\frac{\text{PFOS concentration}}{\text{MAC}_{\text{PFOS}}} + \frac{\text{PFOA concentration}}{\text{MAC}_{\text{PFOA}}} < 1$$

Or

$$\frac{\text{PFOS concentration in } \mu g/L}{0.6\ \mu g/L} + \frac{\text{PFOA concentration in } \mu g/L}{0.2\ \mu g/L} < 1$$

10.5 International considerations

~~A memorandum published by the~~ The U.S. EPA ~~Office of Water indicates a Provisional Health Advisory (PHA~~(2016) has established a lifetime health advisory (LHA) of 0.207 µg/L (0.~~0002~~000 07 mg/L) for PFOS ~~(U.S. EPA, 2009b).~~. This ~~PHA~~LHA was derived from a NOAEL of 0.~~03~~1 mg/kg bw per day for ~~increased levels of TSH in males, reduced total T3 levels in males and females and reduced levels of high-density lipoproteins (HDL) in female Cynomolgus monkeys orally exposed to PFOS for 183 days (Seacat et al., 2002). An uncertainty factor of 300 (×10 for~~ decreased pup body weight following maternal exposure to PFOS for six weeks prior to and during gestation by oral gavage (Luebker et al., 2005a). A reference dose (RfD) of 0.000 02 mg/kg bw per day (0.02 µg/kg bw per day) was derived by applying pharmacokinetic modeling to serum PFOS concentrations to calculate a human equivalent dose (HED) (equivalent to an uncertainty factor of 196 from the NOAEL to the HED to account for interspecies differences in toxicokinetics). An uncertainty factor of 30 (×10 for intraspecies differences, ×3 for interspecies toxicodynamic differences ~~and ×13 for interspecies toxicokinetic differences) was applied, resulting in a reference dose rounded at 80 ng/kg bw per day (U.S. EPA, 2009b). This reference dose (RfD) was also indicated in a memorandum emitted by the U.S. EPA Office of Solid Waste and Emergency Response (U.S. EPA, 2009c). Based on U.S. EPA policy,~~ the PHA (0.2) was applied to the HED. Additionally, when PFOA co-occurs with PFOS at the same time and location in a drinking water source, the U.S. EPA recommends comparing the sum of the concentrations of PFOS and PFOA to the LHA of 0.07 µg/L) ~~was further derived for a 10-~~

~~kg child consuming 1 L water per day using a default assumption that drinking water contributes 20% of total exposure to PFOS (U.S. EPA, 2009b).~~.

The ~~Minnesota~~Australia Department of Health (~~MDH, 2008c; 2008d) derived~~ 2017) has established a ~~Health Risk Limit (HRL)~~ health-based drinking water quality value of 0.~~3 µg~~07 µg/L (0.~~0003~~000 07 mg/L~~).~~) for PFOS based on a TDI calculated by Food Standards Australia and New Zealand (FSANZ, 2017). This drinking water quality value was ~~based on the decreased HDL cholesterol, decreased T3 and increased TSH observed in monkeys exposed to ≥~~derived from a NOAEL of 0.~~03~~1 mg/kg bw per day (~~Seacat~~for decreased pup body weight following maternal exposure to PFOS for six weeks prior to mating and during gestation by oral gavage (Luebker et al., ~~2002; Thomford, 2002). More precisely, the benchmark dose (BMDL; level of response not specified) for these effects~~2005a). A TDI of 0.000 02 mg/kg bw per day (0.02 µg/kg bw per day) was ~~estimated at 35,000 ng/mL PFOS in monkey~~ derived by applying pharmacokinetic modeling to serum~~. A human~~ PFOS concentrations to calculate a HED (equivalent ~~dose (HED) of 2,500 ng/kg bw per day (2.5 µg/kg bw per day, or 0.0025 mg/kg bw per day) was calculated based on the elimination of PFOS in humans (using human half-life data to estimate clearance).~~to an uncertainty factor of 167 from the LOAEL to the HED to account for interspecies differences in toxicokinetics). An additional uncertainty factor of 30 (~~×~~(10 for ~~human variability~~intraspecies differences and ~~×~~3 for interspecies toxicodynamic differences) was applied to the HED~~, resulting in a reference dose rounded at 80 ng/kg bw per day (0.08 µg/kg bw per day, or 0.00008 mg/kg bw per day). Steady-state uptake/elimination was estimated to occur after 27 years of exposure, therefore a time-weighted 95th percentile intake for the first 27 years of life (0.049 L/kg bw per day) was used as~~. From the TDI, a drinking water guidance value of 0.07 µg/L was calculated using a body weight of 70 kg, water consumption of 2 L/day, and an allocation factor of 0.1. Additionally, when PFOS co-occurs with PFHxS, another perfluoroalkyl sulfonic acid, the Australian Department of Health recommends comparing the ~~daily water ingestion. This, along with a relative source contribution of 20%, resulted in a Health Risk Limit (HRL) rounded at 0.3 µg/L (MDH, 2008c; MDH, 2008d).~~ sum of the concentrations of PFOS and PFHxS to the guidance value of 0.07 µg/L.

A drinking water guideline of 0.3 µg/L (0.0003 mg/L) was derived by the UK Health Protection Agency (UK HPA, 2007; 2009) based on a TDI of 300 ng/kg bw per day (0.3 µg/kg bw per day) previously derived by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (UK COT, 2006). This TDI was derived from a point-of-departure (0.03 mg/kg bw per day) corresponding to the NOAEL for decreased serum T3 levels in monkeys exposed for 26 weeks (Thomford, 2002; Seacat et al., 2002), divided by an uncertainty factor of 100 (for intra- and inter-species variation). The drinking water guideline (0.3 µg/L) was derived from this TDI, using an allocation factor of 10%, a body weight of 10 kg and a water ingestion rate of 1 L per day for a one-year-old child (UK HPA, 2007).

In their scientific opinion document on contaminants in the food chain, the CONTAM panel under the European Food Safety Authority derived a TDI of 150 ng/kg bw per day (0.15 µg/kg bw per day) based on a NOAEL of 0.03 mg/kg bw per day (associated with a plasma concentration of 13,200 ng/mL in females)(EFSA, 2008). This NOAEL was taken from an oral dietary study in Cynomolgus monkeys; changes in lipids and thyroid hormones were observed at the next higher dose (0.15 mg/kg bw per day) (Seacat et al., 2002). The NOAEL was divided by an uncertainty factor of 200 (×10 for interspecies differences, ×10 for intraspecies differences and

×2 to compensate for uncertainties in connection to the relatively short duration of the key study and the internal dose kinetics).

11.0 Rationale

PFOS is an anthropogenic compound which was used for water, oil and/or stain resistance on surface and paper-based applications, such as rugs and carpets, fabric and upholstery. It was also used in specialized chemical applications, such as fire-fighting foams, hydraulic fluids, and carpet spot removers. PFOS is no longer manufactured, imported, sold, offered for sale or used in Canada, unless incidentally present, with certain exemptions and under certain conditions (e.g., aviation hydraulic fluids). Because of its extremely persistent nature, PFOS can still be found in the environment. Canadians can be exposed to PFOS in food, consumer products, dust, and drinking water. The major sources of PFOS is expected to be food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Based on its physico-chemical properties, exposure to PFOS via inhalation and dermal routes during showering or bathing is expected to be negligible.

The carcinogenicity of PFOS has not been evaluated by IARC. Chronic exposure to PFOS has been associated with both cancer and non-cancer effects in animals and humans. HBVs for both endpoints have been calculated, with the non-cancer effects resulting in a lower, more conservative HBV.

Epidemiological studies have shown associations between exposure to PFOS and multiple non-cancer health outcomes, such as reproductive, developmental, and immunological effects. However, these studies cannot be used to derive the non-cancer HBV for PFOS due to their limitations, including in terms of study design, bias and confounders. In animals, non-cancer effects observed at the lowest levels of exposure include immunological effects, liver effects, effects on the thyroid and changes in serum lipid levels. For various reasons described in section 10.2, the most appropriate endpoint to derive a HBV for PFOS is hepatocellular hypertrophy (liver effects) in rats, supported quantitatively by the estimated value for thyroid effects in monkeys. Using a TDI approach, a HBV of 0.0006 mg/L (0.6 µg/L) has been calculated for the non-cancer effects of PFOS based on liver effects in rats. This HBV is considered to be sufficiently protective of both cancer and non-cancer effects of PFOS.

A MAC of 0.0006 mg/L (0.6 µg/L) is ~~proposed~~established for PFOS in drinking water. The ~~proposed~~ MAC for PFOS can be measured by available analytical methods and is achievable by municipal and residential treatment technologies.

However, when detected in drinking water, PFOS is often found with other PFAS, including PFOA. Although current science does not justify the use of this approach for other PFAS, it does support additivity for PFOA and PFOS, based on the similarity of the health effects used to establish their respective MACs, and the extensive characterization of their toxicity and toxicokinetics. Thus, when PFOS and PFOA are found together in drinking water, the best approach to protect human health is to consider both chemicals together, by ensuring that the sum of the ratios of the observed concentration to the MAC for PFOA and PFOS does not exceed 1.

As part of its ongoing guideline review process, Health Canada will continue to monitor new research and recommend any change to the guideline that is deemed necessary.

12.0 References

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Appendix A: Reported full-scale drinking water treatment plant PFOS/PFOA removal data[1]

Water Source	Treatment Train[2]	Influent concentration (ng/L)	Effluent concentration (ng/L)	% Removal of PFOS	Reference
Groundwater	DBF, UV, Cl_2	10	9.4	6	Quinones and Snyder, 2009
Surface water	O_3, COA/FLOC, DBF, Cl_2	1.4	1.4	0	Quinones and Snyder, 2009
Surface water	PAC, CHLM, DBF	1.7	1.9	-12	Quinones and Snyder, 2009
Surface water	Cl_2, COA/FLOC, DBF, UV	22	22	0	Quinones and Snyder, 2009
Planned potable indirect reuse facility	MF/RO, UV/H_2O_2, SAT	41	ND	100	Quinones and Snyder, 2009
Planned potable indirect reuse facility	Cl_2, DL, SAT	29	57	-97	Quinones and Snyder, 2009
River water	RSF, O_3, GAC, Cl_2	1.0 (Summer)	0.93 (Summer)	7	Takagi et al., 2008
River water	RSF, O_3, GAC, Cl_2	0.87 (Summer) 3.2 (Winter)	2.8 (Summer) 1.6 (Winter)	-222 (summer) 5 (winter)	Takagi et al., 2008
River water	RSF, O_3, GAC, Cl_2				Takagi et al., 2008
Lake water	RSF, GAC, Cl_2	4.6 (Summer) 4.5 (Winter)	0.16 (Summer) <0.1 (Winter)	97 (summer) >98 (winter)	Takagi et al., 2008
River, lake, subsoil and groundwater (7 plants)	RSF, Cl_2	0.56 – 22 (Sum) 0.54 – 4.2 (Win)	0.45 – 22 (Sum) 0.37 – 4.5 (Win)	20 – 0 (summer) 31 – 0.7 (winter)	Takagi et al., 2008
River water	Membranes, Cl_2	0.37 (Summer) 0.26 (Winter)	0.29 (Summer) 0.20 (Winter)	22 (summer) 23 (winter)	Takagi et al., 2008
Lake water	SSF, Cl_2	2.7 (Summer) 1.8 (Winter)	2.3 (Summer) 1.9 (Winter)	15 (summer) -6 (winter)	Takagi et al., 2008
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.3 (Summer) 3.3 (Winter)	3.7 (Summer) 1.3 (Winter)	-185 (summer) 60 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.6 (Summer) 3.3 (Winter)	2.3 (Summer) 1.7 (Winter)	44 (summer) 48 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.2 (Summer) 2.8 (Winter)	1.6 (Summer) 1.9 (Winter)	-33 (summer) 32 (winter)	Takagi et al., 2011
River water	SED, O_3, GAC, Cl2, SF	1.4 (Summer) 3.3 (Winter)	2.2 (Summer) 2.0 (Winter)	-57 (summer) 39 (winter)	Takagi et al., 2011
Lake water	COA/FLOC/SED, SF, GAC (reactivated), Cl_2	4.4 (Summer) 4.1 (Winter)	<0.5 (Summer) <0.5 (Winter)	>89 (summer) >88 (winter)	Takagi et al., 2011
Ground water	UF, Cl_2	16	16	0	Atkinson et al., 2008
Ground water	GAC (not in operation), super chlorination and dechlorination	135	130	3	Atkinson et al., 2008
Ground water	GAC (2 parallel GAC trains each having 6 beds;	42	45	-7	Atkinson et al., 2008

Water Source	Treatment Train[2]	Influent concentration (ng/L)	Effluent concentration (ng/L)	% Removal of PFOS	Reference
	contactors are mature and act as biological contactors; not been regenerated for some years), Cl_2				
Ground and surface water (60:40)	SSF, O_3, GAC (6 beds-no regeneration for several years), Cl_2using NaOCl	20.6	25	-21	Atkinson et al., 2008
Ground water	Cl_2 using NaOCl				Atkinson et al., 2008
River water	COA/FLOC/SED, O3, GAC, RSF	5.3 (Aug) 5.8 (Oct)	9.4 (Aug) 6.4 (Oct)	-77 (Aug) -10 (Oct)	Shivakoti et al., 2010)
River water	COA/FLOC/SED, O3, GAC, RSF	5.8 (Aug) 8.8 (Oct)	3.9 (Aug) 4.2 (Oct)	33 (Aug) 53 (Oct)	Shivakoti et al., 2010)
Treated wastewater	De-nitrification, pre-O_3, COA/FLOC/SED, DAF, O_3, GAC (acts as biological contactor), O_3	2,2 (Oct) 3.7 (Nov) 3.6 (Nov)	<LOR (0.3 ng/l) (Oct) 0.6 (Nov) 0.7 (Nov)	100 (Oct) 84 (Nov) 81 (Nov)	Thompson et al., 2011b
River water	COA/FLOC/SED, RSF, Cl_2	5.02	0.73	85	Kunacheva et al., 2010)
Treated wastewater	Clarifier/lamellar settler ($FeCl_3$&$(NH_4)_2SO_4$, NaOCl addition), UF, RO, UV+H_2O_2, stabilization/disinfection (addition of lime, CO_2, NaOCl)	38 39 23	<LOR (0.5 ng/L) ND <LOR (0.2 ng/L	100 100 100	Thompson et al., 2011
River water	COA/FLOC, RSF, O_3, GAC, SSF	8.2	<0.23	<97	Eschauzer et al., 2012
River water	Cl_2, COA/FLOC, RSF, O_3, GAC	116	33	69	Flores et al., 2013
River water	Cl_2, COA/FLOC, RSF, O_3, GAC, UF, RO	86	13	86	Flores et al., 2013

[1]developed from Rahman et al. (2014) Table 3

[2] COA/FLOC/SED = coagulation/flocculation sedimentation; DAF = dissolved air flotation; DL=dilution; GAC = granular activated carbon; RSF = rapid sand filtration; SSF = slow sand filtration; SF = sand filtration; NaOCl = sodium hypochlorite; Cl_2 = chlorine; O_3=ozonation; RO = reverse osmosis; UF = ultrafiltration; IX = ion exchange; SF = sand filtration; UV/H_2O_2 = ultraviolet irradiation/hydrogen peroxide; SAT = soil aquifer treatment; CHLM = chloramines

Appendix B: List of Acronyms

AFFF	aqueous film-forming foam
ALT	alanine transaminase
BMD	benchmark dose
BMDL	lower confidence limit on the benchmark dose
$BMDL_{10}$	lower 95% confidence limit on the benchmark dose for a 10% response
BV	bed volume
CAS	Chemical Abstracts Service
CI	confidence interval
CSAF	chemical specific adjustment factor
DI	direct injection
DL	detection limit
EBCT	empty bed contact time
ESI	electrospray ionization
GAC	granular activated carbon
GD	gestational day
GM	geometric mean
HBV	health-based value
HPLC	high performance liquid chromatography
IT	ion-trap
LC	liquid chromatograph
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantitation
LLE	liquid-liquid extraction
MAC	maximum acceptable concentration
MDL	method detection limit
MOA	mode of action
MRL	minimum reporting level
MS/MS	tandem mass spectrometry
NF	nanofiltration
NOAEL	no-observed-adverse-effect level
NOM	natural organic matter
PAC	powdered activated carbon
PBPK	Physiologically-based pharmacokinetic
PEFT	polytetrafluoroethylene
PFAA	perfluorinated alkyl acid
PFAS	perfluoroalkyl substance
PFCA	long-chain perfluorocarboxylic acids
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PND	postnatal day
POD	point of departure

POD_{HEQ}	human-equivalent points-of-departure
PTFE	polytetrafluoroethylene
RBF	river bank filtration
RO	reverse osmosis
SPE	solid phase extraction
TDI	tolerable daily intake
TDS	total diet study
UCMR3	third Unregulated Contaminant Monitoring Rule

General comments:

#	Comments	Response
1	Le sulfonate de perfluorooctane (SPFO) se retrouve un peu partout dans l'environnement, mais son innocuité est très loin d'être démontrée. Les études ont plutôt tendance à démontrer que c'est problématique pour la santé humaine mais vet aspect est minimisé dans le document. Le SPFO s'accumule dans l'organisme, se retrouve dans le lait maternel. Je crois que vous comprenez que ces 2 constats exposent le problème sur la santé d'une accumulation sur toute une vie, ainsi que l'effet sur la santé des nourrissons. Il n'y a pas matière à ignorer cette problématique.	The health based value is based on the latest science for the protection of human health. The document describes the health effects and toxicokinetics associated with PFOS exposure in detail. The established MAC is protective of the human health of the population, including infants. No change to the document.
2	Although we do not object to the establishment of a MAC of 0.0006 mg/L (0.6 µg/L) for PFOS, we ask that it be clear inthe final guideline that it applies to tap water and to explicitly state that the MAC is not applicable to foods or beverages such as bottled water, etc.	Thank you. No change to the document.
3	PFOS is comparatively water soluble, and persistent because it is extremely resistant to metabolism or biodegradation. Despite the enormous amount of research on the fate and behavior of the perfluorinated compounds in the environment, the case for drinking water utilities to invest substantial resources into expensive monitoring for PFOS is weak.	PFOS has been identified as a concern in drinking water in several locations in Canada, thereby meeting our criteria for guideline development. No change to the document.
4	The work invested in this guideline document development would have been wisely deferred until the UCMR3 results were available for analysis, as there is no compelling health risk issue apparent for human exposure to PFOS via drinking water. The human health effects attributed to PFOS are marginal at best, particularly in relation to total exposure and drinking water exposure in particular.	PFOS has been identified as a concern in drinking water in several locations in Canada, thereby meeting our criteria for guideline development. No change to the document.
5	We concur with the proposed MAC, but would suggest that water quality testing for raw and treated water for a few select vulnerable communities should be conducted before implementing the new guideline.	This is outside Health Canada's mandate, and outside the scope of the document. Provinces and territories are responsible for the adoption and/or implementation of guidelines. No change to the document.
6	We would recommend that the MAC for PFOS be lowered based on the U.S. EPA's analysis for their health advisory.	Health Canada derives health based values based on the latest science for the protection of human health, using the Canadian context and assumptions. Other international assessments are considered in our approach. No change to the document.

#	Comments	Response
7	We would recommend that Health Canada, working with its provincial counterparts if necessary, identify Canadian communities and vulnerable populations of Canadians at risk of exposure to elevated PFOA and PFOS in drinking water, and develop and implement a plan to ensure safe drinking water is provided to those communities and populations of Canadians.	This is outside Health Canada's mandate, and outside the scope of the document. Provinces and territories are responsible for the adoption and/or implementation of guidelines. No change to the document.
8	Il serait pertinent que le document précise si des composantes d'un réseau de distribution (ex. conduites) peuvent être une source potentielle de cette substance.	Unlike PFOA salts, PFOS is not used in the production of drinking water materials and would not be expected to leach from components used in the distribution system.
9	Le document détaille bien l'ensemble des données scientifiques disponibles, plus particulièrement l'approche spécifique au contaminant utilisée pour l'extrapolation de l'animal vers l'humain. Cette approche a d'ailleurs été adoptée par les autres organismes de référence pour le SPFO. Néanmoins la lecture de la description des effets à la santé des humains et des animaux serait grandement facilitée par l'ajout de tableaux synthèses.	Due to limitations on web publishing of the documents, the use of tables in our documents is kept to a minimum. No change to the document.
10	Puisque les effets critiques du SPFO et de l'APFO sont les mêmes et que ces derniers sont susceptibles d'être présents simultanément dans l'eau potable, le GSE considère qu'il serait approprié de discuter de la pertinence ou non de présenter une recommandation commune à la fois pour l'APFO et le SPFO.	The text has been modified to include an additive approach for PFOS and PFOA.
11	Enfin, puisque les effets critiques du SPFO et de l'APFO sont les mêmes et que ces derniers sont susceptibles d'être présents simultanément dans l'eau potable, il serait approprié de discuter de la pertinence ou non de présenter une recommandation commune à la fois pour l'APFO et le SPFO.	The text has been modified to include an additive approach for PFOS and PFOA.
12	In preparation for review of the documents on PFOS and PFOA, we undertook sampling of raw and treated water for surface water sources and had the samples analyzed. The sample analysis costs were a staggering $540 per sample for both PFOS and PFOA. If this guideline is adopted and utilities are required to monitor for these compounds, it will likely be a financial challenge for many utilities, especially where it is unlikely that many source waters would be considered high or even medium risk for the presence of these compounds.	The cost of analysis is beyond the scope of the document. The adoption and implementation of guideline is under PT jurisdiction. No change to the document.

#	Comments	Response
13	Having a MAC of 0.6 µg/L, while perhaps a commendable goal from a health standpoint, provides some challenges from a laboratory and treatment perspective. At the present time very few, if any, analytical laboratories in Canada, public or private, seem to be able to measure to this level of MAC and be ISO 17025 accredited for it in drinking water. Consequently, we're not sure what is being achieved by having such a stringent target, notwithstanding the ability of water utilities to obtain a representative drinking water sample and access a Canadian laboratory accredited for this analysis cost effectively.	Thank you for the comment. No change to the document.

Section 2.0: Executive summary

#	Comments	Response
14	2.2 - La dernière phrase de cette section fait état des concentrations susceptibles d'être retrouvées dans l'eau potable à l'aide d'une valeur exprimée en nanogrammes. Il serait plus approprier d'exprimer ces concentrations en milligrammes.	The document has been modified to address this comment.

Section 3.0: Application of the guideline

#	Comments	Response
15	3.1 - La section recommande une vérification ponctuelle des concentrations de SPFO dans l'eau brute, et un suivi trimestriel ou semestriel si la CMA est dépassée à l'eau brute. Il n'est cependant pas fait mention qu'une détection à l'eau brute devrait amener à instaurer un suivi dans l'eau distribuée.	The information in the document has been updated and now indicates that if treatment is required, paired samples of source water and treated water should be taken semi-annually to confirm the efficiency of the treatment.
16	3.1 - Une mention relative aux dépassements transitoires devrait être ajoutée, comme c'est le cas dans les documents relatifs aux substances organiques publiés dans les dernières années.	Text added to section 3.0
17	3.1 - "*Utilities should characterize their source water to assess PFOA concentrations*" should be accompanied by a caution that analysis for PFOA is a highly specialized analytical capability. A routine water quality laboratory without explicit experience in analysis of perfluorinated compounds and documented QA/QC for such methods is likely to be subject to either or both false positives or false negatives.	We agree. The document has been modified to include this information in sections 3.1 and 6.2.

#	Comments	Response
18	3.1 - "*Utilities may consider reduced monitoring when they have data indicating that PFOS does not occur in the source water*" would be more helpful by stating the obvious, substituting "should" for "may". Monitoring for PFOS is very expensive and there needs to be very sound justification for spending valuable funds for monitoring for what will, in the vast majority of cases, be an obscure risk at best.	This is a provincial or territorial decision. No changes to the document

Section 4.0: Identity, use and sources in the environment

#	Comments	Response
19	4.0 - "*PFOS was produced in the U.S. until 2002, when the 3M Company phased out its PFOS production (ATSDR, 2009). Although there are no known Canadian manufacturers of PFAS, including PFOS, almost 600,000 kg of PFAS were imported into Canada between 1997 and 2000 (PFOS represented a very small proportion of this total) (HC, 2006). In 2009, PFOS and its salts were added to the Canadian Virtual Elimination List compiled under subsection 65(2) of CEPA 1999, as required by subsection 3(1) of the Act (SOR/2009-15) (GOC, 2009). The Canadian regulations prohibit the manufacture, import, sale, offer for sale and use of PFOS or products containing PFOS, unless incidentally present, with certain exemptions for aviation hydraulic fluids under certain conditions, and some products used in photographic or photolithographic process (GOC, 2008)*" highlights how unlikely any Canadian water utility is to be affected by PFOS unless there is some identifiable connection with PFOS use.	We refer the reviewer to section 4.1, which describes in detail scenarios that result in PFOA entering Canadian waters. In addition, PFAS are being found in Canadian drinking water supplies near point sources (e.g., airports) in several regions of the country. No change to the document.

Section 5.0: Exposure

#	Comments	Response
20	5.0 - "*The estimated total daily intake of PFAS (estimates not provided for individual PFAS) in Canadians was reported to be 410 ng/day for the general population of Canada (Tittlemier et al., 2007). Drinking water ingestion contributed only a minor amount to the overall estimated exposure (estimated at 0.3 ng/day)*" for total PFAS, not just PFOS should be compared with the proposed MAC for PFOS alone that would yield 900 ng/day of PFOS for consumption of 1.5 L of drinking water. As low as is this proposed MAC, the foregoing comparison suggests that from an exposure perspective alone, excessive PFOA exposure via drinking water is a very unlikely possibility, certainly not one of national or even province-wide relevance.	Canadian exposure to PFOS and PFAS is not limited to drinking water. Considering the bioaccumulative nature of PFOS and its long half-life in humans, cumulative exposure from various sources may have an impact on health of Canadians across the country. Data from the CHMS survey show that PFOS is found in the blood of most Canadians. As PFOS is not routinely monitored in Canadian drinking water, it cannot be assumed that it is not a concern. No change to the document.
21	5.1 Il serait utile de préciser si les échantillons d'eau brute prélevés lors des différentes campagnes d'échantillonnages mentionnées provenaient d'eau souterraine ou d'eau de surface.	The text has been modified to indicate that the samples were sourced from groundwater and surface water (rivers and lakes) in the national survey.

#	Comments	Response
22	5.1 - Des concentrations moyennes de SPFO sont présentées dans cette section. Il serait intéressant de rapporter également les concentrations maximales observées.	The text has been modified to include maximum levels where available.
23	5.1 - "*In Quebec, raw and treated water samples were obtained monthly between April 2007 and March 2008 from seven sites (a total of 84 samples each of raw and treated water). PFOS was detected in 52% of treated samples (MDL of 0.3–0.6 ng/L), with a median value of 1.0 ng/L. The detection rate and median concentrations were higher in treated water than in raw water, for which the detection rate and median were 40% and <1 ng/L, respectively (MDDEFP, 2012)*" need to be viewed with extreme caution. The April 2016 U.S. EPA UCMR3 summary of the 2013-2015 program shows a Minimum Reporting Level (MRL) based on current analytical capability of 0.04 µg/L (40 ng/L) 100 fold higher than the MDL in this study. The summary for PFOS, based on 36,149 analytical results obtained for 4,864 water utilities found only 285 samples (at 94 locations) with results above the MRL and only 119 samples (at 46 locations) above 0.07 µg/L. The comparatively high percentage of PFOS detections in Quebec is at best a reflection of an extremely low MDL and may be no more than a large number of false positives. The median PFOS level detected of 1 ng/L is 600 fold below the proposed PFOS MAC. No other percentiles or maximum values found in Quebec have been reported.	The limit of detection stated in the document is what was reported in the published report. Maximum levels in Quebec have been added to the document to address such concerns.
24	5.1 - "*As part of a national survey of emerging contaminants in drinking water (including PFOS) conducted by Health Canada, treated and raw water were monitored in winter and summer at 35 locations in 2009 and 30 locations in 2010. In the four sampling periods, only one sample contained PFOS above the method detection limit (MDL) of 0.077 ng/L; the PFOS concentration in that sample was 0.082 ng/L, and was obtained in the winter of 2009 (Health Canada, 2013a).*" These results do not provide a compelling case for PFOS monitoring in drinking water in Canada, let alone publication of a MAC that may drive water utilities to spend even more on contaminant monitoring than currently done. This is important because the analytical methods required for the perfluorinated compounds are not needed for other current MAC monitoring purposes.	The section on PFOS in water highlights how infrequently PFOS in drinking water has been investigated. PFOS has been detected in biomonitoring of the Canadian population and due to PFOS's properties discussed in the guideline technical document, it is likely to occur in water. Median results are reported where available. No change to the document.
25	5.6 - This section missed the Alberta biomonitoring data (2008) of randomly drawn serum samples from over 50,000 pregnant women, with analyses done on pooled samples representing 150 to 200 individuals, which yielded age group and regional samples with at least 8 pooled samples per region and age group. Serum PFOS results ranged from 0.3 to 14 ng/g wet weight. The 2010 data reported on 1373 archived serum samples from children, for which analyses were conducted on pooled samples representing 196 to 240 individuals to yield age group samples with at least 3 pooled samples per age group. Serum PFOS results ranged from 7 to 13 ng/mL.	Unfortunately, the Alberta biomonitoring study did not report individual serum levels and PFOS/PFOA in the population sampled, rather, the authors pooled up to 200 individuals to yield age group samples. Due to the large uncertainty introduced using this approach and as a result the lack of information it provided on human exposure to PFOS/PFOA, it was not deemed necessary to include this study in the document. No change to the document.

#	Comments	Response
26	5.7 - « *les coefficients de perméabilité dermique estimés dans les études in vitro prévoient que le SPFO soit imperméable à la peau dans des conditions normales* ». C'est plutôt la peau qui est imperméable au SPFO et non l'inverse.	The text has been modified to reflect that it is indeed the skin that is impermeable to PFOS and not the other way around.

Section 6.0: Analytical methods

#	Comments	Response
27	6.1 - "*The MDL for PFOS is 1.4 ng/L (0.0014 µg/L) and the Lowest Concentration Minimum Reporting Level (LCMRL) is 6.5 ng/L (0.0065 µg/L) (U.S. EPA, 2009a). PFOS has been included in the third Unregulated Contaminant Monitoring Rule (UCMR3), which stipulates that using Method 537 ver. 1.1, an MRL of 40 ng/L (0.04 µg/L) for PFOS must be achieved and reported by the utilities during monitoring (U.S. EPA, 2012b)*" captures the difference between what is possible as a method detection limit (MDL) and what is specified as a minimum reporting level (MRL) for a large survey.	Thank you for the comment. No change to the document.

Section 7.0: Treatment technology

#	Comments	Response
28	Our water treatment plant does not currently test for these two substances. They have been added to our quarterly testing program. We do not believe they are prevalent in our raw water; however, if they are detected in significant quantities (near or above the MAC), our current treatment process may be inadequate. If our treatment process needs to be upgraded, this will require significant increases in both capital and operational costs.	Cost is beyond the scope of the document. The adoption and implementation of guideline is under PT jurisdiction. No change to the document.
29	While most utilities will likely have no difficulty meeting the proposed MACs for PFOS and PFOA in drinking water, for those that do, the cost to remove them will be substantial. These substances are resistant to most conventional treatment and even some advanced processes. In some cases a full system redesign or replacement may be necessary to meet the MAC, which could be beyond the financial capacity of a utility. Would it be possible to propose a higher MAC, or delay the publication of this guideline until the treatment and standardized analytical technologies are less expensive, more readily available and, in the case of the treatment, more effective.	Cost is beyond the scope of the document. The adoption and implementation of guideline is under PT jurisdiction.No change to the document.

#	Comments	Response
30	7.1.2.1 - "*Close monitoring of PFOS breakthrough (treatment objective) is necessary for efficient operation of GAC unit. Studies indicated that PFOS was successfully removed from drinking water when a frequent regeneration or replacement (3 to 6 months) of the GAC was performed (e.g., Wilhelm et al., 2008; Rumsby et al., 2009; Takagi et al., 2011). Takagi et al. (2011) observed that GAC regenerated over periods greater than one year were not effective in removing PFOA and PFOS and suggested regenerating the carbon 2 to 3 times per year*" illustrates how expensive and impractical it would be to operate an expensive unit process like GAC strictly for the purpose of achieving the MAC for PFOS.	GAC treatment is well established and the most widely used technology for small systems because of general ease of use. Cost-effectiveness is beyond the scope of the document. The adoption or implementation of guidelines is under PT jurisdiction. No change to the document
31	Employing appropriate equipment for adequate removal of these substances, if present in the water, will impose additional cost on water systems. The review of the proposed guideline documents shows that treatment such membrane filtration and GAC systems effectively remove 95% and 99% of PFOS and PFOA, respectively. We also have noticed that exhausted GAC system does not achieve 99% removal.	The effectiveness of GAC to remove PFOA in drinking water is dependent on the regeneration frequency and/or replacement of the carbon. Cost-effectiveness is beyond the scope of the document. No change to the document.

Section 8.0: Kinetics and metabolism

#	Comments	Response
32	8.6.2 - «*Comme approche alternative à l'utilisation du modèle PBPK pour les calculs des PDD, les rapports des paramètres de doses prévus par le modèle PBPK ont été utilisés pour calculer les valeurs CA_{FI} pour les doses pertinentes .*» Des organismes (ex : MDH, 2009; ATSDR, 205; US EPA, 2016) utilisent la concentration sérique chez l'animal (modélisée ou mesurée) puis font une extrapolation vers une dose externe chez l'humain à partir de la clairance chez l'humain. Il serait intéressant comparer l'approche choisie avec celle employée par ces autres organismes. En effet, des différentes importantes peuvent être observées entre les doses équivalentes chez l'humain (PDDEQH) issues de ces différentes approches.	It is beyond the scope of this document to directly compare this assessment to approaches used by other agencies. Because PFOS remains in the body for years in humans, compared to days/weeks in rodents, it can be difficult to extrapolate to humans using conventional methods. The EPA's approach used pharmacokinetic modeling and linear clearance-based scaling. HC considered this approach but identified key issues. In particular, it does not account for potential non-linear pharmacokinetics in humans, which makes this approach less accurate across different dose ranges. HC employed a PBPK-derived chemical-specific adjustment factor approach which used PBPK models to generate chemical- and species-specific clearance information for humans and animals, and accounts for PFOS's non-linear kinetics. This approach was supported by external PBPK experts and by external and internal peer-reviewers. No change to the document.
33	8.6.3 - « *L'état d'équilibre n'a également pas été atteint dans le modèle utilisant des humains à des doses inférieures à 0,1 mg/kg p.c. par jour.* » Quel est l'impact sur les valeurs de CAFI calculées? Sont-elles sous-estimées ou surestimées?	The impact of not achieving equilibrium below 0.1 mg/kg bw per day cannot be predicted and it is therefore a source of uncertainty (which is the context within which this information is stated in the text). No change to the document.

Section 9.0: Health effects

#	Comments	Response
34	9.0 - « *Ce résumé comprend seulement les études directement pertinentes au calcul de la valeur basée sur la santé.* » Quels sont les critères qui font qu'une étude est considérée comme «*directement pertinentes au calcul de la valeur basée sur la santé* »?	The text has been modified to indicate that the summary includes reports, reviews, and original papers published concerning PFOS in order to understand toxicity in humans exposed to PFOS via drinking water.
35	9.1 - Aucune donnée sur l'ampleur de l'exposition des populations humaines étudiées n'est présentée, constituant une importante lacune de la section.	The extent of human exposure is discussed in Section 5. No change to the document.
36	9.1 - Aucune mesure d'exposition et pratiquement aucune donnée sur la taille des populations étudiées n'est fournie. Il est difficile pour le lecteur d'apprécier les résultats rapportés.	In order to make the document concise, we do not provide comprehensive descriptions of all studies in order to provide the reader with as much information as possible on the key study. The information presented in section 9.1 was used to verify the relevance of animal to human extrapolation and as such the inclusion of such details was deemed to be unnecessary. No change to the document.
37	9.2, 10 - « *Les résumés mentionnés dans le présent document utilisent les concentrations et les doses indiquées par les auteurs. Cette approche est également utilisée pour les évaluations quantitatives* ». Cette précision est tout à fait pertinente, tout comme le paragraphe entier dans lequel il se trouve. Toutefois l'étude ayant servi a calculer la VBS/CMA (Butenthoff et al., 2012) spécifie clairement que la concentration rapportée est bien celle du K^+SPFO (Table 2) et non celle de l'anion SPFO. Puisque la CMA se rapporte à la concentration de l'ion SPFO et non la concentration de K^+SPFO, il y a nécessairement un biais dans les calculs de la section 10 et dans la VBS/CMA.	Section 9.2 clearly stateS that the PFOS ion contributes to 93% of the weight of K^+PFOS and is released from the compound upon exposure, thus only minor quantitative differences would result from using K^+PFOS and PFOS doses interchangeably. Later, in Section 10.1 (paragraph 5) and Section 10.2 (paragraph 4) we state that the NOAEL was adjusted to account for decreased purity of the test material. No change to the document.
38	9.3, 10.1 - « *l'approche de l'AQT est la méthode la plus appropriée pour l'évaluation du risque* ». La formulation aurait avantage à être revue. Ce n'est pas tant l'approche de l'AQT qui est important ici mais bien le fait que ce soit une approche avec seuil de dose (ce qui n'est pas explicite lorsqu'on utilise AQT dans la phrase). AQT est une valeur et non une approche. De plus, cette affirmation relève davantage de la section 10.	The text has been modified to state that a non-linear low dose extrapolation approach that utilizes the TDI is the most appropriate method for deriving a HBV rather than the TDI approach and to include this information only in Section 10.

Section 10.0: Classification and assessment

#	Comments	Response
39	10.2 - Plusieurs doses sont rapportées et comparée dans cette section afin de justifier le choix du PDD pour les effets non cancérigènes. Or : 1) Puisque les différences dans la toxicocinétique du SPFO entre les humains et les animaux de laboratoire sont spécifiques aux espèces et aux doses administrées, les facteurs d'incertitude pour l'extrapolation inter espèce (composant cinétique) sont variables et peuvent atteindre des valeurs supérieures au facteur par défaut de 4 (soit entre 10 et 16 pour le rat). C'est pourquoi il serait préférable que les comparaisons entre les PDD potentiels dont il est question dans cette sous-section s'effectue sur la base des points de départ équivalents chez l'humain (PDDEQH) et non sur celle des doses administrées à l'animal. 2) un tableau synthèse permettrait de comparer, d'une étude à l'autre, les espèces étudiées, les doses administrées, le(s) mode(s) d'administration, les durées d'exposition, les effets critiques observés et les PDDEQH associés ainsi que le raisonnement pour rejeter ou retenir les PDDEQH pour le calcul de l'AQT.	In fact, in selecting the lowest POD, we did compare the external doses (and the TDIs) for each study. The outcome of the comparisons were the same as that described in the text. The justification for not using the studies with lower PODs was included in the text based on biological plausibility and human relevance. Health Canada limits the use of tables in their documents for web publishing policy reasons. No change to the document.
40	10.2 - Cette section ne fait aucune mention des effets au développement observés chez l'animal dans la discussion portant sur le choix de l'étude clé ayant permis de calculer la VBS. Il serait pertinent, au minimum, de mentionner pourquoi Santé Canada a exclu ce type d'effet de la discussion, d'autant plus que la US EPA a retenu une étude sur la toxicité développementale (Luebker et al. 2005) dans sa plus récente recommandation pour le SPFO dans l'eau potable. Il s'agit de la recommandation la plus récente faite par un organisme de référence. De plus, comme les VBS pour les effets au développement s'appuient sur un scénario pour le nourrisson ou la femme enceinte, celles-ci sont susceptibles d'être moins élevées que les V S fondées sur d'autres effets systémiques comme les effets hépatiques.	The reproductive/developmental endpoints were not included in the discussion on the choice of critical effect because they occurred at much higher doses than the effects that were included in the discussion (e.g., liver effects, thyroid effects). Therefore, the HBV calculated based on liver effects is protective of these possible developmental effects. It is beyond the scope of this document to directly compare this assessment to approaches used by other agencies. The developmental effects used by the USEPA occurred at higher doses than the liver effects. No change to the document.
41	Nous appuyons l'utilisation de facteurs d'incertitude spécifiques au SPFO pour la composante toxicocinétique de l'extrapolation inter-espèce. Toutefois, il serait intéressant que Santé Canada compare les facteurs d'incertitude obtenus avec ceux publiés par les organismes de référence ayant eu recours également à un facteur d'incertitude spécifique, d'autant plus que des différences entre les facteurs calculés par Santé Canada et ceux calculés par d'autres organismes peuvent être observées (MDH, 2009, ATSDR, 2015, US EPA, 2016).	It is beyond the scope of this document to directly compare this assessment to approaches used by other agencies. No change to the document.

#	Comments	Response
42	Toutefois, puisque la justification entourant le choix de l'effet critique retenu par Santé Canada est incomplète, nous ne sommes pas en mesure de nous prononcer sur ce dernier. Dans cette optique, il serait utile de mieux appuyer le choix de l'effet critique au regard des autres effets critiques potentiels, plus particulièrement ceux retenus par la US EPA.	It is beyond the scope of this document to directly compare this assessment with approaches used by other agencies. Health Canada used hepatocellular hypertrophy, which is the most sensitive (lowest) adverse effect POD of all studies in the literature, increases in a dose-related manner, is observed consistently across species and sexes, is considered to be a sensitive indicator and precursor of adverse liver effects, and is supported by human studies that show changes in liver enzymes; mode of action analysis supports human relevance of this endpoint. The reproductive/ developmental effects used by EPA occurred at higher doses (> 0.1 mg/kg bw per day). EPA used the 90th percentile drinking water intake for lactating women of 0.054 L/kg bw per day (i.e., 3.78 L/d assuming 70 kg body weight), almost twice the volume of water assume used to derive their MCLs.
43	10.2 4th paragraph Commentaire: « La NOAEL de 0,024 mg/kg p.c. par jour a été ajustée… ». D'où vient cette valeur? C'est la première fois qu'il est question d'une NOAEL de 0,024 mg/kg p.c. par jour dans le document. À la section 9.2, cette valeur fait plutôt référence à une LOAEL.	Section 9.2.3 was modified to clarify that the when the Butenhoff et al. (2012) study is described in detail, a significant increased incidence and severity of centrilobular hepatocytic hypertrophy was reported at doses equal to or exceeding 0.098 mg/kg bw per day. In the description of the same study, a LOAEL of 0.024 mg/kg bw per day is defined for hepatic cystic degeneration. This endpoint was not used for HBV calculation as described in section 10, thus the next lowest effect is the hepatocellular hypertrophy that occurred at a LOAEL of 0.098 mg/kg bw per day and thus a NOAEL of 0.024 mg/kg bw per day.
44	10.2, tableau 4 - Est-ce que les données des deux études ne permettaient pas de modéliser la dose de référence? Si oui, le mentionner.	The text has been modified to indicate that the data for hepatocellular hypertrophy was modeled with good fit; however, the resulting BMD is 2-fold higher than the NOAEL. In the interest of being protective of human health, Health Canada determined that the BMD approach did not provide a secure basis for risk assessment purposes.
45	10.4 - « *Un mémoire publié par l'Office of Water de l'U.S. EPA indique un avis provisoire pour la santé de 0,2 µg/L (0 0002 mg/L) pour le SPFO (U.S. EPA, 2009b)* » L'USEPA a publié un nouveau « public health advisory » en mai 2016, avec une valeur de 0,07 ug/L. Il faudrait mettre à jour l'information avec la nouvelle publication de l'USEPA (2016).	Information on the U.S. EPA's 2016 Lifetime Health Advisory has been incorporated into section 10.5 of the document.

#	Comments	Response
46	10.4 - De son côté, la US EPA (2016) a retenu une augmentation du poids à la naissance observé chez les souris (Luebker et al., 2005) comme effet critique pour établir sa plus récente recommandation pour le SPFO dans l'eau potable. Il serait particulièrement pertinent que cette évaluation soit au minimum présentée à la section 10.4 et accompagnée d'une analyse critique du document de l'agence américaine, puisque leur recommandation de 0,07 µg/L) est la plus récente publiée sur le sujet et la plus faible publiée par un organisme reconnu.	Information on the U.S. EPA's 2016 Lifetime Health Advisory has been incorporated into section 10.5 of the document. Health Canada derives health based values based on the latest science for the protection of human health, using the Canadian context and assumptions. International assessments are considered in our approach, but it is not appropriate to include a critical analysis of another agency's assessment.
47	10.4 - « *Selon la politique de l'U.S. EPA, un APS (0,4 µg/L; 0,0004 mg/L) a également été calculé pour un enfant de 10 kg consommant 1 L d'eau par jour en utilisant l'hypothèse par défaut que l'eau potable constitue 20 % de l'exposition totale à l'APFO* ». Est-ce qu'une valeur pour les enfants a été calculée ? Si oui, la valeur correspondante devrait être précisée.	This short-term value was the only value available from the U.S. EPA when the consultation document was drafted, but it has not been published to date. This section has been updated with the more recent health advisory adopted by the U.S. EPA. No change to the document.

Section 11.0: Rationale

#	Comments	
48	11.0 - Puisque les effets critiques du SPFO et de l'APFO sont les mêmes et que ces derniers sont susceptibles d'être présents simultanément dans l'eau potable, il serait approprié de discuter de la pertinence ou non de présenter une recommandation commune à la fois pour l'APFO et le SPFO. C'est d'ailleurs l'avenue privilégiée par la US EPA (2016).	The text has been modified to indicate that Health Canada is recommending an additive approach for PFOS and PFOA in new sections (2.4, 9.4, 10.4, and 11.0). Thank you for your comment.

Section 12.0: References suggested for addition:

This guideline technical document is not meant to be a comprehensive review of the literature. All references submitted were reviewed, but only publications deemed to be relevant to Canadians and the MAC have been added to the document.

#	Comments	
	1. Alberta Health and Wellness (2010). The Alberta Biomonitoring Program: Chemicals in Serum of Children in Southern Alberta (2004 2006) – Influence of Age and Comparison to Pregnant Women. Alberta Health and Wellness. Edmonton.	Used pooled blood samples and reported levels by age group. No added value compared to existing information in 5.6. No change to the document.
	2. Alberta Health and Wellness (2008). Alberta Biomonitoring Program: Chemicals in Serum of Pregnant Women in Alberta. Surveillance and Environmental Health. Public Health Division. Edmonton.	Used pooled blood samples and reported levels by age group. No added value compared to existing information in 5.6. No change to the document.

#	Comments	
	3. Beesoon, S., Martin, J.W. (2015). Isomer-specific binding affinity of PFOS and PFOA to serum proteins. Environ. Sci. Technol. 49: 5722–5731.	Added to document.
	4. Beesoon, S., Genuis, S.J., Benskin, J.P., Martin, J.W. (2012). Exceptionally high serum concentrations of PFOS in a Canadian family are linked to home carpet treatment applications. Environ. Sci. Technol. 46: 12960–12967	Added to section 5.5 of document.
	5. Bijland, S., Rensen, P.C., Pieterman, E.J., Maas, A.C., vanderHoorn, J.W., van Erk, M.J., Havekes, L.M., Willems van Dijk, K., Chang, S.C., Ehresman, D.J., Butenhoff, J.L., Princen, H.M. 2011. Perfluoroalkylsulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE*3-Leiden CETP mice. Toxicol. Sci. 123(1):	Added to document.
	6. Bischel, H.N., MacManus-Spencer, L.A., Zhang, C., Luthy, R.G. (2011). Strong associations of short-chain perfluoroalkyl acids with serum albumin and investigation of binding mechanisms. Environ. Toxicol. Chem. 30: 2423–2430.	Not relevant. Only bovine serum albumin. No change to the document.
	7. Bloom, M.S., Jansing, R.L., Kannan, K., Rej, R., Fitzgerald, E.F., 2014. Thyroid hormones are associated with exposure to persistent organic pollutants in aging residents of upper Hudson River communities. Int. J. Hyg. Environ. Health. 217: 473–482.	No PFAS included in study. No change to the document.
	8. Chan, E., Sandhu, M., Benskin, J.P., Ralitsch, M., Thibault, N., Birkholz, D., Martin, J.W. 2009. Endogenous high-performance liquid chromatography / tandem mass spectrometry interferences and the case of perfluorohexanesulfonate (PFHxS) in human serum; are we overestimating exposure? Rapid Commun. Mass Spectrom. 23: 1405–1410.	No PFAS included in study. No change to the document.
	9. Chang, S.C., Thibodeaux, J.R., Eastvold, M.L., Ehresman, D.J., Bjork, J.A., Froehlich, J.W., et al. 2008.Thyroid hormone status and pituitary function in adult rats given oral doses of perfluorooctanesulfonate (PFOS). Toxicology 243: 330–339.	Added to document.
	10. Egeghy, P.P., Lorber, M. 2011. An assessment of the exposure of Americans to perfluorooctanesulfonate: A comparison of estimated intake with values inferred from NHANES data. J. Exposure Sci. Environ. Epidemiol. 21(2):150–168.	No added value. Overly simplistic PK modeling to estimate PFOS intake based on American serum PFOS levels.
	11. Ehresman, D.J., Froehlich, J.W., Olsen, G.W., Chang, S.-C., Butenhoff, J.L. 2007. Comparison of human whole blood, plasma, and serum matrices for the determination of perfluorooctanesulfonate ,(PFOS), perfluorooctanoate (PFOA), and other fluorochemicals. Environ.Res. 103:176–184.	Methods paper. No change to the document.
	12. Fisher, M., Arbuckle, T.E., Wade, M., Haines, D.A. 2013. Do perfluoroalkyl substances affect metabolic function and plasma lipids? – analysis of the 2007–2009, Canadian Health Measures Survey (CHMS) cycle1. Environ.Res. 121: 95–103.	Added to document.

#	Comments	
	13. Glynn, A., Berger, U., Bignert, A., Ullah, S., Aune, M., Lignell, S., Darnerud, P.O. 2012. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends1996–2010. Environ.Sci.Technol. 46(16): 9071–9079.	Serum levels in Swedish pregnant women. No added value. No change to the document.
	14. Goosey, E., Harrad, S. 2011. Perfluoroalkyl compounds in dust from Asian, Australian, European, and North American homes and UK cars, classrooms, and offices. Environ. Int. 37(1): 86–92.	Added to document.
	15. Hanssen, L., Dudarev, A.A., Huber, S., Odland, J.O., Nieboer, E., Sandanger, T.M. 2013. Partition of perfluoroalkyl substances (PFASs) in whole blood and plasma, assessed in maternal and umbilical cord samples from inhabitants of Arctic Russia and Uzbekistan. Sci. Total Environ. 447: 430–437	No added value. Serum levels in Russian/Uzbekistan pregnant women. No change to the document.
	16. Hanssen, L., Roellin, H., Odland, J.O., Moe, M.K., Sandanger, T.M. 2010. Perfluorinated compounds in maternal serum and cord blood from selected areas of South Africa: results of a pilot study. J. Environ. Monit. 12:1355–1361.	No added value. Serum levels in South African pregnant women. No change to the document.
	17. Hebert, P.C., MacManus-Spencer, L.A. 2010. Development of a fluorescence model for the binding of medium-to long-chain perfluoroalkyl acids to human serum albumin through a mechanistic evaluation of spectroscopic evidence. Anal. Chem. 82:6463–6471.	Methods paper. No change to the document.
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Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Perfluorooctanoic Acid (PFOA)

Prepared by the
Federal-Provincial-Territorial Committee on
Drinking Water
of the
Federal-Provincial-Territorial Committee on
Health and the Environment

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Other Guideline Technical Documents for the Guidelines for Canadian Drinking Water Quality can be found on the following web page: www.healthcanada.gc.ca/waterqualite

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Perfluorooctanoic Acid

Part I. Overview and Application

1.0 ~~Proposed guideline~~Guideline

~~4~~*The maximum acceptable concentration (MAC)* ~~*of 0.0002 mg/L (0.2 µg/L) is proposed*~~ *for perfluorooctanoic acid (PFOA) in drinking water is 0.0002 mg/L (0.2 µg/L), based on exposure solely to PFOA.*

As the toxicological effects of PFOA and perfluorooctanoyl sulfonate (PFOS) are considered to be additive, the sum of the ratios of the detected concentration to the MAC for PFOS and PFOA should not exceed 1.

2.0 Executive summary

PFOA is a man-made compound that does not occur naturally in the environment. It is used in the manufacture of stain/water-resistant coatings for various consumer products and in specialized chemical applications, such as fire-fighting foams, hydraulic fluids, and carpet spot removers. Environmental concentrations, and therefore potential exposure levels, may be higher in areas near facilities using high amounts of PFOA and near locations with extinguished fires if PFOA-containing fire-fighting foams were used.

This guideline technical document reviews and assesses all identified health risks associated with PFOA in drinking water. It incorporates available studies and approaches and takes into consideration the availability of appropriate treatment technology. Based on this review, the ~~proposed~~ drinking water guideline for PFOA is a maximum acceptable concentration (MAC) of 0.0002 mg/L (0.2 µg/L), based on the general population.

~~During its fall 2015 meeting, the Federal-Provincial-Territorial Committee on Drinking Water reviewed the guideline technical document on PFOA and gave approval for this document to undergo public consultation.~~

2.1 Health effects

PFOA and its salts have been classified as possibly carcinogenic to humans (Group 2B) by the International Agency for Research on Cancer (IARC), based on limited epidemiological evidence demonstrating associations between PFOA and testicular and renal cancers, and on limited evidence in experimental animals. Non-cancer effects occurring at the lowest level of exposure to PFOA in animals include liver effects, reproductive and developmental ~~effects, liver~~ effects and changes in serum lipid levels.

Both cancer and non-cancer endpoints were considered in the derivation of the ~~proposed~~ MAC for PFOA in drinking water. The non-cancer approach, based on liver effects in rats, was used to calculate a ~~proposed~~ MAC that is protective of human health from both cancer and non-cancer effects.

2.2 Exposure

Canadians can be exposed to PFOA in food, consumer products, dust, and drinking water. Exposure is mainly from food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Although PFOA is not regularly monitored at water treatment plants in Canada, the analysis has

been performed for a few locations. When detected in drinking water, it is usually found at levels below ~~2 or 3 ng~~0.003 µg/L.

2.3 Analysis and treatment

To date, the United States Environmental Protection Agency has not approved any ~~analytical~~ methods for the analysis of PFOA in drinking water. There are some methods that can be used to measure PFOA in drinking water at levels well below the ~~proposed MAC. However, they require good quality control procedures to get accurate results.~~MAC.

The selection and effectiveness of a treatment strategy for PFOA removal is driven by several factors, including source water chemistry, concentration of PFOA and/or other perfluoroalkyl substances and pre-existing treatment processes. Conventional treatment is not effective for PFOA removal. Other treatment methods are promising, although full-scale studies are limited. Activated carbon adsorption can achieve treated water concentrations of PFOA below the ~~proposed~~ MAC. However, proper operation of the system is essential to ensure that the performance of granular activated carbon (GAC) is not affected by the presence of natural organic matter in the source water. Membrane filtration techniques (reverse osmosis and nanofiltration) and anion exchange may also be effective. Although there are no residential treatment devices certified to remove PFOA, it is expected that the same treatment technologies would also be effective at the residential scale.

2.4 Additivity

The health effects of PFOA and PFOS are similar and well documented. Recent scientific evidence shows that PFOS and PFOA affect the same organ in similar ways. Thus, when PFOS and PFOA are found together in drinking water, the best approach to protect human health is to consider both chemicals together when comparing to the screening values. This is done by adding the ratio of the observed concentration for PFOA to its MAC with the ratio of the observed concentration for PFOS to its MAC; if the result is below or equal to one, then the water is considered safe for drinking. Science currently does not justify the use of this approach for other PFAS.

3.0 Application of the guideline

~~*Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.*~~

~~3.1 Monitoring~~

PFOA ~~is~~ and perfluorooctane sulfonate (PFOS) are typically found in groundwaters and surface waters impacted by aqueous film-forming foam (AFFF) (i.e., fire-fighting foams). ~~groundwater and surface water~~ They may also be found in groundwaters and surface waters contaminated by: discharges from industrial facilities~~,~~; effluents from wastewater treatment plants treating domestic ~~and~~or industrial waste~~,~~; storm water runoff ~~and~~; or applications of biosolids from a municipal wastewater treatment plant to agricultural land ~~application of biosolid amended soils. It may also be found in groundwater and surface waters that are or may be , impacted by aqueous film-forming foam (AFFF) (i.e., fire-fighting foams).~~ Like other groundwater contaminants, PFOA can reach drinking water wells through migration of a contaminated groundwater plume. It can also reach ~~groundwater~~surface waters from air emissions of industrial facilities. Particle-~~bounded~~bound volatile perfluoroalkyl substances (~~PFASs~~)PFAS) including PFOA may be carried ~~by wind~~ from disposal sites by the wind and deposited on ~~the~~ land or ~~the~~

surface water, thus explaining ~~the~~their presence ~~of these anthropogenic chemicals~~ in remote locations and, in waters not impacted by a point source. PFOA migrates very slowly through the soil to groundwater.

PFOA salts are used as a processing aid in the production of fluoropolymers which are used in joining and sealing materials, which may contain trace amount of PFOA. Some of these materials may be used in distribution systems. The use of distribution system components that are certified to NSF/ANSI 61 would minimize the leaching of PFOA into drinking water.

For drinking water supplies that occasionally experience short-term exceedances above the MAC, it is suggested that a plan be developed and implemented to address these situations. For more significant long-term exceedances that cannot be addressed through treatment, it is suggested that alternative sources of drinking water be considered.

3.1 Monitoring

~~may not be detected in~~It is important to note that the ~~source water~~analysis for ~~years~~PFOA is highly specialized and should be conducted by a laboratory that is accredited or that has a stringent quality assurance/quality control (QA/QC) program in place to ensure data quality.

3.1.1 Source charcterization

Utilities should characterize their source water to assess PFOA and PFOS concentrations. ~~In~~, particularly if source waters are impacted by firefighting training areas, military bases, airports, manufacturing sites and/or waste disposal sites. Once contamination is detected, the source ~~waters where PFOA is present at levels exceeding the proposed MAC, quarterly~~should be sampled semi-annually to confirm that the sum of the ratios of the observed concentration to the MAC for PFOA and PFOS does not exceed 1. If treatment is required, the source should be sampled in conjuction with compliance monitoring ~~of surface water and semi-annual monitoring of groundwater should be conducted.~~

~~The monitoring frequency of the treated water depends on the treatment technology the utility employs.~~ Utilities that ~~use a GAC system for PFOA removal may want to enhance monitoring of the treated water in order to assess the performance of the GAC system and to determine the timing of the regeneration. Utilities may consider reduced monitoring when they have data indicating that PFOA does not occur in the source water. However, if the main source of groundwater~~have baseline data showing the absence of PFOA and PFOS may conduct less frequent monitoring.

If the main source of contamination is suspected to be from the use of AFFF, utilities may want to consider monitoring for other ~~perfluorinated alkyl acids (PFAAs; i.e.,~~PFAS, including shorter chain compounds such as perfluorobutanoic acid and perfluorobutane sulfonate~~).~~. These other ~~PFAAs~~PFAS are likely to co-occur at AFFF-impacted sites and are typically more mobile. As such, they can serve as an early warning sign of PFOA and PFOS contamination of a groundwater source.

3.1.2 Operational monitoring

Treatment systems should be specifically designed, operated and maintained for removal of PFOA and PFOS. The operational monitoring frequency will depend on the treatment technology the utility employs. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance. Utilities that use a GAC system for PFOA and PFOS removal may require quarterly monitoring of the treated water in order to assess the performance of the GAC system and to determine the timing of the regeneration or replacement. Utilities should also be aware that ozone or advanced oxidation processes (AOPs) may oxidize polyfluorinated

pecursors present in the source water, which could result in an increased concentration of PFOA in the finished water.

3.1.3 Compliance monitoring

When treatment is in place for PFOA and PFOS removal, semi-annual monitoring of the treated water is recommended. Samples should be collected after treatment, but prior to distribution, typically at the entry point to the distribution system. Paired samples of source and treated water should be taken to confirm the efficacy of the treatment. The sum of the ratios of the measured concentration to the MAC for PFOA and PFOS should not exceed 1.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Perfluorooctanoic acid (PFOA) is an anthropogenic compound with a chain length of eight carbons, of which seven are perfluorinated. It belongs to the class of chemicals known as perfluorocarboxylic acids (PFCAs), one of a broader class of chemicals known as perfluoroalkyls (PFAs) (Environment Canada and Health Canada, 2012~~)~~), or perfluoroalkyl substances (PFAS). In this report, the term "PFOA" may refer to the free acid ($C_8HF_{15}O_2$; CAS number 335-67-1; 414.07 g/mol) or its conjugate base ($C_8F_{15}O_2^-$; CAS number 45285-51-6). The term APFO (ammonium perfluorooctanoate) refers to the ammonium salt ($C_8F_{15}O_2^- NH_4^+$; CAS number 3825-26-1), its principal salt, and K^+PFOA refers to the potassium salt (CAS number 2395-00-8). The main synonyms of PFOA are pentadecafluorooctanoic acid, perfluorooctanoate, C8, FC-143, pentadecafluoro1-octanoic acid, pentadecafluoro-n-octanoic acid, perfluorocaprylic acid, perfluoroctanoic acid, perfluoroheptanecarboxylic acid and octanoic acid.

PFOA is highly soluble in water, with estimates as high as 3,500 mg/L in neutral to alkaline pH and 9,500 mg/L in pure water, and as low as 0.7 mg/L at acidic pH (Kauck and Diesslin, 1951; Barton et al., 2007; Environment Canada and Health Canada, 2012). Solubility depends on the acid dissociation constant (pKa) of the acid form. Data for pKa indicate values ranging from –0.5 to 4 (Kissa, 1994; Burns et al., 2008; Goss, 2008; ATSDR, 2009; Goss and Arp, 2009; Environment Canada and Health Canada, 2012), and it was suggested that with such a low pKa value, the environmental partitioning of PFOA will be dominated by the anionic form (Goss, 2008).

PFOA has combined hydrophobic and hydrophilic properties over different portions of its molecule (Environment Canada and Health Canada, 2012). Due to this particularity, PFOA is thus expected to behave differently than traditional hydrophobic chemicals. The octanol:water partition coefficient (K_{ow}) cannot be determined directly (because multiple layers are formed in octanol/water) and the parameters usually estimated from the K_{ow} (e.g., K_{oc}, bioconcentration factor) cannot be calculated using this method (ATSDR, 2009; Environment Canada and Health Canada, 2012). The values of $LogK_{ow}$ estimated by modelling range from 3.62 to 6.30 (Arp et al., 2006; Jasinski et al., 2009; Environment Canada and Health Canada, 2012).

PFOA is essentially non-volatile, with a vapour pressure of 2.24×10^{-5} atm at 20°C (Barton et al., 2007; ATSDR, 2009; Environment Canada and Health Canada, 2012). Its Henry's law constant was estimated at 2.4×10^{-5} atm-m^3/mol (Barton et al., 2007).

Precursors of PFOA (polyfluoroakyl phosphate diesters, fluorotelomers, perfluorinated phosphonic acids) represent an indirect source of PFOA in the environment (Ellis et al., 2004; D'Eon et al., 2009; Lee, 2010).

The main producers of PFOA are located principally in the United States, Europe and Asia. Industrial information obtained in 2004 indicates no known manufacturers of perfluoroalkyl and fluoroalkyl substances in Canada; however, APFO was imported into Canada in quantities ranging between 100 and 100,000 kg (Environment Canada and Health Canada, 2012). Regulations established under the *Canadian Environmental Protection Act, 1999* prohibit the manufacture, use, sale, offer for sale, or import of PFOA or its salts, unless designed for specific uses (Government of Canada, 2012). APFO is mainly used as a commercial polymerization aid for fluoropolymer manufacturing. Fluoropolymers are used in the manufacture of stain/water-resistant coatings for textiles and carpets, hoses, cable and gaskets, non-stick coatings on cookware and personal care products. APFO is also used in aqueous fluoropolymer dispersions that are used in paints and in photographic film additives as well as within the aerospace industry (e.g., it may be a component of aqueous film-forming foams [AFFFs] for firefighting;

Environment Canada and Health Canada, 2012). Fluorochemicals (potential PFOA precursors) are also used in the treatment of food packaging materials (Environment Canada and Health Canada, 2012) such as microwaveable popcorn bags (Dolman and Pelzing, 2011). The term PFOA is not interchangeable with commercial mixtures containing PFOA, as these mixtures are often not well characterized and could include any product that contains even a small amount of PFOA (Environment Canada and Health Canada, 2012).

4.1 Sources to water

A source of ~~PFAAs~~PFAS in water is the discharge of AFFF for extinguishing fires. Discharge of AFFF was presumed to have resulted in increased levels of ~~PFAAs~~PFAS in water surrounding the Toronto International Airport, based on spatial and temporal trends of ~~PFAAs~~PFAS in water (Awad et al., 2011). Although the study focused on PFOS contamination, as this was the primary ~~PFAA~~PFAS in the AFFF used at the location, PFOA-containing AFFFs could plausibly also result in similar increased concentrations of PFOA in water near discharge sites. Data supporting the possibility of contamination in the vicinity of firefighting training areas include measurements of elevated PFOA concentrations in groundwater near a Michigan air force base (Moody et al., 2003), at a firefighting training ground in Australia (Baduel et al., 2015), and in private drinking water wells proximate to an industrial site in Cologne, Germany (Weiß et al., 2012).

Elevated PFOA concentrations measured in surface water downstream from fluorochemical manufacturing plants have also been used as indications of the potential for industrial sources of PFOA in water (Hansen et al., 2002; Frisbee et al., 2009).

Mass balance studies of ~~PFAAs~~PFAS at wastewater treatment plants commonly report similar or higher PFOA concentrations in effluents in comparison to raw influents, suggesting that the degradation of other fluorinated organic compounds (i.e., fluoropolymers) into PFOA may take place during wastewater treatment (Clarke and Smith, 2011) and that conventional wastewater treatment plants are not effective in removing ~~PFAAs~~PFAS (Ahrens, 2011). PFOA was detected in effluent wastewater treatment facilities at concentrations ranging from 0.007 to 0.055 µg/L in Canada (Environment Canada and Health Canada, 2012) and at average concentrations ranging from 0.080 to 0.12 µg/L in effluents of seven different locations in the U.S. (Quinones and Snyder, 2009).

Although measures are in place in North America and Europe to restrict the production, use and/or the major exposure risks to ~~PFAAs~~PFAS (primarily PFOS, but to some extent PFOA), the ubiquitous use of ~~PFAAs~~PFAS within the built environment still causes their transfer to biosolids (sludge) (Clarke and Smith, 2011). The use of biosolids as fertilizers may thus represent a source of soil and water contamination with PFOA (Clarke and Smith, 2011). Elevated concentrations of PFOA were found in surface and well water in Decatur, Alabama, after biosolids from a municipal wastewater treatment plant (at which waste from local fluorochemical facilities were received) were applied in agricultural fields (Lindstrom et al., 2011).

4.2 Environmental fate

The elevated water solubility of PFOA and the negligible volatility of its ionized species suggest that PFOA species will partition primarily to the aquatic environment (Environment Canada and Health Canada, 2012).

PFOA may be found in air, surface water, sediment, groundwater and soil around the world (including the Arctic). Two long-range transport pathways have been proposed to explain this ubiquity (Post et al., 2012). The first pathway involves the atmospheric transport of volatile precursors (e.g., fluorotelomer alcohol) and their oxidation to PFOA (and other ~~PFAAs~~PFAS) and

further deposition onto land or water. The second pathway involves a long-range aqueous transport of the anionic forms of emitted perfluorinated carboxylates, such as PFOA, from the vicinity of industrial sources via the surface water currents (Butt et al., 2010; Post et al., 2012).

Experimental values of $LogK_{oc}$ vary between 1.2 and 4.5 (Dekleva, 2003; Higgins and Luthy, 2006; Prevedouros et al., 2006; ATSDR, 2009; Environment Canada and Health Canada, 2012; Zareitalabad et al., 2013). Data suggest that the sorption of PFOA can be described reasonably as a partitioning-like process with an average $LogK_{oc}$ of 2.8 (Zareitalabad et al., 2013).

PFOA may bioaccumulate in tissues of aquatic and terrestrial living organisms. Bioaccumulation data for different species of marine and terrestrial ecosystems indicate that PFOA has a low to moderate potential to accumulate in aquatic species (on a whole-body basis), while accumulation may be higher in certain organs/tissues (e.g., liver, blood) (Environment Canada and Health Canada, 2012). Briefly, the PFOA log bioaccumulation factors (BAFs) ranged from 0.02 to 0.63 for trout and from 9.6 to 19.4 for Pacific oysters. Log bioconcentration factors (BCFs) were estimated at 4.0 for the rainbow trout (carcass), 3.1–9.1 for carp, 1.8 for fathead minnows (whole body) and 0.8–3.0 for Pacific oysters. PFOA may also biomagnify in certain food webs (e.g., polar bears) (Environment Canada and Health Canada, 2012).

Under environmental conditions, PFOA does not hydrolyze, photolyze or biodegrade, and is considered extremely persistent in the environment (OECD, 2006; Environment Canada and Health Canada, 2012). PFOA is also resistant to microbial degradation (Liou et al., 2010). Moreover, biodegradation of precursor compounds could lead to increasing concentrations of PFOA in the environment (Ahrens, 2011; Clarke and Smith, 2011). Considering its empirical and physico-chemical properties, it was concluded that PFOA and its salts meet the persistence criteria in water, soil, sediment and air (half-lives of $\geq$ 182 days in soil and water, $\geq$ 365 days in sediment and $\geq$ 2 days in air) (Environment Canada and Health Canada, 2012).

The adsorption of PFAS onto natural sediments with varying organic carbon and iron oxide content, onto kaolinite, alumina and geothite was investigated in aqueous solution (Higgins and Luthy, 2006; Johnson et al., 2007; Pan and Yu, 2010; Tang et al., 2010; Wang et al., 2011; Xiao et al., 2011; 2015). Higgins and Luthy (2006) and Johnson et al. (2007) reported that the adsorption of PFAS on sediments collected from various riverines and lacustrine sites was influenced by the organic carbon, rather than the mineral content, of the sediment. Other studies demonstrated that the adsorption of PFOA/PFOS onto minerals was influenced by pH, ionic strength and the type of the cations present in the aqueous solution (Tang et al., 2010; Wang et al., 2011; Xiao et al., 2011).

5.0 Exposure

Canadians can be exposed to perfluorinated compounds present in food, consumer products, dust and drinking water. The major sources of perfluorinated compounds are expected to be food and consumer products, including solution-treated carpeting and treated apparel (Tittlemier et al., 2007); however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water.

The estimated total daily intake of ~~PFAAs~~PFAS (estimates not provided for individual ~~PFAAs~~PFAS) in Canadians was reported to be 410 ng/day for the general population of Canada (Tittlemier et al., 2007). Drinking water ingestion, estimated at 0.3 ng/day, contributed only a minor amount to the overall estimated exposure. Although some exposure data are available, they are considered insufficient to justify modifying the default allocation factor for drinking water of 20%. This default allocation factor for drinking water is used as a "floor value" when drinking

water is not a major source of exposure (Krishnan and Carrier, 2013); therefore, this value is applicable for PFOA, even though water is expected to be only a minor contributor to PFOA exposure for the general population.

5.1 Water

Although PFOA is not regularly monitored at water treatment plants in Canada, the analysis has been performed for a few locations. PFOA was not detected (method detection limit [MDL] of 0.51 ng/L) in raw or finished water from samples obtained in 2012 from two water treatment plants in Calgary (Alberta Environment and Water, 2013). In Quebec, raw and treated water samples were obtained monthly between April 2007 and March 2008 from seven sites (a total of 84 raw and treated water samples each). PFOA was detected in 75% of treated samples (MDL of 0.3–0.6 ng/L), with a median value of 2.5 ng/L, and a maximum value of 98.0 ng/L. The detection rate and median concentrations were higher in treated water than in raw water, for which the detection rate and median were 55% and 2.0 ng/L, respectively (~~Ministère du Développement durable, de l'Environnement, de la Faune~~Berryman et ~~des Pares,~~al., 2012). The reported PFOA concentration in 5 tap water samples from Niagara-on-the-Lake, Ontario, was 2.1 ng/L (Mak et al., 2009). Lower concentrations of PFOA (0.2 ng/L) were reported in tap water from Calgary and Vancouver (Tanaka et al., 2006).

~~For~~In a national survey of emerging contaminants in drinking water (including PFOA) performed by Health Canada, treated and raw water from groundwater and surface water sources (rivers and lakes) was monitored in winter and summer at 35 locations in 2009 and 30 locations in 2010. PFOA was detected (MDL of 0.023 ng/L) in 68% of raw water samples and 64% of treated water samples in summer 2009, with averages of 0.067 ng/L and 0.071 ng/L, respectively (median values of 0.050 and 0.060 ng/L, respectively). PFOA concentrations were slightly lower in winter 2009, with an average of 0.057 ng/L in detected raw samples (59% detection) and 0.056 ng/L in detected treated samples (55% detection). Detection rates for PFOA were lower in the 2010 locations, with detection rates in the summer of 18% in raw water (average of 0.066 ng/L and median of 0.030 ng/L) and 15% in treated water (average of 0.046 ng/L and median of 0.025 ng/L), and in winter of 33% in raw water (average of 0.055 ng/L and median of 0.040 ng/L) and 27% in treated water (average of 0.05 ng/L and median of 0.030 ng/L) (Health Canada, 2013a). Maximum levels of 0.220 ng/L and 0.180 ng/L were detected in raw and treated water samples, respectively.

PFOA levels in Etobicoke Creek, Ontario (a tributary of Lake Ontario) ranged from not detected (limit of quantification: 9 ng/L) to 11.3 µg/L following a fire alarm malfunction that released flame retardants containing PFAS (Moody et al., 2002). Interestingly, PFOA was also found upstream of the spill site at 0.02 µg/L.

5.1.1 Co-occurrence with other PFAS

Limited data show that PFOA is co-detected with other substances in several locations across Canada. In all of these studies, PFOS and PFOA were the predominant PFAS detected. PFOA is co-detected with:

- PFOS, perfluorohexane sulfonate (PFHxS), perfluoroethanesulfonate (PFEtS), perfluorooctanesulfonamide (PFOSA), perfluoroundecanoic acid (PFUDA), perfluorodecanoic acid (PFDA), perfluorononanoic acid (PFNA), perfluoroheptanoic acid (PFHpA), perfluorohexanoate (PFHxA), perfluoro-n-pentanoic acid (PFPeA), and perfluorobutanoate (PFBA) in tap water in Niagara-on-the-Lake, Ontario (Mak et al., 2009);

- PFOS, PFNA and PFUDA in treated and raw water in Québec (Ministère du Développement durable, de l'Environnement, de la Faune et des Parcs, 2012);
- PFOS, PFBA, PFPeA, PFHxA, PFHpA, PFNA, PFBS, and PFHxS in groundwater at former fire-fighting training areas in British Columbia, Alberta, Nova Scotia, and Ontario (Paterson et al., 2008; Environmental Sciences Group, 2015);
- PFOS and PFDA in Nova Scotia and Ontario, and PFUDA, PFDoA, and PFOSA in Nova Scotia (Environmental Sciences Group, 2015).

5.1.2 Leaching from drinking water materials

Polymers and elastomers used as joining and sealing materials in water distribution systems may contain trace amount of PFOA. PFOA salts are used as a processing aid in the production of fluoropolymers such as polytetrafluoroethylene (e.g., Teflon®) and in fluoroelastomers (e.g., Viton®). An important consideration for reducing exposure to PFOA is to address leaching from these materials by specifying that they meet health-based standards. NSF/ANSI Standard 61 (Drinking Water System Components—Health Effects) limits the leaching of PFOA into drinking water. The standard ensures that materials meet health-based leaching requirements and are safe for use in potable water applications by specifying the single product allowable concentration (SPAC) for contaminants. Although the current SPAC for PFOA is 0.0003 mg/L (NSF/ANSI, 2016a), it is presently under review by NSF International to reflect up-to-date science. Polymers and elastomers used as joining and sealing materials in water distribution systems that meet NSF/ANSI Standard 61 would be expected to leach very low concentrations of PFOA into drinking water.

5.2 Food

Food is generally considered to be the main source of ~~PFOA~~ exposure to PFOA for the majority of the Canadian population, but exposure from food is still well below what is considered unsafe to humans. PFOA was measured in a selection of Canadian food composite samples (samples from the Canadian Total Diet Study [TDS]) conducted in 2004 and additional samples collected within 1992 and 2001) to estimate the dietary intake. PFOA was detected in 3 out of 54 food composites. The detected PFOA concentrations (on a w.w. basis) were 0.74 ng/g (pizza; the sample was above the limit of detection but below the limit of quantitation), 2.6 ng/g (roast beef) and 3.6 ng/g (microwave popcorn). Values were used to estimate the average dietary daily exposure of Canadians; food was estimated to contribute 250 ng/day of perfluorinated compounds, of which approximately 70 ng was attributed to PFOA (Tittlemier et al., 2007).

Store-bought and restaurant foods commonly consumed by Canadians were collected in Whitehorse (Yukon Territory, Canada) in 1998 and analyzed for ~~PFAAs~~PFAS. PFOA was detected in several composite samples (0.36–0.77 ng/g w.w. for cookies, processed cheese, peppers, canned lunchmeats, and pizza), but all measurements were below the limits of quantification (0.65–1.52 ng/g w.w.) (Ostertag et al., 2009a).

The concentrations of ~~PFAAs~~PFAS in the traditional foods of Inuit in Northern Canada was measured to estimate their dietary exposure. PFOA was ~~rarely~~infrequently detected (9% out of 68 samples) in the traditional foods collected from Chesterfield Inlet, Igloolik, Pond Inlet and Qiqiktarjuak in Nunavut, between 1997 and 1999. PFOA was detected in ringed seal (liver: 0.3 ng/g; blood: 0.1 ng/g), eider duck (whole body: 0.4 ng/g), caribou liver (baked: 0.7 ng/g; raw: 0.1 ng/g) and caribou stomach (raw: 0.8 ng/g); the other concentrations were below the detection limit (<0.1 to <0.6 ng/g) (Ostertag et al., 2009b).

PFOA is a processing aid in the manufacture of polytetrafluoroethylene (PTFE), which is used for many purposes, including non-stick cookware. Residual PFOA was detected in PTFE

cookware and film (Begley et al., 2005); however, only minor transfer of PFOA from these products was observed in investigations on the migration into watery and fatty simulated foodstuff (Begley et al., 2005; Powley et al., 2005; Washburn et al., 2005; Sinclair et al., 2007). PFOA has also been detected in microwave popcorn bags (Begley et al., 2005; Sinclair et al., 2007; Dolman and Pelzing, 2011), and found in food contact papers treated with polyfluoroalkyl phosphate surfactant (PAPs) or di-perfluoro-alkyloxy-amino-acid (PAA) (Xu et al., 2013). The migration rates of PFOA from food contact papers treated with these compounds ranged from 7% to 92% for five different food simulants (Xu et al., 2013).

5.3 Air

The inhalation intake of PFOA for Canadians was considered negligible due to its low volatility (Tittlemier et al., 2007).

The levels of ~~PFAAs~~PFAS in outdoor air were determined in a Canadian study conducted in 2007 in Vancouver (Shoeib et al., 2011). PFOA samples were collected using outdoor passive samplers deployed in residential yards for approximately 3 months. PFOA was detected in 4 out of 6 samples (<0.47–9.2 pg/m^3; mean: 1.4 pg/m^3) (Shoeib et al., 2011). Similar concentrations were measured in the Canadian Arctic (Resolute Bay, Cornwallis Island, Nunavut) in 2004, with a mean concentration (gas and particulate phase of atmospheric air) of 1.4 pg/m^3 (Stock et al., 2007).

In indoor air, the levels of PFOA primarily depend on its concentration in air particulates and are thus related to the levels in indoor dust, as well as the number, type and age of the potential sources (e.g., carpeting, furniture and paint) (Fraser et al., 2012). To date, data on indoor air concentrations of PFOA are limited to those reported in the aforementioned residential study (Shoeib et al., 2011). The authors collected PFOA in indoor air using passive samplers deployed for approximately 4 weeks in bedrooms of 59 participants. PFOA was the dominant ionic ~~PFAA~~PFAS, with a geometric mean concentration of 28 pg/m^3 (arithmetic mean: 113 pg/m^3, median: 21 pg/m^3, range: 3.4–2,570 pg/m^3).

5.4 Consumer products

Owing its use patterns, human exposure to PFOA would likely result from contact with, or the use of, certain consumer products (Health Canada, 2006). Estimates of the contribution of solution-treated carpeting and treated apparel to Canadians' daily intakes of total perfluorinated compounds were 120 ng/day and 12 ng/day, respectively (Tittlemier et al., 2007). As no Canadian data were available on exposure to PFOA in consumer products, data from other countries are summarized below.

PFOA has been measured in a variety of consumer products, including waterproofing agents, fluorotelomer-treated textiles, apparel and carpeting, aqueous firefighting foams, non-stick ware, industrial floor waxes and wax removers, latex paint, home and office cleaners, PTFE-coated dental floss and dental tape, and PTFE film/sealant tape (Begley et al., 2005; Washburn et al., 2005; Herzke et al., 2012). PFOA has also been measured in ski waxing blocks and glider powders, with occupational exposure to airborne ~~PFAAs~~PFAS measured during professional ski waxing (Freberg et al., 2010).

5.5 Soil and household dusts

The estimated contribution of dust to Canadians' daily intakes of total perfluorinated compounds was 28 ng/day (Tittlemier et al., 2007). The study did not estimate the total daily contribution of soil to perfluorinated compound exposure.

PFOA concentrations in dust from Canadian houses were reported to vary from <2.3 to 1,234 ng/g with a median value of 19.7 ng/g (mean: 106 ng/g). House age and fraction of floor covering were reported to be significantly correlated with the concentration of ~~PFAAs~~PFAS in dust—older houses and those with smaller fractions of the floor covered with carpet were characterized by lower concentrations of ~~PFAAs~~PFAS (Kubwabo et al., 2005).

In another Canadian study conducted in ~~the City of~~ Vancouver, BC, PFOA was detected in all house dust samples analyzed for this compound (n = 132). The PFOA concentrations ranged from 1.9 to ~~1,390~~1390 ng/g (median: 30 ng/g, mean: 97 ng/g) (Shoeib et al., 2011). PFOA levels in dust collected from homes in Toronto, Ontario (n=19) ranged from <0.98 ng/g to 4000 ng/g (median: 69 ng/g, mean: 270 ng/g) (Goosey and Harrad, 2011). Another Canadian study investigating PFAS levels in household dust in a family home in Edmonton, Alberta found PFOA in the housedust (550.0 ng/g) and carpets (16.0 – 153.0 ng/g) (Beesoon et al., 2012). The authors attributed the high levels of PFOS to carpet treatment with Scotchgard carpet protector.

No study reporting background PFOA levels in soils was located. Some data are available in soil surrounding perfluorochemical industrial facilities (as reviewed by ATSDR, 2009).

5.6 Human biomonitoring data

Human PFOA blood levels have been shown to be influenced by gender and age. The Canadian Health Measures Survey (CHMS), Cycle 1 (2007–2009) indicates that PFOA plasma levels in adult males (geometric mean [GM]: 2.94 ng/mL; 95% CI: 2.74–3.15, 95th percentile: 5.98 ng/mL, n=1376) are higher than in adult females (GM: 2.17 ng/mL; 95% CI: 1.99–2.36, 95th percentile: 4.99 ng/ml, n=1504) (Health Canada, 2010). This effect persisted in Cycle 2 of the study (2009–2011) (Males—GM: 2.6 ng/mL, 95% CI: 2.4–2.9, 95th percentile: 6.0, n=511; Females—GM: 2.0 ng/mL, 95% CI: 1.8–2.2, 95th percentile: 4.4 ng/mL, n=506) (Health Canada, 2013b).

5.7 Multi-route exposure through drinking water

The multi-route exposure assessment process is not applicable for PFOA, due to the compound's high molecular weight and low volatility (Krishnan and Carrier, 2008); therefore, the relative contributions of exposure to PFOA from both inhalation and dermal routes during showering and bathing were not estimated. Based on the high molecular weight of 414.07 g/mol and the ionic properties of PFOA at pH levels typical in drinking water, volatility and dermal penetration are expected to be low. Moreover, dermal permeability coefficients measured in *in vitro* studies predict that PFOA is impermeable to skin under typical conditions (Fasano et al., 2005; Franko et al., 2012). Consequently, exposure to PFOA via inhalation and dermal routes during showering or bathing is expected to be negligible.

6.0 Analytical methods

To date, the United States Environmental Protection Agency has not approved any analytical methods for the analysis of PFOA in drinking water. There are some methods that can be used to measure PFOA in drinking water at levels well below the ~~proposed~~ MAC. However, they require good quality control procedures to produce accurate results.

6.1 Available methods

EPA Method 537 ver. 1.1, International Standard Organization (ISO) Method, 25101 and 3M Method ETS-8-154.3 can all be used for the analysis of PFOA in drinking water (3M, 2008; ISO, 2009; U.S. EPA, 2009a). All methods use a solid phase extraction (SPE) technique followed

by a liquid chromatograph (LC) coupled to electrospray ionization (ESI) tandem mass spectrometry (MS/MS) operated in negative ion mode. For the purpose of trace quantitation of PFOA in drinking water, the chromatographic conditions are selected such that all isomers (linear and branched) are co-eluted together.

In the EPA method, a water sample is fortified with labelled internal standards and passed through a SPE cartridge to extract target analytes in addition to their corresponding internal standards. The compounds are eluted from the SPE cartridge, concentrated and injected into a LC-MS/MS. The mass spectra and retention times of the analytes are identified by comparison to internal standards. The MDL for PFOA is 1.7 ng/L (0.0017 µg/L) and the Lowest Concentration Minimum Reporting Level (LCMRL) is 5.1 ng/L (0.0051 µg/L) (U.S. EPA, 2009a). PFOA has been included in the third Unregulated Contaminant Monitoring Rule (UCMR3), which stipulates that using Method 537 ver. 1.1, an MRL of 20 ng/L (0.02 µg/L) for PFOA must be achieved and reported by the utilities during monitoring (U.S. EPA, 2012b).

The results of an inter-laboratory trial (Taniyasu et al., 2013), conducted in 2006, were used to establish whether ISO Method 25101 was reliable for the analysis of PFOA and PFOS in environmental water samples, including drinking water. The intra- and inter laboratory precisions were in the range of 3–7% and 15–22%, respectively for PFOA for all environmental water samples analyzed. The recovery of the internal standards for PFOA ranged from 91 to 98%. These results confirmed that this analytical method was reliable and can be used for the analysis of PFOA in environmental water samples. The method uses SPE, LC-MS/MS and is applicable for the quantification of the linear and branched isomers of PFOA and PFOS. The branched isomers can be separated from the linear isomers by using specific chromatographic column and optimized conditions. ISO Method 25101 was found to be appropriate for determination of PFOA levels in unfiltered samples of drinking water, groundwater and surface water with concentrations in the range of 10 – 10,000 ng/L (0.01 – 10 µg/L) (ISO, 2009).

Method (ETS-8-154.3) was developed and validated by 3M for PFOA analysis in drinking water, groundwater and surface water samples. The analytical steps are similar to EPA Method 537 Ver 1.1 and the method has a limit of quantitation (LOQ) of 25 ng/L (0.025 µg/L) for PFOA (3M, 2008).

6.2 Analytical challenges

In spite of the significant improvements in ~~the~~ analytical methods for the determination of PFAS in environmental water samples, challenges, uncertainties and drawbacks still remain. Major challenges associated with the trace quantitation of ~~PFASs~~PFAS included matrix effects and a background contamination in the analytical blanks. In order to generate accurate data, quality control ~~(QC)~~ procedures (i.e., matrix spikes, duplicates, spike-recovery experiments, surrogate recovery checks) are critical. In addition, the use of isotope-labelled internal standards is a standard practice and must be used in the analysis of PFAS. In addition, PFOA analyses should be conducted by an accredited laboratory or by a laboratory with a stringent quality assurance/quality control (QA/QC) program in place to ensure data quality.

6.2.1 Matrix effect

Although LC-MS/MS is a highly selective and sensitive technique, it is susceptible to matrix effects which is one of the major uncertainties in the trace quantitation of PFOA in environmental water samples (Martin et al., 2004; Yamashita et al., 2004; Taniyasu et al., 2005; van Leeuwen et al., 2006; Arsenault et al., 2008). Matrix effects result from the co-extracted components from the sample, which affect the signal intensity of the target analyte and either suppress or enhance the spectral signal. The extent of the matrix interference varies, depending on

the nature of the samples. Although the matrix interferences are negligible for drinking water and groundwater (ISO, 2009), the PFOA quantification requires efficient extraction and clean-up procedures. The aim of these procedures is to separate the compounds in the sample by their chemical and physical properties, to concentrate the target analyte and to purify the extract prior to the instrumental determination. The most frequently used technique for the extraction of PFASs from drinking water samples includes SPE cartridges with different packing material such as reverse phase (C18) cartridge (Loewen et al., 2005; Wolf and Reagen, 2011; Zainuddin et al., 2012), mixed hydrophobic/polar (Oasis HLB) cartridges (Yamashita et al., 2004; Taniyasu et al., 2005; Villaverde-de-Saa et al., 2015) and a weak anion exchange (WAX) cartridges (Taniyasy et al., 2005; 2013). Several studies conducted a liquid-liquid extraction (LLE) technique to extract and concentrate PFASs in different environmental aqueous matrices prior to LC-MS/MS (Gonzales-Barreiro et al., 2006; Szostek et al., 2006; Backe et al., 2013). A laboratory study (Gonzales-Barreiro et al., 2006) used an LLE to extract PFASs (C6-C12) from tap water. The recovery of the PFASs with a carbon chain greater than C8 was in the range 80-93%. The authors indicated that the method was less efficient in extracting short-chained PFASs when compared to the SPE technique (Gonzales-Barreiro et al., 2006).

The clean-up procedures involved a washing step after the sample enrichment on the SPE cartridge and a filtration to remove solids from the final extract (Yamashita et al., 2004; Larsen and Kaiser, 2007; van Leeuwen and Boer, 2007). Care should be taken to avoid contamination of the extract or losses of PFASs during the clean-up procedures. Prior to a SPE, a sample pre-treatment (filtration) may be required to facilitate extraction or to remove matrix constituent that will interfere with analyses (van Leeuwen and Boer, 2007; Ding et al., 2012).

The most suitable approach to assist in the quantification of PFASs is to use of isotopically-labelled internal standards (isotope dilution). It is important that the appropriate isotope-labelled internal standards are used for the quantitation of the corresponding native compound. Isotope-labelled internal standards will have the same retention time as the target analytes (excluding isomeric separation) and the monitoring of their signals will determine whether the analytes signal are suppressed or enhanced. The application of surrogates or isotopically-labelled internal standards early in the sampling or the sample preparation steps will compensate for the inefficiency/losses in the extraction and other sample preparation steps (Martin et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007). Wolf and Reagen (2011) reported that an addition of isotope-labelled internal standards prior to sample collection simplified the sample preparation procedures. The method demonstrated an accuracy of 105% and a precision of 12% for PFOA in laboratory Milli-Q water samples (Wolf and Reagen, 2012).

If isotope-labelled internal standards are not available, a standard addition quantitation, which involves spiking known quantities of a standard into the sample, is an alternative to use when matrix effects are unavoidable (Weremiuk et al., 2006; Furdui et al., 2007; van Leeuwen et al., 2009).

The use of MS/MS for analysis of PFOA enables the detection of product (daughter) ions. The transitions from m/z ratio 413 (parent ion $C_7H_{15}COO^-$) to m/z ratio 369 and 169 (daughter ions) are used for PFOA quantification (ISO, 2009; U.S. EPA, 2009a).

6.2.2 Background contamination in the analytical blanks

A known source of background contamination is the presence of fluoropolymers, such as polytetrafluoroethylene (PTFE) and perfluoroalkoxy compounds in various laboratory consumables. Ammonium perfluorooctanoate and ammonium perfluorononanoate are used as fluoropolymer processing aids and are common components in the laboratory products. These fluoropolymers may lead to quantifiable background levels in the analytical blanks especially

when quantifying trace levels in water samples. Contacts with such laboratory materials and products during analysis of PFOA should be avoided (Martin et al., 2004; Yamashita et al., 2004; ISO, 2009).

Yamashita et al. (2004) studied the sources of background contamination at various analytical steps, including sample collection, extraction and sample clean up prior to the instrumental analysis. Polypropylene bottles used for sample collection and storage, in addition to different types of SPE cartridges and purified reagent water, were found to be sources of PFASs contamination in the analytical blanks. Taniyasu et al. (2005) and Berger et al. (2011) found that the polypropylene containers are unsuitable for collection and storage of water samples intended for analysis of long-chain PFCAs such as perfluoroundecanoic and perfluorododecanoic acids, because of the adsorption of the compounds on the containers' surface. The authors recommended the use of high density polyethylene or glass containers. However, ISO method 25101 and EPA Method 537 recommended against the use of glassware for sampling due to the potential adsorption of PFOA on the walls (ISO, 2009; U.S. EPA, 2009a). The storage and sample preservation steps prior to the instrumental analysis should prevent changes in composition of the sample matrix and the concentration of the analyte (van Leeuwen et al., 2007).

SPE cartridges can also be a source of contamination and the U.S. EPA (2009a) recommends that SPE devices be tested prior to using them for analysis to ensure that there is no contamination of the sample. Several studies ~~performed on~~were conducted with a direct injection (DI) of the water samples into ~~LC-MS/MS.~~liquid chromatograph column. The method avoids the use of additional materials and sample preparation- processes, which may limit possible contamination and target compound losses (Schultz et al., 2006; Furdui et al., 2008; Dickenson and Higgins, 2013).

HPLC tubing, nylon filters, auto-sampler vial caps made of Teflon or Viton fluoropolymers, valve seals and degassers were identified as the potential sources of contamination of the instrumental blanks with PFOA (Yamashita et al., 2004; Taniyasu et al., 2005; Schultz et al., 2006; Larsen and Kaiser, 2007) and to lesser ~~extend~~extent with PFOS (Yamashita et al., 2004). The instrumental background contamination can be reduced by replacing or bypassing the fluoropolymers parts such as a degasser (Arbuckle et.al, 2013) with offline degassing of mobile phases; replacing fluoropolymer components with stainless steel, polyetheretherketone (PEEK) tubing, installing an upstream guard column, extensively flushing of the LC system or reducing the LC-column equilibration time (Martin et al., 2004; Yamashita et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007; Nakayama et al., 2007; Shoemaker et al., 2009; Arbuckle et.al, 2013).

6.3 Analytical performance

Recent analytical improvements have been realized through the availability and use of high quality standards and stable isotope internal standards to compensate for the matrix effect and for inefficiencies in the extraction procedure and/or other sample preparation steps (Yamashita et al., 2004; Lowen et al., 2005; Taniyasu et al., 2005; Nakayama et al., 2007; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). There are currently, a number of high quality analytical-grade standards that are commercially available and the list of these standards continues to expand (van Leeuwen et al., 2009, Berger et al., 2011).

In the early 2000s, quantification of PFASs was biased by the lack of proper analytical standards, isotopically labelled surrogates and reference material and there was a significant analytical variability between laboratories. Two inter-laboratory studies were conducted to analyze PFASs, including PFOA and PFOS, in environmental water samples and found a varying degree of accuracy. In the first study (van Leeuwen et al., 2006), conducted in 2004/2005, factors

resulting in poor agreement between participating laboratories, were determined to be low PFOA/PFOS concentrations (below 20 ng/L) in water samples; the use of low purity standards, high matrix effect, and a high background contamination in the analytical blanks. The relative standard deviation (RSD) reported in the study was 118% for PFOA (van Leeuwen et al., 2006). In the second inter-laboratory study, the performance of the participating laboratories improved due to the minimization of the matrix effects; the use of higher quality (purity and isomeric composition) shared standards (provided by a single source), and the use of mass-labelled internal standards. The reported RSD value in this study was 32% for PFOA.

Methods using SPE and DI procedures followed by LC/ESI/MS/MS have been reported in the literature for the determination of ~~PFAAs~~PFAS, including PFOS in water samples (Yamashita et al., 2004; 2005; Taniyasu et al., 2005; 2013; Furdui et al., 2008; Hansen et al., 2010; Berryman et al., 2012; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). Details regarding the preconditioning procedures of the SPE cartridges, eluent, clean-up procedures, MS quantification parameters and QC procedures specific to each method are available in the cited reference.

A study reported a limit of detection (LOD) (signal-to-noise [S/N] = 3:1) of 0.28 ng/L and an LOQ (S/N= 10:1) of 0.94 ng/L using an SPE followed by LC-MS/MS for analyzing PFOA in surface water. A water sample of 500 mL was loaded on the Oasis WAX cartridge, a target fraction was eluted, dried under nitrogen gas and before the analysis the samples were filtered. The recovery value of 115±6% for PFOA was calculated by isotopically-labelled internal standards calibration (Sun et al., 2011; Li et al., 2011).

Villaverde-de-Saa et al. (2015), using an SPE followed by LC–MS/MS, developed a method for the determination of seven PFCAs (C6–C12) and PFOS in environmental waters samples. A water sample of 1.0 liter, fortified with internal standards, was loaded on the Oasis HLB cartridge. The method reported a LOD of 0.03 ng/L and a LOQ of 0.11 ng/L for PFOA, (LOD and LOQ were calculated as 3 and 10 times the standard deviation, respectively). The recovery value of 89±4% for PFOA was calculated by isotopically-labelled internal standards calibration.

Furdui et al. (2008) investigated the concentration of PFASs in water samples from the Great Lakes. The analysis of nine target contaminants including PFOA, were performed by directly injecting the samples into LC-MS/MS. Quantification was performed using internal standard correction and standard addition. An isotope dilution provides the most accurate and precise results. The method had a LOQ (signal-to-noise [S/N] =10:1) of 0.5 ng/L for PFOA (Furdui et al., 2008).

The province of Québec reported results of the monitoring PFASs at 16 sites, including seven drinking water treatment plants. A total of 226 water samples (84 raw, 84 treated and 58 surface water samples) were analyzed. Both raw and treated water were sampled monthly for a period of one year. Sampling of the surface water was limited through the year. The samples were analyzed using C18 cartridges and LC-MS/MS in positive ionization mode. Reported DLs ranged from 0.5 to1.0 ng/L and 0.3 to 0.6 ng/L for untreated (250 mL analysed sample) and finished water (500 mL sample), respectively. In order to compensate and correct the instrumental variations and the matrix effect, isotopically-labelled internal standards were added prior to the LC (Berryman et al., 2012). Although the photoionization technique is less sensitive than the electrospray ionization, it is less prone to matrix effect (Martin et al., 2004).

Berger et al. (2004) compared different mass spectrometric techniques (time-of-flight [TOF] high resolution MS, triple-quadrupole tandem MS, and IT-MS) coupled with a high performance liquid chromatography (HPLC) for analysis of PFASs including PFOA. The instrument parameters such as vaporizer temperature, collision energy, and cone voltage fragmentation were optimized for each mass spectrometry technique. Negative electrospray

ionization was selected as the ionization mode for all instruments. The study indicated that both TOF high resolution MS and triple-quadrupole tandem MS methods had higher sensitivities than IT-MS for all tested PFASs. Although IT-MS had a higher DL and smaller linear range, it provided the best results for tentative structure elucidation and qualitative analysis of branched PFASs isomers (Berger et al., 2004; Jahnke and Berger, 2009).

The analysis of PFASs in environmental water samples has been dominated by the use of LC coupled to MS or MS/MS, although other techniques such as ^{19}F nuclear magnetic resonance (NMR) and gas chromatography (GC)–MS have also been explored. ^{19}F NMR analysis is a less sensitive and non-specific method due to the determination of the presence of CF_2 and CF_3 moiety in the sample. Gas chromatography (GC) can be used to determine neutral and volatile PFASs and fluorotelomer alcohols. ~~PFAAs~~PFAS are derivatized in order to be amenable for GC analysis. However, the use of the derivatization techniques is limited for PFOS analysis due to the instability of the PFOS's derivatives (Moody et al., 2001; Villagrassa et al., 2006).

7.0 Treatment technology

The available data and calculated pKa (2.8) values indicate that PFOA is a strong acid which predominantly dissociates to a negatively charged form (anion) at environmentally relevant pH values (U.S. EPA, 2005; Lange et al., 2006; Prevedouros et al., 2006). Based on the physical-chemical properties of the ionized form (a negligible vapor pressure, a high solubility in water and moderate sorption to solids), Prevedouros et al. (2006) suggested that PFOA would accumulate in surface water. Given the hydrophobic and oleophobic nature of the fluorinated alkyl chain and the hydrophilic nature of the carboxylate group, hydrophobic and electrostatic effects likely influence PFOA adsorption (Higgins and Luthy, 2006; Xiao et al., 2011). The nature of the chemical structure of PFOA (i.e., strong carbon - fluorine (C-F) bonds) makes it resistant to hydrolysis and biodegradation as well as to several chemical treatment processes (Lange et al., 2006; ATSDR, 2009).

7.1 Municipal scale

Dickenson and Higgins (2013) evaluated the ability of wide range of full-scale treatment techniques to remove PFASs, including PFOA and PFOS, from raw water or potable water reuse plants. The treatment trains varied, but generally consisted of coagulation followed by physical separation, aeration, chemical oxidation, UV irradiation, and disinfection. Regardless of the treatment train applied, there was little or no decrease in PFOA and PFOS concentrations and the authors concluded that these treatment methods are not effective in removing PFASs.

GAC adsorption and membrane filtration techniques appear promising for removal of PFOA in drinking water, achieving treated water concentrations below 0.2 µg/L (Tang et al., 2006; Lampert et al., 2007; Wilhem et al., 2008; Deng et al., 2010; Takagi et al., 2011; Appleman et al., 2014). In order to achieve a PFOA concentration below 0.2 µg/L, the GAC system must be specifically designed and appropriately operated for PFOA removal in drinking water. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance by directly competing for adsorption sites and preloading (fouling) the GAC beds. Therefore, the effectiveness of GAC to remove PFOA in drinking water appears to be dependent on the regeneration frequency and/or replacement of the carbon (Kolstad 2010; Takagi et al., 2011; Appleman et al., 2014). Membrane filtration such as reverse osmosis (RO) and bench-scale nanofiltration (NF) studies demonstrated effective removal of all tested short-and long-chain PFASs including PFOA in drinking water. Although the RO process is effective, it is likely to be

an expensive treatment method (Steinle-Darling et al., 2008); Quinones and Snyder, 2009; Appleman et al., 2013; Flores et al., 2013). Anion exchange resins may also be effective in removal of PFOA. However full-scale evaluation of this technology has not been conducted specifically for PFOA removal in drinking water.

The selection and effectiveness of each treatment strategy is driven by several factors, including source water chemistry, concentration of PFOA and/or other PFASs and pre-existing treatment processes. If long-chain PFASs are detected in the drinking water sources, the utility may consider the implementation of treatments such as GAC. However, utilities that have shorter chain PFASs in their raw water source may choose to implement RO or NF. The treatment technologies need to be designed specifically for PFASs removal and operated appropriately in order to achieve contaminants removal objectives in drinking water (Dickenson and Higgins, 2013).

The ability of various drinking water treatment processes and treatment trains to remove PFOS have been summarized by Dickenson and Higgins (2013) and Rahman et al. (2014). Appendix A summarizes the percentage removal of PFOA in full-scale plants where both raw and finished water concentrations were reported (Rahman et al., 2014). Data show that the treatment technologies employed by these plants (with the exception of GAC, RO and NF) did not appreciably remove PFOA. They also show that in some cases concentrations in the finished water were higher than in the raw water, likely due to the breakdown of precursor compounds to form PFOA during the treatment (Takagi et al., 2008; Shivakoti et al., 2010). Takagi et al. (2011) also postulated that these higher finished water levels may result from desorption from GAC filters used for long periods of time without reactivation and the leaching of these compounds from Teflon-coated treatment equipment.

7.1.1 Conventional treatment

Conventional drinking water treatment processes generally incorporate coagulation, flocculation, sedimentation, and filtration, followed by primary and secondary disinfection. Common coagulants used in drinking water include aluminum sulfate (alum), ferric hydroxide, ferric chloride, polyaluminum chloride and coagulant aid polymers. Filtration media can consist of sand (single media); sand and anthracite (dual media); or sand, anthracite, and garnet (multi or mixed garnet media). GAC may also be used as the filter media.

Conventional full-scale drinking water treatment techniques have been found ineffective in removing PFOA from source waters. Samples collected from several full scale conventional treatment plants indicated essentially no difference in the PFOA concentrations between plant influent and concentrations in water following the coagulation, sedimentation, and sand filtration steps (Loos et al., 2007; Shivakoti et al., 2009; Takagi et al., 2011; Thompson et al., 2011). Similarly, Eschauzier et al. (2012) reported that slow- and rapid- sand filtrations were ineffective for PFOS and PFOA removal. The inability of conventional water treatment to remove PFOA and PFOS may be due to their extremely low concentrations in water and their hydrophilicity which renders them unamenable to removal by conventional treatment processes (Rahman et al., 2014). These findings are in agreement with recently conducted bench-scale studies of the removal of PFOA from water (Deng et al., 2011; Xiao et al., 2013).

Jar tests (Xiao et al., 2013) achieved an approximately 3% removal of an influent concentration of 0.083 µg/L (83 ng/L) of PFOA, with an alum dose of 30 mg/L and pH of 7.9. A removal efficiency below 10% was reported under a range of alum doses ranging from 10 to 60 mg/L and pH levels ranging from 6.5 to 8.0. Removal rates of approximately 25% were observed using enhanced coagulation with alum doses greater than 60 mg/L and pH 4.5 – 6.5. In general, the removal efficiencies were below 35% under the examined coagulation conditions

(alum doses 3-110 mg/L and pH 4.5-8.0). Ferric chloride coagulation exhibited similar results. The authors indicated that removal rates were lower for PFOA than PFOS in both conventional and enhanced coagulation conditions, possibly due to PFOA having a lower molecular size and a potential for being less hydrophobic.

However, Deng et al. (2011) demonstrated that the addition of powdered activated carbon (PAC) before the coagulation process was capable of enhancing the removal efficiency of PFOA in water after the coagulation. In the experiments, an initial PFOA concentration of 21.2 µg/L was decreased to 5.8 µg/L with a polyaluminium chloride (PACl) dose of 10 mg/L. A concentration below 1.0 µg/L was measured in the finished water after the addition of 10 mg/L of PACl and PAC doses up to 16 mg/L, to the initial PFOA concentrations in the range of 0.5-3.0 mg/L. The study found that the concentration of PFOA in the finished water decreased with increasing initial turbidity and PACl dose, and increased with increasing pH or temperature

7.1.2 Adsorption

Adsorbents typically used in drinking water treatment include activated carbon, activated alumina, zeolites, clays, metal oxides, hydroxides, and carbonates (AWWA, 2011; U.S. EPA, 2012). GAC is used in a fixed bed, while PAC is generally added directly to the raw water as a powder or mixed with water to form a slurry.

Several laboratory studies of PFOA and PFOS adsorption kinetics indicate that PAC reached sorption equilibrium in 4 hours while GAC reached equilibrium in 168 hours, (Yu et al., 2009) and that PFASs removal percentages were generally higher for PAC than for GAC (60–90% versus 20–40%, respectively) for 10 minutes adsorption time (Hansen et al., 2010). These results may be due to PAC's smaller particle size, and higher specific surface area per volume of carbon when compared to GAC (Yu et al., 2009; Hansen et al., 2010). If PFASs are present in the raw water year round, Rahman et al. (2014) suggested that GAC adsorption may be the preferred method for PFASs removal, while PAC may be more appropriate for short-term spill response remediation.

7.1.2.1 GAC

Full-scale evaluations of the effectiveness of GAC adsorption for the removal of PFOA in drinking water sources have been mixed. Several full-scale studies, specifically designed and operated for PFASs removal in drinking water, observed successful removal of PFOA by GAC with a long empty bed contact time (EBCT) and an appropriate regeneration regime (MDH, 2008a; Wilhem et al., 2008; Rumsby et al., 2009; Little Hocking Water Association, 2010; Appleman et al., 2014). Other water treatment plants found similar levels of PFOA in both source and finished water, suggesting that GAC treatment only partially removes this contaminant, if at all. These treatment plants were not specifically designed for PFASs removal in drinking water. As the GAC had been in place for a variable period of time, it was likely that the preloading by NOM had deteriorated the GAC performance leading to similar PFOA levels in the influent and treated water (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012, Flores et al., 2013).

A full-scale GAC treatment system with a flow rate of 1.5 m^3/minute was specifically designed for PFASs removal in groundwater. The system used two GAC contactors in a lead/lag configuration with an EBCT of 13 minutes each. The lead vessel operated for approximately 10 months and treated 30,129 BVs before the concentration of PFOA exceeded 0.05 µg/L. The GAC unit was capable of reducing an influent PFOA concentration in the range of 0.45–0.83 µg/L to below 0.05 µg/L, in the treated water from the lag vessel, for 72,775 BVs (approximately 22 months). At that point, the lead vessel water reached 0.25 µg/L PFOA, its carbon was replaced

with virgin media and the vessel was put in the lag position (Appleman et al., 2014). Another full-scale 400 gpm (1.5 m^3/minute) GAC treatment system proved effective for the removal of PFOA in surface water, with an influent concentration decreasing from 0.9 µg/L to below the DL of 0.01 µg/L in the treated water. An increase in PFOA concentration in the treated water was observed after approximately 3 months with levels exceeding the treated water goal of 0.1 µg/L after 5 months of operation (Wilhelm et al., 2008; Rumsby et al., 2009).

The behaviour and fate of PFASs, including PFOA and PFOS, was assessed by analyzing influent and treated water from several drinking water treatment plants that included GAC in the treatment train. These plants were not specifically designed for PFASs removal in drinking water. The hydraulic retention time of individual treatment steps was considered when the efficiency of each these steps was assessed (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013). The studies found that only the GAC step was capable of removing PFASs in drinking water. Removal of approximately 50% of PFOA was reported when a GAC process was included in the treatment train (Eschauzier et al., 2012; Flores et al., 2013). The paragraphs below provide more details on some of these studies.

A full-scale 5 million gallons per day (MG/D) treatment plant, designed to remove trace levels (ng/L) of organic contaminants in surface water, consisted of river bank filtration, softening, UV/H_2O_2, biologically-active GAC filtration and six GAC contactors. The GAC system operated in parallel mode with an EBCT of 10.5 minutes. Water samples analyzed before and after the GAC system demonstrated reduction of an influent PFOA concentration of 9.7 ng/L to below 5 ng/L (Appleman et al., 2014).

Eschauzier et al. (2012) monitored the concentrations of PFOA and PFOS in a drinking water treatment train consisting of coagulation, rapid sand filtration, dune passage, softening, ozonation and GAC treatment. Only the GAC step was effective for PFASs removal. The system used two-stage GAC contactors in a lead/lag configuration. Of the 40 filters, 20 were used in parallel mode as a first stage and the other 20 were used as a second stage filter. Each GAC filter operated at a flow rate of 348 m^3/hour and an EBCT of 20 minutes, resulting in a total EBCT of 40 minutes. Each virgin GAC filter was installed as a second stage filter and was switched to the first stage after 15 months of operation. After another 15 months, the carbon was reactivated and put back in service as a second stage filter. The GAC system achieved approximately 50% reduction on the average influent PFOA concentration of 8.8 ng/L in the feed water to the first GAC stage (Eschauzier et al., 2012). Flores et al. (2013) reported similar results for the removal of PFOA (45%) in a water treatment plant, which had 24 GAC contactors installed and that were regenerated approximately once a year.

Takagi et al. (2008, 2011) investigated the behaviour, fate and removal efficiency of PFOA and PFOS in drinking water treatment processes from several drinking water treatment plants that included GAC in the treatment train. The removal efficiency of PFOA and PFOS were less than 50% in many of the water treatment plants. A negative removal rate in certain plants suggested that desorption from GAC filters, used for long periods of time without reactivation, may be responsible for these observations. The negative removal rates could also result from the formation of PFOA and PFOS from the degradation of the precursor compounds found in the raw water (Takagi et al., 2011). However, greater than 90% removal of PFOA was observed for 4 months in a 1.5 MLD water treatment plant after the replacement of its activated carbon in the GAC unit. The treatment train consisted of coagulation/sedimentation, rapid sand filtration and two GAC contactors (coal and coconut-shell carbon) in parallel mode. Both GAC contactors were capable of reducing the PFOA concentrations in the range of 25–44 ng/L to below the LOQ of 0.7 ng/L for 4 months. The concentration of the GAC filtered water gradually increased to13 ng/L at the end of the 8 month study period (Takagi et al., 2011).

Rapid small-scale column tests (RSSCTs) are a common bench scale test used to evaluate GAC. Using RSSCTs, Appleman et al. (2013) compared the effectiveness of three different types of GAC for removal of several PFASs including PFOA and PFOS. The column experiments were conducted with an EBCT of 0.38 minutes using deionized water and surface water [dissolved organic carbon (DOC) of 1.7 mg/L], both spiked with 1.0 µg/L of each PFASs. The tests were run for a total of 125,000 BVs (approximately 33 days). Carbon performance varied based on the type of carbon and water chemistry, with GAC being more effective at removing PFASs in deionized water. Of the three carbons, F300 achieved the best results. In the experiments conducted with deionized water, a concentration greater than 0.02 µg/L PFOA (2% of influent concentration C0) was observed at approximately 30,000 BVs (8 days) and a filtered water concentration of 0.05 µg/L (5% of C0) was measured after 56,000 BVs. However, the filtered water concentration reached 0.2 µg/L (20% of C0) after 11,000 BVs (3 days) and full (100%) breakthrough was observed at a run length of 26,000 BVs in spiked surface water. Although RSSCTs are not suitable for evaluating the effect of preloading/fouling of GAC columns by DOC, the observed rapid breakthrough in the spiked natural water demonstrated that the presence of DOC affects the GAC performance in the removal of PFASs by directly competing for adsorption (Appleman et al., 2013).

The efficiency of PFOA removal by GAC adsorption is impacted by NOM in source water which competes for the carbon adsorption site and will adsorb irreversible, causing the carbon's capacity for the target compound to be reduced. When the adsorption capacity of the GAC is exhausted, it must be removed from the contactor and replaced with fresh or reactivated carbon. GAC is used in a fixed bed reactor, as a substitute for existing filtration media (i.e., sand) in a conventional filter, as a layer in a multi-media rapid filter, or in a separate contactor. The reactor can be located at the beginning of the treatment train in a dual-media or sand-replacement mode, or later in the treatment train as a second-stage contactor. The rate of GAC exhaustion will vary substantially for the same water source depending in which configuration GAC will be employed. A dual media (GAC and sand) is used when turbidity removal and the adsorption/removal of the contaminants are combined in a single unit process. The dual media filter (typically located after sedimentation) is likely to be exposed to higher DOC concentrations, and this filter will be exhausted faster. A GAC contactor located at the end of a treatment train will likely experience slower preloading/fouling, since the treatment steps prior to a GAC contactor will reduce the DOC influent concentrations. GAC contactors in lead/lag configuration have also been shown to achieve a PFOA concentration below 0.2 µg/L in treated water (Appleman et al., 2014; Little Hocking Water Association, 2010). This treatment strategy will assist in completely utilizing the entire GAC capacity and reducing operating cost (i.e., carbon replacement cost) (Crittenden et al., 2012).

Close monitoring of PFOA breakthrough (treatment objective) is necessary for efficient operation of GAC unit. Studies indicated that PFOA was successfully removed from drinking water when a frequent regeneration or replacement (3 to 6 months) of the GAC was performed (e.g., Wilhelm et al., 2008; Rumsby et al., 2009; Takagi et al., 2011). Takagi et al. (2011) observed that GAC regenerated over periods greater than one year were not effective in removing PFOA and PFOS and suggested regenerating the carbon 2 to 3 times per year. A GAC replacement at approximately every 3 months was needed to achieve PFOA removal to below 0.004 µg/L in a system where the influent PFOA concentrations ranged from 1.9 to 15 µg/L (Little Hocking Water Association, 2010). A full-scale 2,500 gpm GAC treatment plant, using two GAC contactors in series observed breakthrough of PFOA and PFOS after 286 days and 550 days, respectively. With the replacement of the GAC at the earliest time of PFOA breakthrough,

the system was able to treat 1.9 million gallons of water for 23 months (MDH, 2008a; Kolstad, 2010).

Eschauzier et al. (2012) observed that the removal efficiencies of PFASs by GAC increased with increasing carbon chain length and that sulfonate compounds were removed for a longer period of time than the carboxylate compounds. Shorter-chained PFASs (especially perfluorobutanoic acid [PFBA] and perfluorobutane sulfonate [PFBS]) were not removed by GAC. These findings were in agreement with previous batch experiments showing that the sorption of PFASs on activated carbon decreased with decreasing the carbon chain-length and perfluorosulfonates adsorbed stronger than perfluorocarboxylates with the same carbon chain length (Ochoa-Herrera and Sierra-Alvarez, 2008; Hansen et al., 2010; Dudley et al., 2012; Appleman et al., 2014). Branched isomers of PFOS and PFOA were found to be less sorbable to GAC than linear isomers. Desorption of shorter chain PFASs due to competition for sorption sites with longer chain PFASs or NOM (i.e., DOC) may result in higher levels of shorter chain PFASs in the treated water (Eschauzier et al. (2012).

7.1.2.2 PAC

No full-scale data were reported on the efficacy of PFOA removal by PAC. Most published studies on the efficacy of PAC were conducted at the bench-scale. PFOA concentrations in some of these bench-scale studies were order of magnitude higher than the concentration observed in natural waters. However, trends observed for PAC in terms of preferential adsorption (chain-length dependence) and competition with NOM were similar to that documented for GAC (Hansen et al., 2010; Dudley et al., 2012).

Dudley et al. (2012) evaluated the adsorbability of ten PFASs with different carbon chain lengths (from C4 - C10) on commercially available PACs (coconut shell, lignite, wood, and bituminous coal) and superfine PACs (S-PACs) obtained by wet-milling the commercially obtained PACs. Sulfonate substances were found to be more adsorbable than carboxylate substances and sorption kinetics were faster with S-PACs when compared to PACs. The removal efficiencies of ~~PFAAs~~PFAS increased with increasing carbon chain length (i.e., negligible removal of C4 compounds but greater than 90% removal for C7-C10 compounds). The presence of NOM was found to decrease the effectiveness of PFAS removal by PAC in batch studies. The authors also concluded that significant removal of smaller chain PFASs may not be achievable at practical PAC dosages (Dudley et al., 2012).

Yu et al. (2009) investigated the sorption kinetics and isotherms of PFOA and PFOS on PAC, GAC and an anion-exchange resin. The anion exchange resin had the highest sorption capacity for PFOA while PAC was found to be the adsorbent of choice for PFOS. Another laboratory experiment found 88% and 25% removal of PFOA by PAC and GAC, respectively, based on an initial concentration of 1.4 µg/L in groundwater. The study also observed that PFOS sorption on PAC was faster than on GAC, suggesting that the sorption kinetics were influenced by the size of the activated carbon (Hansen et al., 2010). Qu et al. (2009) inferred that PAC could be used as an effective adsorbent for the removal of PFOA from water because the removal efficiency increased from 51.1% to 99.9% when the PAC doses were increased from 0.1 g/L to 10 g/L (initial PFOA concentration of 20 mg/L).

7.1.3 Membrane filtration

There are four main types of membrane filtration processes in drinking water treatment applications: microfiltration (MF), ultrafiltration (UF), nanofiltration, and reverse osmosis. Low pressure membranes such as MF and UF are not capable of rejecting PFASs since their pores sizes are larger than the effective diameter of the PFASs molecules (~1 nm) (Tsai et al., 2010;

Rahman et al., 2014). Bench-scale studies indicated that the membrane molecular weight cut-off (MWCO) of NF/RO is probably the most important factor for removal of PFASs for these technologies. In general, NF membranes have a lower rejection (95%) than RO (greater than 99%), which is consistent with the fact that NF membranes have larger pores (Tang et al., 2006, 2007; Steinle-Darling and Reinhard, 2008; Lipp et al., 2010; Appleman et al., 2013; Rahman et al., 2014).

The available scientific information on the removal of PFOA and PFOS from drinking water supplies by membrane filtration is limited to one full-scale RO drinking water utility (Flores et al., 2013) and several indirect potable water reuse plants (Quinones and Snyder, 2009; Appleman et al., 2014). Due to the physical location of these indirect potable water reuse plants, they were considered to be major potential contributors to the drinking water facilities' source water in the conducted studies (Quinones and Snyder, 2009).

Although a full-scale conventional treatment was reported as being ineffective for PFOA removal in surface water; 92% removal of PFOA was achieved when RO followed the conventional treatment train (Flores et al., 2013). The RO system's feed water was filtered by the conventional treatment process and blended with untreated groundwater. Feed water PFOA concentration ranged from 15 to 26 ng/L (average 21 ng/L) and the RO system was capable of reducing these PFOA concentrations to an average of 2.1 ng/L (Flores et al., 2013).

Two indirect potable water reuse plants with RO units in their treatment trains were capable of reducing a PFOA concentration to below 55 ng/L in the RO treated water. Both RO systems had a flux rate of 12 gallons per square foot per day (gfd) (20 $L/m^2/h$) and water recovery in the range 80-85%. The feed PFOA concentrations to the RO units ranged from 9.5 to 200 ng/L (Dickenson and Higgins, 2013; Appleman et al., 2014). A survey of several drinking water utilities and indirect potable water reuse plants showed that the PFOA concentrations in the treated water were comparable to the levels found in the raw water samples in almost every case. However, removal was only observed in one planned potable reuse facility when an integrated membrane treatment consisting of MF and RO was employed. The membrane system was capable of rejecting a feed PFOS concentration of 15 ng/L to below 5 ng/L (Quinones and Snyder, 2009).

Bench-scale experiments evaluated the rejection behaviour of unfouled and fouled NF membranes on the removal of PFASs, including PFOA (Appleman et al., 2013). The study found that a polyamide thin film composite flat-sheet NF membrane was capable of rejecting all of tested compounds in the range of 93 to 99%. Greater than 97% rejection of an average influent PFOA concentration of 664 ng/L (LOQ of 20 ng/L) was observed in all experiments using virgin membranes and spiked de-ionized water; virgin membranes and spiked groundwater; and fouled membranes and spiked groundwater. The fouling layer on the NF membrane showed no negative effect on PFOA rejection (Appleman et al., 2013). Another bench-scale study was conducted on one RO (MWCO of 100 Da) and three NF (MWCO range of 200 – 360 Da) membranes for the removal of PFOA. The RO membrane achieved a 99.9% rejection of PFOA from the feed water concentration of 3500 ng/L with a permeate PFOA concentration in the range of 3–6 ng/L. The RO system was operated with a flux rate of 30–40 $L/m^2/h$ and a feed pressure of 8 bars (116 psi). All tested NF membranes achieved a rejection in the range of 95.5–99.8% of an average feed PFOA concentration of 3000 ng/L, with a flux rate of up to 70 $L/m^2/h$ and an operating pressure in the range of 4–7 bars (58-101 psi) (Lipp et al., 2010).

Although there is limited information on full-scale RO and only bench-scale NF treatment information, both technologies are considered effective for PFOA removal from drinking water (Appleman et al., 2014). The results of the NF studies are promising since NF is a less energy intensive process than RO. Testing of the selected NF membrane for PFOA removal at both pilot- and full-scale is an important step for utilities when considering this treatment process. Since the

size exclusion is an important mechanism for PFASs rejection by NF membranes, consideration should be taken to select membranes with MWCO smaller than the size of PFOA.

Considerations when using RO treatment include disposal of the reject water and the potential for increased corrosivity of the treated water. RO rejects a significant portion of the influent water as contaminant-rich brine, and the concentrate discharge must be disposed of appropriately. The removal of contaminants can cause mineral imbalances that could increase the corrosive nature of the treated water. In most cases, post-treatment corrosion control measures need to be taken.

7.1.4 Ion exchange

PFOA is in an anionic form at ambient water pH values and therefore is expected to be amenable to removal by anion exchange resins (Senevirathna et al., 2010). Two primary mechanisms, hydrophobic and electrostatic interactions, were proposed for the removal of PFOA by ion exchange resins (Carter et al., 2010; Deng et al., 2010; Xiao et al., 2012).

Appleman et al. (2014) reported results for the only one known full scale application of ion exchange for the removal of PFASs. However, this system was not specifically designed for PFASs removal in drinking water. A 350 gpm full-scale ion exchange plant reduced the concentrations of PFOA in the range of 68–120 ng/L to an average concentration 24 ng/L in groundwater. A strong base anion resin impregnated with iron oxide used for arsenic removal was assessed for PFOA removal after the resin had been in use for 5 and 9 months. The highly porous strong base anion exchange resin, achieved greater than 75% removal of PFOA, partial removal of perfluoroheptanoic acid (PFHpA) (46%), and high removal of both PFOS (>92%) and perfluorohexanesulfonate (PFHxS) (97%). Shorter carbon chain compounds such as PFBA, and perfluorohexanoic acid (PFHxA) exhibited little to no removal. Results also indicated that perfluorosulfonic acids were preferably removed by anion exchange resin over the perfluorocarboxylic acids.

Exchange resins exhibit a degree of selectivity for various ions, depending on the concentration of ions in solution and the type of resin selected. Laboratory-scale evaluations of different types of resins (i.e., ion exchange resins, non-ion exchange resins) for removal of PFASs in water have been reported in the literature (Lampert et al., 2007; Carter et al., 2010; Deng et al., 2010; Senevirathna et al., 2011; Xiao et al., 2012; Chularueangaksorn et al., 2013). Batch kinetic tests conducted with a high initial PFOA concentration (mg/L) demonstrated a greater than 99% removal of PFOA in 25 hours of contact time using a commercial anion exchange resin, while another anion resin achieved only 37% removal. The study also observed that PFOS anions were preferably removed over PFOA anions in the ion exchange process (Lampert et al., 2007). In laboratory experiments, anion exchange resins demonstrated greater capacity for PFASs removal than non-ion exchange resins (Chularueangaksorn et al., 2013, 2014). Laboratory-scale fix-bed columns compared the performance of anion exchange and non-ion exchange resins. The tests were conducted with an influent concentration of 5 µg/L PFOA for 120 days of operation. The breakthrough goal of 0.5 µg/L was observed with run lengths of 119,880 BVs (111 days) and 68,040 BVs (60 days) by the anion exchange and non-ion exchange resins, respectively (Chularueangaksorn et al., 2013).

While findings showed that anionic resins had a higher capacity for PFOA than non-ion exchange resins (Deng et al., 2010; Chularueangaksorn et al., 2013, 2014), it was also observed that moderately polar non-ionic resins performed better than non-polar non-ionic resins for removal of PFOA from water (Xiao et al., 2012).

Studies indicate that the ion-exchange process is a promising technology (Dickenson and Higgins, 2013) for the removal of ~~PFAAs~~PFAS, including PFOA, from drinking water. However,

additional studies on the, selectivity of the resins, kinetic limitations, the impact of DOC, regeneration rates, and the presence of competing ions such as sulfate and nitrate on removal efficiency are needed (Dickenson and Higgins, 2013; Rahman et al., 2013).

7.1.5 Oxidation, UV irradiation and advanced oxidation processes

Advanced oxidation processes (AOPs) have been developed for removal of contaminants that are resistant to more typical chemical oxidation treatment processes. They include the use of appropriate combinations of ultraviolet (UV) light, chemical oxidants and catalysts (e.g., ozone, hydrogen peroxide, titanium dioxide) to generate highly reactive radicals, such as hydroxyl radicals, which are strong oxidants and react rapidly and non-selectively with organic contaminants.

Rahman et al. (2014) summarized studies that have demonstrated that ~~PFAAs~~PFAS like PFOA will likely be resistant to oxidation, even by molecular ozone and hydroxyl radicals. Due to the low reactivity of PFOA with ozone and AOPs, chlorine–based oxidation processes will likely not oxidize PFOA under typical drinking water conditions. The resistance of PFOA to oxidation is due to the shielding effect of the fluorine atoms and the strength of the carbon-fluorine bonds (3M, 1999; ATSDR, 2009). These conclusions have been confirmed in surveys of full-scale treatment plants (Quinones and Snyder, 2009; Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013) described below.

In a survey of several drinking water utilities, Quinones and Snyder (2009) observed that PFOA was resistant to chlorination, chloramination and ozonation even in a combination with other treatment processes such as coagulation/flocculation, deep bed filtration and UV irradiation. Results from drinking water treatment plants in Japan reported similar concentrations of PFOA in samples of water treated with an ozonation process and in the raw water samples (Shivakoti et al., 2010; Takagi et al., 2011). Ozone doses in the range 0.37–0.85 mg/L and contact time as high as 120 minutes showed that the ozonation process was ineffective to degrade PFOA at four utilities (Takagi et al., 2011). Thompson et al. (2011) observed that an ozone dose of 5 mg/L with a contact time of 15 minutes in reclaimed water was not effective at reducing PFOA concentrations in the range of 7.1–12.4 ng/L.

A full scale treatment plant employing two UV reactors, each capable of treating 3 MG/D groundwater with a UV dose of 80 mJ/cm^2 and UV transmittance of 95%, were not capable of reducing an influent PFOA concentration in the range of 11–15 ng/L. Another full scale 5 MG/D treatment plant reported that a UV dose of 500 MJ/cm^2 in combination with a dose of 4 mg/L H_2O_2 was also ineffective at degrading 19 ng/L PFOA in surface water (Appleman et al., 2014). Oxidation/AOPs and UV irradiation appear ineffective for PFOA removal in drinking water. However, ozone or AOPs may be able to oxidize polyfluorinated precursor chemicals that may be present in raw water, resulting in the potential for increasing the concentration of PFOA and PFOS in the finished water (Rahman et al., 2014).

7.1.6 Aeration/air stripping

The removal of compounds using air stripping is based on the equilibrium partitioning of chemicals between air and water, which is affected by the contact surface area between the air and the water, as well as temperature, vapour pressure and the pH of the water.

Dickenson and Higgins (2013) evaluated 23 PFASs (including PFOA and PFOS) in raw and finished drinking water and at various steps along the treatment train. They found that aeration was ineffective at removing PFOA and PFOS (10% removal).

7.1.7 River bank filtration (soil aquifer treatment)

River bank filtration (RBF) is a drinking water treatment method where surface water flows through the subsurface sand and gravel layers of the bank or bed of a river to extraction wells and contaminants are removed through the processes of filtration, sorption, dilution and biodegradation.

A drinking water utility utilizing RBF with a hydraulic residence time of approximately 10 days observed approximately 30% removal for PFOA, variable removal of some PFASs, and increases in concentration for other PFASs (Appleman et al., 2014). The authors concluded that this variation was possibly due to the variability in the influent concentrations from wastewater effluents impacted the drinking water sources and/or due to breakdown of precursor compounds through the river bank. Dickenson and Higgins (2013) concluded that RBF was not likely to result in significant removal of PFASs.

7.1.8 Emerging technologies

Other potential treatment technologies for removal of PFOA and PFOS have promise, but are still being researched actively. They have not yet all been evaluated on drinking waters by laboratory, pilot, or full-scale studies, but have been mentioned in reviews of bench scale studies of some PFASs removal from drinking water and wastewater (Vecitis et al., 2009; Eschauzier et al., 2012).

7.1.8.1 Nanomaterials and nanotechnologies

Nanomaterials are being developed for drinking water treatment applications, including ion exchange, sorption and oxidation processes, and abiotic reduction (e.g., nanozerovalent iron) (Boyd et al., 2013). Different nanomaterials/nanotechnologies show promise for removal of PFOS including carbon nanotubes (CNTs), chitosan-based molecularly imprinted polymers (MIPs), electrospun nanofibrous membranes (ENFMs), and titanium dioxide (TiO_2) assisted photocatalysis (Yu et al., 2008; Deng et al., 2012; Dai et al., 2013). CNTs are carbon molecules composed of carbon lattices that can take the form of tubes. Chitosan is a natural polysaccharide based on the shells of crustaceans. It may be prepared as a nanoparticle or electrospun in nanofibers (Sonia and Sharma, 2011; Zhao et al., 2011a; Boyd et al., 2013). Molecular imprinting is a technique where specific sites for target compounds are constructed on a polymer so that specific adsorbates are recognized in the sorption process. ENFMs are prepared by electrospinning nanofibers of polymer or polymer composite materials to create membranes of non-woven fibers with diameters ranging from several hundreds to tens of nanometers (Greiner and Wendorff, 2007; Dai et al., 2013; Boyd et al., 2013).

Deng et al. (2012) have demonstrated the effectiveness of CNTs for removal of perfluorinated contaminants, including PFOA and PFOS, from aquatic environments when the hydrophobic interactions were involved in the sorption of perfluorinated contaminants onto the CNTs. The sorption of the perfluorinated contaminants was increased with increasing carbon-fluorine chain length with the same functional group.

7.1.8.2 Photolysis and photochemical degradation

Although a full-scale UV treatment process was reported ineffective in removal of PFOA in drinking water, several laboratory-scale evaluations of synthetic waters, wastewaters and industrial waters have reported that UV-visible light, UV in the presence of persulfate, UV in the presence of TiO_2 and perchlorate, UV in the presence of iodide and UV irradiation using carbonate radical ions may degrade PFOA concentrations (Hori et al., 2004a, 2005; Chen and

Zhang, 2006; Chen et al., 2007; Fujii et al., 2007; Giri et al., 2011, 2012, 2013; Dillert et al., 2007; Panchangam et al., 2009; Qu et al., 2010).

A laboratory-study reported 87% degradation and defluorination of an initial PFOA concentration of 25 mg/L under 185 nm UV light irradiation in the presence of persulfate. When compared to direct photolysis the photochemical reaction enhanced PFOA degradation. The study observed a formation of short-chain PFCAs (Chen and Zhang, 2006). Another laboratory-study reported on the effectiveness of sulfate radical anion ($SO_4^{\cdot-}$) to decomposed PFOA in a photochemical reaction. The authors reported that PFOA concentration of 1.35mmol was completely decomposed by the photochemical system using $SO_4^{\cdot-}$ and 4 hours of UV visible light irradiation. The study also reported on the formation of shorter-chain PFCAs in a stepwise manner (Hori et al., 2005). After UV-visible light irradiation was applied under 0.48 MPa of oxygen, 89.5% of an initial PFOA concentration of 1.35 mmol was decomposed and the formation of CO_2, F^- and short-chain PFCAs was observed. The authors also reported that heteropolyacids due to their high stability are attractive photocatalysts in the degradation reactions of PFCAs. In the presence of heteropolyacid, 7.44 µmol PFOA in aqueous solution were completely degraded after 24 hours of UV irradiation. The photocatalyst enhanced the PFOA degradation and suppressed the formation of the short-chain PFCAs (Hori et al., 2004a). Tang et al. (2012) studied the effectiveness of the UV–Fenton technique for PFOA removal in water and found almost complete degradation and defluorination of PFOA within several hours, while PFOA was hardly degraded by a conventional Fenton system alone.

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to municipally treated water. In cases where an individual household obtains its drinking water from a private well, a private residential drinking water treatment device may be an option for reducing PFOA concentrations in drinking water.

Although there are no certified residential treatment devices for the reduction of PFOA from drinking water, available data suggests that residential activated carbon and reverse osmosis can achieve treated PFOA concentrations of 0.2 µg/L and below 0.05 µg/L, respectively. In addition, treatment devices using anion exchange may be effective for the reduction of PFOA.

The Minnesota Department of Health (MDH, 2008b) completed a study of the effectiveness of point-of-use (POU) water treatment devices for PFOA, PFOS and PFBA removal and demonstrated that RO and activated carbon filters were capable of reducing PFOA concentrations typically found in drinking water. Laboratory screening tests and field evaluation of devices installed in municipal water systems were undertaken. In the laboratory tests, the challenge waters had a PFOA concentration of 3.0 µg/L and the target goals for performance was 0.2 µg/L. The field testing involved monitoring and sampling of four activated carbon and seven RO point-of-use devices installed at two municipal wells. One of the wells had concentrations of 0.6 µg/L PFOA, 0.9 µg/L PFOS, and 1.4 µg/L PFBA, while only PFBA was present (1.5 µg/L) at the second well. All RO devices were equipped with an activated carbon pre-filter (before the RO membrane) and a post-treatment (after the RO membrane) activated carbon polishing filter. Results indicated that all activated carbon and RO devices were effective in removing PFOA to below the quantification limit of 0.2 µg/L and below the detection limit of 0.05 µg/L, respectively. Based on these results, activated carbon and RO are expected to be effective at reducing the level of PFOA in drinking water to levels below the ~~proposed~~ MAC of 0.2 µg/L.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National

Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2015):

- CSA Group (www.csagroup.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- UL LLC (www.ul.com);
- Bureau de normalisation du Québec (www.bnq.qc.ca); and
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

Activated carbon filtration systems may be installed at the faucet (POU) or at the location where water enters the home [point-of-entry (POE)]. RO systems are intended for POU installation, as larger quantities of influent (incoming) water are needed to obtain the required volume of treated water, which is generally not practical for residential-scale point-of-entry systems. RO systems should only be installed at POU as the water they have treated may be corrosive to internal plumbing components. A consumer may need to pre-treat the influent water to reduce fouling and extend the service life of the membrane.

Ion exchange treatment technology using anion exchange resins may also be a feasible for PFOA removal in residential scale applications. Ion exchange treatment devices is typically designed and constructed for residential use by drinking water treatment system providers or dealer. ~~Health Canada strongly recommends that homeowners ensure that these systems are constructed using materials certified to NSF/ANSI Standard 61 (NSF/ANSI, 2014).~~ If an ion exchange system is used, the water may need to be filtered through a GAC filter to remove any chlorine or chloramine (if connected to a treated water supply) from the water before it reaches the resin.

Health Canada strongly recommends that chemicals used in treatment systems be certified to NSF/ANSI Standard 60 – Drinking Water Treatment Chemicals Health Effects (NSF/ANSI, 2015a) and that materials and components be certified to NSF/ANSI Standard 61 – Drinking Water System Components Health Effects (NSF/ANSI, 2016a) and NSF/ANSI Standard 372 – Drinking Water System Components Lead Content (NSF/ANSI, 2016b). These standards ensure that these materials meet health-based leaching and lead content requirements and are safe for use in potable water applications. Activated carbon filters are covered in NSF/ANSI Standard 53: Drinking Water Treatment Units-Health Effect (NSF/ANSI, 2015b) and reverse osmosis systems are covered in NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems (NSF/ANSI, 2015c).

Before a treatment device is installed, the water should be tested to determine general water chemistry and verify the presence and concentration of PFOA. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Devices can lose removal capacity through use and time and need to be maintained and/or replaced.

8.0 Kinetics and metabolism

PFOA is considered chemically unreactive, and it is not metabolized. The oral absorption of PFOA is rapid and complete (Kemper, 2003; Hundley et al., 2006; Lau et al., 2007). Once absorbed, PFOA is primarily restricted to plasma and extracellular fluid (Butenhoff et al., 2004a; Han et al., 2012) and excreted in urine.

8.1 Absorption

PFOA is rapidly and nearly completely absorbed in the GI tract. In rats, studies consistently estimated the oral absorption rates of PFOA at >93% after a single dose (0.1 to 25 mg/kg bw) by gavage (Johnson and Ober, 1979, 1999; Kemper, 2003; Cui et al., 2010). Hundley et al. (2006) derived similar absorption rates for mice, rats, hamsters and rabbits after a single oral bolus of PFOA at 10 mg/kg bw. The estimated absorbed fractions were generally higher in males (rats: 89%, mice: 82%, hamsters: 92%) than in females (rats: 76%, mice: 61%, hamsters: 75%) except for rabbits (88% in both sexes). Fasted rats exhibited PFOA plasma concentrations approximately 2–3 times higher after a single oral bolus at 10 mg/kg bw (Hinderliter et al., 2006).

No controlled study data regarding the oral absorption of PFOA in humans are available; however, studies of residents living in areas with contaminated drinking water (Emmett et al., 2006a; Wilhelm et al., 2008) provide evidence of elevated serum PFOA concentrations. Emmett et al. (2006a) correlated the number of glasses of tap water ingested per day with blood concentrations, indicating this was the primary exposure route for populations with elevated PFOA concentrations in drinking water.

Limited inhalation or dermal studies have reported PFOA kinetics; however, the physicochemical properties of the compound suggest that these routes of exposure are not important when PFOA is found in drinking water (see Section 5.7).

8.2 Distribution

PFOA is mainly present in serum/plasma (Johnson and Ober, 1999; Kudo et al., 2007). The volume of distribution, which is similar across species (approximately 170 mL/kg bw), suggests extracellular distribution (Butenhoff et al., 2004a; Han et al. 2012). PFOA is tightly bound to serum protein, which plays an important role in distribution in blood and to tissues (Han et al., 2005). Binding in blood is primarily to serum albumin, with >90% of PFOA in serum expected to be bound to albumin in rats and humans (Han et al., 2003). To a lesser extent, PFOA can also bind to plasma γ-globulin, α-globulin, α-2-macroglobulin, transferrin and β-lipoproteins (Kerstner-Wood et al., 2003; Butenhoff et al., 2012a). Protein binding also occurs in organs and tissues. Luebker and coworkers (2002) reported *in vitro* binding of PFOA to rat liver fatty acid binding protein (L-FABP). PFOA has also been shown to bind to rat kidney and urine α2μ-globulin; however, dissociation constants were low compared to other ligands known to induce hyaline droplet nephropathy (Han et al., 2004). Linear PFOA isoform preparations bound more tightly to human serum albumin compared to branched isoforms, although the binding affinities were similar to one another (within one order of magnitude) (Beesoon and Martin, 2015).

PFOA kinetics are non-linear at high doses, which is hypothesized to be due to the saturation of organic ion transporters (OATs) responsible for renal reabsorption at high doses; (e.g., 20 mg/kg bw per day administered in capsules), resulting in a higher excretion rate at high doses than at low doses (e.g., 0.1 mg/kg bw per day) (Andersen et al., 2006). Serum levels did not increase proportionally with increasing dose, except at lower doses in some studies and steady-state was reached more rapidly than expected at high doses with classical kinetics (4–5 half-lives).

However, at lower gavage doses closer to those relevant to human environmental exposures, kinetics are consistent with linear first order processes, and serum levels are proportional to administered dose (Loveless et al., 2006; Lou et al., 2009). This non-linearity can affect PFOA distribution; for example, after a single intravenous dose in male rats, a lower proportion of the dose was distributed to the liver (27%) at 17 mg/kg bw compared to 52% at 0.4 mg/kg bw (Kudo et al., 2007).

Few data have been gathered on the human tissues to which PFOA is typically distributed. However, the tissue distribution is well documented in experimental animals, including monkeys, rats, and mice. In monkeys, PFOA distribution to the liver has been documented following administration of oral capsules containing PFOA (Butenhoff et al., 2002; 2004a). PFOA levels in other organs were not investigated. In orally exposed rats, PFOA has been detected most frequently and at the highest levels in the liver (Ylinen et al., 1990; Kemper, 2003; Martin et al., 2007). Additional primary tissues of distribution include the testes, spleen, lung, kidney, brain, skin, muscle, bone gastrointestinal tract and adipose tissue (Ylinen et al., 1990; Kemper, 2003). In orally exposed mice, PFOA has been detected in the liver, kidney, and bile (Lou et al., 2009; Minata et al., 2010).

In humans, PFOA was detected in approximately one half of the analyzed liver samples (in 6 males and 6 females from Catalonia, Spain; aged 27–79 years), and was significantly higher in males than in females (Kärrman et al., 2010), but was below the limits of quantification in livers in cadavers with environmental exposure (Olsen et al., 2003a). Neither cerebrospinal fluid (Harada et al., 2007) nor thyroid (Pirali et al., 2009) have been observed to be relevant partitioning sites for PFOA.

In rats, PFOA concentrations were consistently higher in males than in females after single or repeated exposures (Ylinen et al., 1990; Kemper, 2003). The differences have been attributed to more rapid elimination of PFOA in females than males. In mice and non-human primates, there do not appear to be sex differences in PFOA concentrations (Griffith and Long, 1980; Butenhoff et al., 2004a; Lou et al., 2009). Lou et al. (2009) reported similar serum, liver and kidney PFOA concentration time-courses in male and female CD-1 mice after a single oral gavage of 1 or 10 mg/kg bw; however, the 95% confidence intervals on the mean half-lives do not overlap, indicative of possible sex differences in mice. Sex differences in PFOA concentrations have also been noted in human biomonitoring studies (see Section 5.6). As previously described in Section 5.6, serum PFOA levels in humans appeared to be influenced by age and gender in CHMS. The effect was also observed in U.S. studies, such as the National Health and Nutrition Examination Survey (NHANES) 1999–2008 (Kato et al., 2011) and other reference populations (Harada et al., 2004; Hölzer et al., 2008; Ingelido et al. 2010). As age increases, PFOA concentration has been shown to decrease in males and increase in females (Kato et al. 2011). Plausible explanations are menstrual bleeding, especially in nulliparous women (Ingelido et al., 2010), pregnancy and lactation. Supporting this hypothesis is the observation of higher serum PFOA levels in primiparous women than multiparous women (Kim et al., 2011), as well as the significant decrease in serum PFOA levels with duration of lactation (2–7 weeks vs. 3–4 months after delivery) (von Ehrenstein, 2009; Monroy et al., 2008).

PFOA exposure can occur transplacentally and lactationally. Fetal transfer via the placenta has been demonstrated in rats (Hinderliter et al., 2005) and mice (Fenton et al., 2009). In humans, concentrations of PFOA in cord blood of newborns are similar to maternal blood concentrations (Tittlemier et al., 2004; Midasch et al., 2007; Monroy et al., 2008; Beesoon et al., 2011; Needham et al., 2011; Gützkow et al., 2012). Moreover, serum concentrations in young children have been noted to be higher than serum concentrations in their mothers in a reference (i.e., not PFOA-contaminated) area (Hölzer et al., 2008) and in an area with elevated environmental PFOA

levels (Mondal et al., 2012); however, serum concentrations were similar between children and mothers in an area with elevated PFOA levels in drinking water (Hölzer et al., 2008). Lactational transfer of PFOA has been measured in various mammal species, including humans, rats, mice, and sheep (Hinderliter et al., 2005; Fenton et al., 2009; Kim et al., 2011; Needham et al., 2011). Concentrations of PFOA in milk are consistently lower than in maternal plasma (Hinderliter et al., 2005; Fenton et al., 2009~~); in~~; Liu et al., 2011); Milk PFOA levels were approximately 10% and 25% of maternal plasma levels in rats and mice, respectively. In humans, a review of milk and maternal serum concentrations found the maternal milk:serum ratios across several studies to be approximately 0.11–0.12 (Liu et al., 2011). PFOA levels in human milk decrease significantly throughout the lactation period (Thomsen et al., 2010), and with increasing number of infants breastfed (Tao et al., 2008; Kadar et al., 2011). In a community with PFOA-contaminated water, infants breastfed for ≥ 12 months had significantly higher serum PFOA concentrations than infants who were not breastfed (Mondal et al., 2014); however, the authors noted that the estimates may be imprecise as they are based on only 8 infants in the long-duration group. Similarly, a study of Faroese infants with serum PFOA data at birth and at 11, 18, and 60 months estimated an increase in serum PFOA concentrations of about 28% per month during the period of exclusive breastfeeding and of about 4% per month during periods of partial breastfeeding (Mogensen et al., 2015a). In this study, serum PFOA levels measured up to five years of age did not decline to serum PFOA levels at birth, which the authors attributed to ongoing dietary exposure to PFOA (in particular through traditional intake of pilot whale meat).

8.3 Metabolism

The available data indicate that PFOA is not metabolized. Studies conducted in rodents and non-human primates did not reveal quantitatively significant metabolism of PFOA, and PFOA was not metabolized when incubated with microsomal fractions of human or rat intestine, kidney or liver homogenates (Kemper and Nabb, 2005; EFSA, 2008; ATSDR, 2009).

8.4 Excretion

Remarkable species-dependent differences in elimination half-life have been observed, with PFOA remaining in human bodies for a much longer duration than other species, including non-human primates, rats and mice (Post et al., 2012). Elimination half-lives from serum in humans are significantly longer than in non-human primates and rats. Species- and sex-related differences are primarily attributed to elimination kinetics where, at higher doses, the kinetics of PFOA in rodents and primates do not follow one-compartment or simple first-order models (Andersen et al., 2006). Half-life values for serum elimination of PFOA in humans were derived from data obtained in retired workers from a 3M Company factory in Alabama, U.S.A (arithmetic mean of PFOA serum half-life = 3.8 years; range = 1.5–9.1 years; 95% CI = 3.1–4.4 years; Olsen et al., 2007) and current workers in a fluorochemical plant in China (geometric mean of PFOA serum half-life = 4.1 years; range = 0.44–3663 years; no 95% CI reported; Fu et al., 2016). In populations exposed environmentally through the consumption of PFOA-contaminated drinking water, half-life values could be estimated using measured declines in serum or plasma PFOA levels after exposures ceased due to filtration of drinking water. The geometric average half-life in Germany was reported as 3.26 years (range = 1.03–14.67; no 95% CI reported; Brede et al., 2010), and the average value for Mid-Ohio Valley was 2.3 years (95% CI = 2.1–2.4 years; no range provided; Bartell et al., 2010). An additional cross-sectional study in the Mid-Ohio Valley (with estimated, rather than measured, initial serum concentrations) identified average half-life values of 2.9–10.1 years (with values varying depending on the average serum concentrations in the community and duration since cessation of exposure) (Seals et al., 2011). The arithmetic mean

of the elimination half-life was estimated as 2.1 years (95% CI = 1.8–2.4 years; range = 0.19–5.2 years) in young females and 2.6 years (95% CI = 2.2–3.0 years; range = 0.06–14 years) in males and older females in healthy adult volunteers in China (Zhang et al., 2013). In a study of Faroese children followed from birth to 5 years, the biological half-life of the serum-PFOA concentration was estimated as 4.2 years (Mogensen et al., 2015a). The authors cautioned against drawing conclusions regarding differences in elimination kinetics between children and adults based on this data because the cohort is not representative of the general population and the half-lives were calculated assuming negligible subsequent exposures following peak exposure levels. The half-life of PFOA in animals varies depending on experimental protocols, but is on the order of days to weeks in rodents and monkeys (see Table 1).

Table 1: Serum half-life estimates in humans and experimental animals

Species	Dosing regime	Mean half-life (days)	Reference
Rat	Single oral dose of 0.1 mg/kg bw; followed for 22 days (M) or 5 days (F)	8.41 ± 1.56[a] (M) 0.13 ± 0.04[a] (F)	Kemper, 2003
	Single oral dose of 0.1 mg/kg bw; followed until PFOA < quantitation limits	11.55 ± 2.36[a] (M) 0.14 ± 0.05[a] (F)	
	Single oral dose of 1 mg/kg bw; followed for 22 days (M) or 5 days (F)	5.76 ± 1.33[a] (M) 0.14 ± 0.05[a] (F)	
	Single oral dose of 5 mg/kg bw; followed for 22 days (M) or 5 days (F)	7.26 ± 1.21[a] (M) 0.19 ± 0.03[a] (F)	
	Single oral dose of 25 mg/kg bw; followed for 22 days (M) or 5 days (F)	6.56 ± 1.60[a] (M) 0.68 ± 0.41[a] (F)	
	Single i.v. dose of 1 mg/kg bw; followed for 22 days (M) or 5 days (F)	7.73 ± 0.815[a] (M) 0.12 ± 0.02[a] (F)	
Mouse	Single oral dose of 1 or 10 mg/kg bw; followed for up to 80 days	21.7 (19.5–24.1)[b] (M) 15.6 (14.7–16.5)[b] (F)	Lou et al., 2009
Monkey	Single i.v. dose of 10 mg/kg bw; followed for 123 days	20.9 ± 12.5 (M) 32.6 ± 8 (F)	Butenhoff et al., 2004b
	Daily oral dose of 10 mg/kg bw for 6 months; followed for up to 147 days post-dosing	19.5[c] (M)	
	Daily oral dose of 20 mg/kg bw for 6 months; followed for up to 147 days post-dosing	20.8[c] (M)	
Human	26 former workers with an average of 31 years of work and 2.6 years retired; external exposure data not provided	1387 (1132–1606)[b]	Olsen et al., 2007
	138 adults and children, 2 years after reduction of PFOA concentrations in drinking water; doses not provided (Arnsberg, Germany)	1190[c]	Brede et al., 2010
	200 adults, ~1–2 years after reduction of PFOA concentrations in drinking water; doses not provided (Mid-Ohio Valley)	840 (767–876)[b]	Bartell et al., 2010
	86 adults; external exposure data not provided	767 (657-876)[b] (F) 949 (803-1095)[b] (M &	Zhang et al., 2013

Species	Dosing regime	Mean half-life (days)	Reference
		F)	
	81 children; prenatal exposure assessed from mother's serum-PFOA at pregnancy week 32; external exposure data not provided	1533[c] (M & F)	Mogensen et al., 2015a
	302 workers before and after PFOS was restricted in 2009; years of service not reported; external exposure data not provided	1497[d] (M & F) 1716[d] (M) 1132[d] (F)	Fu et al., 2016

[a] ± Standard deviation
[b] 95% confidence interval
[c] No standard deviation or confidence interval was provided by authors
[d] Geometric mean since authors did not provide arithmetic mean

Urinary excretion is the major route of elimination in rats (particularly females, which have much greater urinary elimination rates than males) (Vanden Heuvel et al., 1991; Kudo et al., 2001) and monkeys (Butenhoff et al., 2002, 2004a). The urinary excretion process involves glomerular filtration, secretion into the tubular fluid, and reabsorption from tubular fluid. Glomerular filtration of PFOA is limited by extensive binding of PFOA to plasma proteins. Renal reabsorption of PFOA is thought to be driven by OAT proteins residing on membranes of proximal tubular cells (Yang et al., 2010; Han et al., 2012), and contribute to rat sex-related differences in renal clearance (Yang et al., 2009a). Unlike the rat, no gender differences in PFOA urinary elimination are apparent in the mouse (ATSDR 2009) or monkey (Butenhoff et al., 2004a). A dose-dependent (non-linear) upward trend for urinary excretion of PFOA was observed in male rats after dosing with capsules containing PFOA (Butenhoff et al., 2004b). Consistent with observations in animals given low doses, the relationship between external dose and internal dose (serum level) is linear in humans with environmental exposures to PFOA (Clewell, 2009); however, non-linear kinetics—as seen in animals at higher doses—might occur at higher human exposures. The relevance of urinary clearance in humans has been questioned, as renal clearance of PFOA was substantially lower than in animals (Harada et al., 2005). It is important to note that the non-linear toxicokinetics of PFOA have only been investigated in experimental animals following bolus oral exposures to PFOA, therefore, it is not clear if non-linear toxicokinetics are applicable to other modes of administration.

Biliary and fecal excretion also contributes to the elimination of PFOA, which may be subject to extensive enterohepatic recirculation (Vanden Heuvel et al., 1991; Kudo et al., 2001; Harada et al., 2007; Kudo et al., 2007). The relative importance of fecal excretion of PFOA depends on the urinary clearance. Fecal excretion is less important than urinary excretion in rats (Harada et al., 2007) and monkeys (Butenhoff et al., 2004a); however, data in rats indicate that the proportion of excretion occurring from this route becomes greater as doses and exposure durations increase (Cui et al., 2010). The relevance of this excretion route in humans is unclear. Harada et al. (2007) reported that the biliary excretion rate in four humans was significantly higher than serum clearance via urine and concluded that biliary excretion may represent a major excretion route in human; however, these data are not consistent with a case history that reported detection of PFOA in urine but not feces in a man with elevated serum PFOA levels (Genius et al., 2010).

In females, lactation can be a significant route of excretion, as shown in mice (Abbott et al. 2007) and in women (von Ehrenstein, 2009; Kim et al., 2011~~)~~.; Mondal et al., 2014; Mogensen et al., 2015a). Menstrual bleeding may be a significant route of excretion for women (Harada and Koizumi, 2009) and could potentially contribute to differences in serum levels measured between genders in humans.

8.5 Physiologically-based pharmacokinetic (PBPK) models

Several models with varying complexities have been developed to describe the kinetics of PFOA in both experimental animals and humans (Andersen et al., 2006; Tan et al., 2008; Loccisano et al., 2011, 2012a, 2012b, 2013). Due to the non-linear nature of PFOA pharmacokinetics, where faster clearance is seen with high bolus oral dosing, physiological models can provide an improved means of assessing cross-route and cross-species dosimetry for risk assessment.

The first model developed for PFOA was a biologically-motivated compartmental pharmacokinetic (PK) model for monkeys, which included saturable renal resorption of filtered PFOA (Andersen et al., 2006). Subsequent work to refine the model included the addition of a liver compartment and of time-dependent functions for protein binding and volume of distribution to fit high-dose monkey and rat oral and intravenous plasma, urine and feces kinetic data (Tan et al. 2008). PFOA PBPK models for adult rats (Loccisano et al., 2012a), monkeys (Loccisano et al., 2011) and humans (Loccisano et al., 2011) built upon the compartmental models. Further models for lactation and pregnancy were developed for rats (Loccisano et al., 2012b) and humans (Loccisano et al., 2013). No models have been developed for mice, and no pregnancy and lactation models have been developed for monkeys. The basic structure of the PBPK model was the same for all three species, with only time-dependent changes in physiology included to describe pregnancy and lactation along with the time-dependency for plasma and tissue binding. The models included tissue compartments for gut (for oral/dietary dosing), skin (human and monkey model only; for dermal dosing), liver, fat, and kidney, with remaining body tissues grouped together (and not divided into richly and poorly perfused compartments). Biliary excretion and fecal elimination of the unabsorbed bolus oral dose or dietary exposure was added to the rat model; moreover, the rat version did not include a fat compartment (which became lumped with the rest of the body) or physiological gut, which was described as a one compartment non-physiological compartment. The PBPK model assumes only the free plasma fraction of PFOA is available for uptake into tissue, excretion or resorption. Elimination from plasma is described as glomerular filtration of the free fraction into a filtrate compartment. The filtered PFOA can either be eliminated in urine or resorbed into the kidney where it can return to systemic circulation. The models were relatively good at reproducing controlled dosing data for rats (dietary, oral gavage, and IV routes of exposure; Loccisano et al., 2012a), and monkeys (IV and oral gavage routes of exposure; Loccisano et al., 2011). Although no controlled dosing data were available for humans, biomonitoring data (for typically only a single timepoint) were within similar ranges as model simulations (using measured water concentrations for the biomonitored populations, along with assumptions on ingestion patterns; Loccisano et al., 2011).

The Loccisano models for humans (2011), monkeys (2011) and rats (2012a) were considered for use in the current assessment (see Section 10~~); moreover~~). Additionally, a mouse model (~~that~~ was scaled from the rat model was used, but ~~that~~it could not be validated~~) was used~~. Further specifics of the models used for this assessment, including the values used for each of the physiological and chemical-specific parameters, are described in Campbell and Clewell (2013). Exposure was described as a constant intake of PFOA in humans (ingesting 1.5 L of water per day) and the model was allowed to reach steady state conditions prior to determining the

predicted drinking water concentration consistent with the internal dose metric. To be conservative, the longest regularly reported half-life (3.8 years) was used, as this would result in the lowest predicted water concentration. The human was simulated as a 70 kg adult.

The Andersen et al. (2006) pharmacokinetic model was modified by Wambaugh and colleagues (2013) by adding a gut compartment for oral absorption and specifying an upper limit on tissue distribution. The authors used the model to translate dose regimes and available LOEL, NOEL, and benchmark dose (BMD) values from 9 *in vivo* studies of PFOA into internal dose metrics (area under the curve, average, and maximum serum concentrations). The data were modelled for cynomolgus monkeys, male and female Sprague-Dawley rats, and CD-1 and C57Bl/6 mice. A Bayesian approach was employed to model ranges of various physiological parameters. Wambaugh et al. (2013) identified relatively good concordance between predicted and measured (at study termination) serum concentrations, with few outliers, and identified that mean and maximum serum concentrations were most consistent among the various adverse endpoints. Dose metrics for points-of-departure (PODs) tended to be similar, indicating consistency between species and adverse outcomes. However, this model could not be fully validated based on existing human pharmacokinetic data.

Dermal and inhalation routes from contact with drinking water were not included in as potential routes of exposure in this effort, as their contribution to exposure is considered to be negligible (see Section 5.7).

8.6 Animal-to-human extrapolation

Although animal-to-human extrapolations are typically discussed after the selection of potential PODs, consideration has been given to this extrapolation earlier in the PFOA assessment, as the large variability between species can affect POD selection. The large differences in PFOA clearance between humans and other species must be accounted for when using animal studies as a basis for human risk assessments. The application of default approaches for animal-to-human extrapolation—such as the use of an interspecies uncertainty factor of 10 or allometric scaling—might not be sufficiently protective of humans, who receive longer internal exposures to target tissues. For this reason, chemical-specific approaches that can account for pharmacokinetic differences between species and nonlinear behavior of PFOA were considered for the risk assessment. These approaches include the application of chemical-specific adjustment factors (CSAFs) and PBPK modelling. A discussion and application of each of these approaches is outlined below, and further details can be found in a report prepared for Health Canada by Summit Toxicology (2015).

8.6.1 Derivation of CSAFs

A major advantage of the application of CSAFs over default uncertainty or allometric scaling factors is that the approach incorporates both species- and chemical-specific data. Despite this strength, the approach relies on single values representative of pharmacokinetics in each species, and does not necessarily account for non-linear pharmacokinetics.

IPCS guidelines on calculating CSAFs (IPCS, 2005) were applied to derive the toxicokinetic portion of the interspecies uncertainty factor (AK_{UF}). IPCS recommends that the default interspecies uncertainty factor of 10 be divided into values of 4.0 ($10^{0.6}$) for the toxicokinetic portion (AK_{UF}) and 2.5 ($10^{0.4}$) for the toxicodynamic component (AD_{UF}). The default AK_{UF} of 4.0 becomes replaced with any AK_{UF} values calculated based on chemical-specific data (IPCS, 2005). As data were not available to quantitatively evaluate toxicodynamic differences between species, no AD_{UF} was calculated.

To calculate the AK_{UF} (i.e., reflecting interspecies toxicokinetic differences), the following equation was used:

$$AK_{UF} = \frac{CL_{animal}}{CL_{human}}$$

where:

- AK_{UF} is the toxicokinetic component of the interspecies uncertainty factor; and
- CL is clearance in animals and humans (e.g., mL/kg bw per day).

In rats, a single oral dose of 0.1 mg/kg bw per day was provided to Sprague-Dawley rats (4/sex), who were followed for 22 days (males) or 5 days (females) (Kemper et al., 2003). Increased clearance and decreased half-life in female vs. male rats has been repeatedly demonstrated (see Section 5); females appear to have increased urinary excretion of PFOA over males, but the reason for this phenomenon is not clear. For this reason, AK_{UF} values are presented separately for each sex. Clearance rates for male and female rats were 23.1, and 777, respectively.

Clearance was not reported directly for monkeys, mice, or humans, and must be calculated based on species-specific half-life values using the following equation:

$$CL = \frac{Ln\ 2 \times V_d}{T_{½}}$$

where:

- CL is clearance in animals and humans (L/kg bw per day);
- ln 2 is the natural log of 2;
- V_d is the volume of distribution, which is the theoretical volume of blood in which the amount of a chemical would need to be uniformly distributed to produce the observed blood concentration; and
- $T_{½}$ is the half-life of a compound.

A half-life of 20.15 days was obtained from cynomolgus monkeys, which was averaged from monkeys provided a daily oral dose of 10 and 20 mg/kg bw for 6 months and followed for up to 147 days post-dosing (Butenhoff et al., 2004a). No volume of distribution was presented for monkeys in the chronic exposure study, but an average value of 190 mL/kg ~~was~~wbw as obtained from the single dose study that was presented in the same publication (Butenhoff et al., 2004a). Half-life values in mice were obtained from a study that provided a single oral dose of 1 or 10 mg/kg bw per day to CD-1 mice (3/sex/dose) that were followed for up to 80 days (Lou et al., 2009); the average value was 18.7 days. In humans, a half-life of 1387 days (3.8 years) was calculated from decreases in serum concentrations of 26 workers previously occupationally exposed to PFOA, with an average of 31 years of work and 2.6 years retired (Olsen et al., 2007). Despite the availability of half-life values for general populations, the occupationally-derived half-life was selected to be conservative, as it is the longest of half-life values estimated from longitudinal data (see Section 8.4). Volume of distribution values for PFOA are typically relatively consistent among species (Thompson et al., 2010); as no volumes of distribution were provided in the human and mouse studies, a value of 200 mL/kg ~~was~~bw was used to represent a chemical that is mostly distributed extracellularly. Using the above equation, the resulting clearance values were 6.5 mL/kg bw per day in monkeys, 7.4 mL/kg bw per day in mice, and 0.1

mL/kg bw per day in humans. Using the human:animal ratios of clearance values described above, the calculated AK_{UF} values for PFOA for monkeys, mice, and average, male, and female rats were 65, 74, 231, and 7774, respectively.

Clearance was selected as the dose metric for the derivation of AK_{UF} values because data for this metric were readily available in most species, and could be calculated from half-life data in humans. Moreover, the use of clearance as a dose metric is a reasonable assumption for chemicals with long half-lives (i.e., in the order of days to years). Preliminary analyses have suggested that peak concentrations might be more predictive of PFOA toxicity for certain adverse endpoints (Haber et al., 2013); PFOA was not investigated in these analyses. Although this hypothesis was not further explored for the present analysis, using clearance is considered to be a more conservative alternative to using peak concentrations as the dose metric for AK_{UF} derivation. Finally, ratios of clearance levels are considered an appropriate basis for AK_{UF} derivation typically only if first-order kinetics are assumed to apply; however, as urinary clearance of PFOA is complex, this assumption might not be appropriate.

8.6.2 PBPK modelling

A typical approach for PBPK modelling is to use the model to calculate human-relevant PODs, which are derived by applying a human PBPK model to internal dose metrics (e.g., concentrations of PFOA in plasma) that were either calculated or measured in animals. With sufficiently validated models, this approach is considered to be the most robust approach for performing animal-to-human extrapolations. However, there is only medium confidence in human, monkey, and rat models, because different model codes were used for different species, and model fits to some datasets were not optimal. Moreover, the limited understanding of reasons for the observed sex differences in clearance in rats means there are weaknesses in how this could be addressed in the model. Finally, a major drawback in using the standard PBPK modelling approach is that human models have not been fully verified. Human data available for verification are limited to biomonitoring studies that allow for only rough estimates of exposure scenarios, and for which serum concentration measurements were typically only performed once (with a few populations with measurements at two timepoints) (see Section 5.6). Loccisano and colleagues did not develop PBPK models for mice, but Health Canada modelling approaches using mouse studies scaled the rat models using mouse data. As insufficient toxicokinetic data exist to verify whether the mouse model is appropriate, confidence in the mouse model is low. Therefore, there is insufficient confidence to use precise PBPK model results as points-of-departure for the risk assessments.

As an alternative approach to using the PBPK model for POD calculations, ratios of PBPK model-predicted dose metrics were used to calculate AK_{UF} values for relevant doses. This approach is thought to provide more robust estimates of the AK_{UF} than the traditional calculations described in Section 8.6.1, as it can address the non-linear kinetics of PFOA, identifying different values at steady state for different oral dose levels. In contrast, the AK_{UF} values calculated above are dependent on the specific doses and dose regimes used in the pharmacokinetic studies; uncertainties arise in the values obtained from these studies, as the AK_{UF} values are calculated for animals ~~were provided only~~administered single doses, which cannot account for non-linear kinetics, and the human data were not obtained from controlled dosing studies. Furthermore, clearance-based AK_{UF} values are ratios of low doses in humans to high doses in animals, and therefore exposures between the species are not of the same magnitude; using the PBPK model to derive the AK_{UF} allows for a more appropriate comparison of doses of the same magnitude.

The selected dose metric for the PBPK-derived AK_{UF} values was steady-state concentrations of PFOA. Steady-state concentration was selected as it is typically relevant for

chemicals with long half-lives, and is a conservative assumption. Although alternative dose metrics—including peak concentrations (Haber et al., 2013)—might be more predictive of PFOA toxicity for certain adverse endpoints, additional work was not performed to further investigate the most appropriate dose metric. Plasma was selected as the relevant tissue for steady-state concentrations, as it is a metric that can act as a relevant proxy for a wide variety of organs, because blood flows to these different organs. Liver steady state concentrations were also incorporated into the assessment for comparison with plasma-based AK_{UF} values, as the liver has been identified as a primary organ for PFOA distribution in pharmacokinetic studies, and is also a potential target organ for toxicity. However, there is lower confidence in liver-based values than plasma values, as very little pharmacokinetic data exists to be able to perform verification of the PBPK model for liver concentrations. Liver concentrations could not be verified for humans, mice, and monkeys; for rats, minimal verification could be performed, but as data were available for only one to two timepoints in each study, the comparisons are not robust. Moreover, the use of plasma concentrations as a proxy for a variety of organs simplifies the application of AK_{UF} values in the assessment, which is already complex due to the use of AK_{UF} values that are species- and dose-specific.

Using the Loccisano PBPK models described in Section 8.5, steady-state plasma and liver concentrations were obtained at various doses in each of the species. The same doses were used for each of the species. For each dose run in the PBPK model, ratios of steady-state PFOA concentrations in humans vs. other species were calculated to obtain dose- and species-specific AK_{UF} values (Summit Toxicology, 2015). Steady-state concentrations and AK_{UF} values for plasma and liver at potentially relevant doses are listed in Table 2.

To select the appropriate AK_{UF} for each POD, the POD is rounded down to the nearest value in the oral dose column (i.e., values within the same order of magnitude are used). As discussed above, low confidence is placed on the mouse PBPK model. Until a PBPK model has been developed based on mouse data, the use of rat AK_{UF} values for mice is recommended (Summit Toxicology, 2015).

Table 2: PBPK dose metrics and PBPK-derived AK_{UF} values at relevant doses

Metric	Species	Oral dose (mg/kg bw per day)			
		0.001	0.01	0.1	1
Steady-state plasma PFOA predictions (µg/mL)	Human	8.74	86.1	706	1493
	Monkey	0.17	1.61	11.5	38.9
	Mouse	0.05[a]	0.47	4.74	47.4
	Rat	0.09	0.9	8.96	89.5
Steady-state liver PFOA predictions (µg/mL)	Human	19.2	189	1555	3289
	Monkey	0.37	3.58	25.5	88.3
	Mouse	NC	NC	NC	NC
	Rat	0.32	3.16	31.6	316
AK_{UF} derived based on plasma predictions	Monkey	52	53	62	38
	Mouse[b]	184	182	149	31
	Rat	97	96	79	17
AK_{UF} derived based on liver predictions	Monkey	52	53	61	37
	Mouse[b]	NC	NC	NC	NC
	Rat	61	60	49	10

[a]NC = could not be calculated due to limitations in the PBPK model
[b]AK_{UF} values for rats will be applied due to low confidence in the PBPK model

8.6.3 Recommended interspecies extrapolation approach

The recommended approach for interspecies extrapolation is the use of a PBPK model for the calculation of the AK_{UF} component of the CSAF, using steady-state plasma concentrations as the dose metric. The use of plasma concentrations ensures the relevance of the dose metric to adverse effects that occur in a variety of organs. Organ-specific dose metrics are typically preferred over blood-based values, whenever available; however, using the plasma metrics for this assessment provides consistency in the application of the AK_{UF} over a wide variety of adverse endpoints. AK_{UF} values were calculated for liver metrics for comparison with plasma values; the behaviour of PFOA in the liver was similar to that in the plasma, and AK_{UF} estimates were on the same order in both compartments. These results indicate that plasma values are appropriate proxies to be used for adverse hepatic effects. The liver-based values in rats were slightly lower than plasma-based values; however, greater confidence is placed in the plasma values because more data were available to verify this compartment of the PBPK model. The dose- and species-specific AK_{UF} values (for steady-state plasma concentrations) in Table ~~3~~2 are applied in ~~Sections~~sections 10.1 and 10.2.

Although PBPK-derived AK_{UF} values were selected as the recommended approach for this assessment, several weaknesses have been identified. As described above, the AK_{UF} was plasma based rather than being organ specific. Steady state concentrations were also selected as the dose metric, as a conservative assumption relevant to the nature of the compound; detailed work was not performed to identify whether other dose metrics (e.g., peak concentrations) would be more appropriate for the various adverse endpoints. Steady state was also not reached in the human model at doses below 0.1 mg/kg bw per day. Furthermore, PBPK models have not been developed specifically for the mouse, and have been scaled instead from the rat, without further pharmacokinetic data for mice to be used for verification; the application of AK_{UF} values for rats is therefore recommended for use in mice in the absence of robust data in the species. AK_{UF} values for rats ~~are also~~were derived based on male rats~~ only, despite faster~~, which experience slower clearance~~ and therefore greater~~ of PFOA compared to female rats, in order to minimize the interspecies differences~~ observed in females~~.

Despite these weaknesses, using the PBPK model to derive the AK_{UF} was thought to be equally or more robust when compared with other potential interspecies extrapolation approaches. The selected approach quantitatively incorporates pharmacokinetic differences among species; however, non-linear kinetics of PFOA are addressed, which cannot be done using the default AK_{UF}-derivation approach. Moreover, the PBPK-derived AK_{UF} values do not rely on individual pharmacokinetic studies that are often single-dose studies and not easily comparable among species. An ideal approach to address species differences would be to use blood concentrations of PFOA—either by using pharmacokinetic models to estimate the concentrations, as employed by Wambaugh et al. (2013), or using the values specifically measured in individual studies—as PODs for the assessment. However, the human PBPK models that would be used to extrapolate from this serum concentration cannot be fully verified based on existing human pharmacokinetic data, which decreases the level of comfort of using this approach to estimate precise PODs. The recommended approach was selected as a means of quantifying interspecies differences while addressing the non-linear kinetics of PFOA, without relying on precise PBPK-derived estimates of PODs.

9.0 Health effects

The summary of literature on health effects for PFOA is largely based on a comprehensive review conducted by a consultant (Sanexen Environmental Services Inc., 2013), and includes only

the studies of direct relevance to the derivation of the health-based value. More specifically, this summary includes reports, reviews, and original papers published concerning PFOA in order to understand toxicity in humans exposed to PFOA via drinking water.

9.1 Effects in humans

9.1.1 Acute toxicity

No information related to acute or short-term epidemiological studies could be located.

9.1.2 Subchronic and chronic toxicity

Many quality epidemiological studies have been conducted. Large cohorts of workers and environmentally-exposed populations have been followed, with observations of significant relationships between exposure to PFOA and various health endpoints, such as haematological and clinical biomarkers (cholesterol, uric acid, serum liver enzymes), cancer (testicular, kidney), preeclampsia, immunological, endocrine (thyroid), renal functions, and fecundity (semen quality, birth weight) outcomes. Although all of these studies present limitations to some extent, including in terms of study design, bias and confounders, the human weight of evidence provides a strong argument in favor of detrimental health effects of the compound. This information should support the choice of a health endpoint; however, deriving a safe human exposure dose based on studies in humans remains a challenge because of the difficulties in characterizing a dose-response pattern with current studies. Their use in the present assessment is important to verify the relevance of animal to human extrapolation, and the monitoring of future studies will help in determining the accuracy of the observed associations.

Most environmental studies among ~~PFAA~~PFAS-exposed populations were conducted in the Mid-Ohio Valley within the C8 Science Project. The C8 Science Panel was convened as a result of a class action settlement against DuPont, and is composed of independent epidemiologists jointly selected by lawyers for the community and DuPont. The C8 Health Project is the largest study of a population exposed to ~~PFAAs~~PFAS in drinking water, containing residents of Ohio and West Virginia communities surrounding the DuPont Washington Works plant. The health survey was conducted in 2005–2006 on approximately 69,000 individuals, including children and adults. The median PFOA serum concentrations in this population were 28.2 ng/mL, compared to 4.2 ng/mL in the general American population during the same period (Frisbee et al., 2009). Some longitudinal/prospective studies were also conducted among this population after a follow-up period. Some recent data in the project have not yet been published in peer reviewed literature; summaries of these studies—as well as panel conclusions and further information on the members of the panel—are available on the C8 Science Panel website (www.c8sciencepanel.org/panel.html).

9.1.2.1 Liver effects

Some level of association between PFOA exposure and alteration in liver enzymes has been observed, but no clear trend has been defined. A negative association for bilirubin and a positive association for aspartate transaminase (AST) and gamma glutamyl transpeptidase (GGT) have been reported in workers (Sakr et al., 2007a~~; Sakr et al., 2007b)~~., 2007b). ~~Abnormal increases of liver enzymes (ALT and GGT) were reported in a cross-sectional study of adults aged 18 years or older in the general U.S. population, particularly in obese or in subjects with insulin resistance and/or metabolic syndromes (Lin et al., 2010).~~ The clinical significance of results in the occupationally-exposed population is unclear, because the magnitudes of the changes were small and inconsistent (Steenland et al., 2010a). Moreover, the high number of endpoints analyzed also increases the likelihood of chance findings. Abnormal increases of liver

enzymes (ALT and GGT) were reported in a cross-sectional study of adults aged 18 years or older in the general U.S. population, particularly in obese or in subjects with insulin resistance and/or metabolic syndromes (Lin et al., 2010). An association between serum PFOA levels and uric acid, ALT, GGT, and total bilirubin was reported in a cross-sectional survey in the general U.S. population recruited as part of NHANES (Gleason et al., 2015). Causal interpretation of general population results is limited by the study design, and multiple covariates were not included in the analysis.

9.1.2.2 Lipidemia

Increased exposure to PFOA has been associated with increases in serum cholesterol levels in several studies. A recent study including large cohorts of workers and environmentally-exposed residents found an increased risk of hypercholesterolemia with higher PFOA exposure compared to lower exposure (Winquist and Steenland, 2014). A small longitudinal study conducted in workers in Italy showed a positive association between PFOA and total cholesterol (Costa et al., 2009). A cross-sectional study and a longitudinal study were conducted among DuPont production workers. In the cross-sectional study, positive associations between PFOA and total cholesterol, LDL and VDLD were observed (Sakr et al., 2007a). In the longitudinal study, a negative association with bilirubin was observed, whereas positive associations between serum PFOA and total cholesterol were found after adjustment for cofounders (Sakr et al., 2007b).

Inconsistent results were found concerning the association between PFOA and cholesterol and lipoproteins in studies of fluorochemical production workers from U.S. and European 3M plants (Olsen and Zobel, 2007). No association between serum PFOA levels and plasma lipids (measured as triglycerides, HDL, LDL, and total cholesterol) was found as measured in a subsample of Canadians as part of the CHMS (Cycle 1 2007 – 2009) (Fisher et al., 2013). An increase in HDL level, a decreased total cholesterol/HDL ratio and no changes in total cholesterol and non-HDL cholesterol were observed in an occupational study (Olsen et al., 2012). Under the C8 Health Project, associations between serum PFOA and different blood components, such as an increase in cholesterol levels, were found in children and adults (Steenland et al., 2009, Frisbee et al., 2010, Kerger et al., 2011). Associations also occurred for lipoproteins (LDL, HDL), but were inconsistent between studies. A positive association with cholesterol was also found in the general U.S. population (Nelson et al., 2010), while another cross-sectional study conducted in the Mid-Ohio valley found no association (Emmett et al., 2006b). A longitudinal study conducted in 560 adults (2005–2006 with follow-up in 2010) indicated that the level of LDL decreased with the decreased serum PFOA level. A similar (but not statistically significant) pattern was found for total cholesterol; however, there were no changes for HDL or triglycerides (Fitz-Simon et al., 2013).

Overall, cross-sectional and longitudinal study data from the studies reviewed in the preceeding paragraphs indicate some level of association between serum PFOA and total cholesterol and/or LDL observed in different populations, although results were inconsistent in terms of exposure and effects observed. The strength of association was generally higher in the general population than in workers. This discrepancy could be due to the lack of lower range serum PFOA levels in occupationally exposed populations compared to the general population that is exposed to a wider range of PFOA levels (low to high). Considering the weight of evidence, the C8 Science Panel (2012a) concluded that there is a probable link between elevated cholesterolemia and PFOA. The clinical significance is uncertain, given the results inconsistencies, the unknown mechanism of action, the limits inherent to the study design, and the low magnitude of the changes. In particular, the conclusions and associations found from the cohort studies are limited by the risk of selection and misclassification bias, and uncontrolled

variables, as some associations were lost when the participants were stratified by location (Costa et al., 2009; Winquist and Steenland, 2014).

9.1.2.3 Thyroid disruption

Inconsistent effects on thyroid hormone levels were observed in PFOA-exposed populations. An occupational study conducted among 552 employees in three plants found a negative association between PFOA and free thyroxine and a positive association between PFOA and triiodothyronine, after adjusting for confounders (Olsen and Zobel, 2007). However, no adjustment for PFOS was performed, and the authors indicated there were no associations between PFOA and thyroid hormones because the results were inconsistent and within normal values. Moreover, no significant association of PFOA with T3, T4, or TSH was observed in two other occupational studies (Olsen et al., 1998, 2003b). Multiple cross-sectional studies (C8 Health Project and NHANES) have evaluated the relationship between environmental exposure to PFOA and thyroid functions. These studies have reported alterations in the levels of thyroxin, T3 uptake, serum albumin, hypothyroidism in children, thyroid disease in women (Chan et al., 2011; Knox et al., 2011b; Lopez-Espinosa et al., 2012). However, temporality cannot be established with the study design, and it is not possible to know the PFOA serum levels before the development of thyroid disease. A positive correlation between maternal serum PFOA levels and fetal TSH levels (but not T3 or T4 levels) was found after adjustment for covariates in a South Korean study (Kim et al., 2011).

9.1.2.4 Hypertension and cardiovascular outcomes

Cardiovascular outcomes were not consistently found to be associated with PFOA in cohort and cross-sectional studies (Sakr et al., 2007a; Costa et al., 2009; Steenland et al., 2010b). Elevated PFOA exposures were associated with higher cerebrovascular risk in an occupational cohort study (Lundin et al., 2009), and with cardiovascular, peripheral arterial disease, systolic blood pressure, and a marker of inflammation in cross-sectional studies of the general U.S. population (Shankar et al., 2012; Min et al., 2013). These results are equivocal and were not confirmed in other occupational cohort studies (Leonard et al., 2008; Sakr et al., 2009; Steenland and Woskie, 2012), nor in another cross-sectional study in the general population (Melzer et al., 2010). The C8 Science Panel concluded there is not a probable link between exposure to PFOA and diagnosed high blood pressure and coronary artery disease (including myocardial infarction, angina and coronary bypass surgery) (C8 Science Panel, 2012a).

9.1.2.5 Kidney effects

An association between adverse kidney effects and PFOA was observed; however, several factors limit the generalizability of the results to the general population. An increased risk of renal disease was found in a cohort mortality study conducted in 5,791 workers at a DuPont Chemical Plant (Steenland and Woskie, 2012). This level of evidence does not support a causal relationship between reduced kidney function and exposure to PFOA, particularly because altered kidney function could cause an increase in serum PFOA levels. Likewise, if PFOA induces adverse effects on the kidney, elevated PFOA levels may induce alterations of the kidney function. Moreover, only a small number of cases were observed in the occupational study (as attested by the large margin of error), and many workers were lost to follow-up, increasing the risk of selection bias, and was not supported by the results of an unpublished cohort study conducted in the same region (C8 Science Panel, 2012a).

9.1.2.6 Diabetes

The possible association between PFOA and diabetes was studied in mortality studies conducted among workers occupationally exposed to PFOA (Leonard et al., 2008, Lundin et al., 2009, Steenland and Woskie, 2012), and in two environmental studies regarding the prevalence of diabetes conducted within the C8 Health Project (MacNeil et al., 2009, C8 Science Panel, 2012b). The results from the occupational studies of employees of a 3M Company plant in Cottage Grove, MN, and of the DuPont polyfluorimer plant were inconsistent. Considering that diabetes is usually not fatal (and is not necessarily indicated on death certificates) and that mortality may thus not be the best way to study diabetes (C8 Science Panel, 2012b), the findings based on diabetes prevalence within exposed residential populations may be more reliable. The data available from cross-sectional environmental studies conducted within the C8 Health Project (MacNeil et al., 2009~~;~~; C8 Science Panel, 2012b) suggest that there is no link between PFOA and Type II diabetes. Additionally, no association between serum PFOA levels and metabolic function (calculated using fasting glucose and insulin levels) was found in a subsample of Canadians as part of Cycle 1of the CHMS (Fisher et al., 2013).

9.1.2.7 Immune suppression

Studies in environmentally-exposed populations have identified associations between PFOA levels and decreased antibodies against various illnesses, but the influence of PFOA exposure on clinical immunosuppression (i.e., incidence of illnesses) appears to be more tenuous. A study in children found an inverse relationship in immune response with ~~PFAA~~PFAS exposure (Grandjean et al., 2012; Grandjean and Budtz-Jørgensen, 2013), with prenatal PFOA exposure negatively correlated with antidiphtheria antibody concentrations. A two-fold increase in the PFOA concentration in children in this population was associated with increased odds of not reaching antibody protective levels for tetanus and diphtheria after vaccination at 7 years old (Grandjean et al., ~~2012).~~2012; Mogensen et al., 2015b) and 13 years old (Grandjean et al., 2017), although antibody levels had increased at 13 years compared to 7 years of age. The prospective nature, sample size, low risk of selection bias and defined objectives make the results relevant to the studied population; however, relevance to other populations is questionable, as increased exposure to the other potential immunosuppressants occurring in this region (Faroe Islands) was not accounted for in the study. Additionally, a portion of the 13-year old cohort had received booster vaccinations during emergency room visits, which could add variance to the study design (Grandjean et al., 2017). Increased PFOA exposure was also associated with decreased antibodies against rubella (in children from a prospective birth cohort of pregnant women from Norway, 2007–2008) (Granum et al., 2013) and influenza (for A/H3N2 only; in adults living in communities with PFOA-contaminated drinking water) (Looker et al., 2014). A higher risk of not attaining the recognized influenza A/H3N2 threshold was also observed (Looker et al., 2014). Cord blood IgE decreased with maternal PFOA in female infants in a prospective cohort study of pregnant women from 2002 to 2005 in Japan (Okada et al., 2012).

Hospitalizations for infections were not associated with prenatal exposure to PFOA in a Danish Cohort (1996–2002) (Fei et al., 2010a); however, positive associations between maternal PFOA and the incidence of colds and gastroenteritis were observed in the Norwegian birth cohort (Granum et al., 2013).

There is some level of consistency across studies since they generally observed an association between environmental ~~PFAA~~PFAS exposure and immunomodulatory effects in children of different ethnicities. The diversity of the study settings and the prospective nature of the observational study designs lower the risks of spurious associations and enhance generalizability of the results. However, the dataset remains relatively small with only 5 studies,

which were all observational, and the risk of residual confounding, bias and chance cannot be discounted. Although all studies investigated the effects on the immune system, the outcomes were not specific (measured different effects), no clear dose-response was observed, and most associations were weak. Conflicting results were common in the dataset, with variations observed between genders, specific microbial immunoglobulins, ~~PFAAs~~PFASs, infections, mother vs. child exposure, and child years, amongst other characteristics. These flaws impede concluding on a causative mechanism, and the nature of the association remains unclear. Similarly, in a systematic and critical review of the epidemiological evidence on the association between various immune-related health outcomes and exposure to PFOA and PFOS, Chang et al. (2016) concluded that the available epidemiological evidence is insufficient to reach a conclusion about a causal relationship. The authors recommended further work to confirm these suggestive associations, including large, prospective studies with repeated exposure assessment in independent populations. On the other hand, the U.S. National Toxicology Program conducted a systematic review of the literature related to PFOA-induced immunotoxicity and concluded that PFOA is presumed to be an immune hazard to humans based on moderate level of evidence in humans and high level of evidence that PFOA suppressed the antibody response in experimental animals (see Section 9.2.2.3), and after considering biological plausibility (NTP, 2016).

9.1.2.8 Autoimmune disease

The C8 Science Panel (unpublished study) found an increased risk of inflammatory bowel disease with increased cumulative exposure to PFOA, which was driven by associations for ulcerative colitis. The C8 Science Panel concluded that there is a probable link between PFOA and ulcerative colitis (C8 Science Panel, 2012c). However, there is a risk of selection bias because the panel was able to include only a portion of the sample population—participants were only included if their medical charts could be accessed and if exposure estimates could be derived. These results are concerning and should be corroborated in future studies.

9.1.3 Carcinogenicity

Several occupational and environmental cohort studies have been developed for PFOA. The U.S. studies are considered to be the highest quality studies, because they were based on registries covering all residents in the study area, were conducted in districts with large and measured contrasts in PFOA concentrations in water, were linked to cancer registry data, had a large study population and were adjusted for major confounders.

A case-only study that investigated the relationship between cancer and exposure to PFOA through drinking water among Mid-Ohio residents living near the DuPont Teflon-manufacturing plant found that higher PFOA concentrations were associated with testicular and kidney cancers in some of the areas (Vieira et al., 2013). Amongst all cancer endpoints, the odds of testicular cancer were elevated only in one of the two areas with the highest concentration of PFOA in drinking water. There was no statistically significant increase in the odds of testicular cancer in the total exposed, in the other districts, or in any dose level categories (except for the highest dose category). Kidney cancer was increased significantly in one district and in the two highest levels of individual exposure. Associations were not significant for cancers of the breast, prostate, ovarian and non-Hodgkin lymphoma. Although this study shows some cancer associations with PFOA exposure, the meaning of the cancer results remain uncertain because no dose-response was observed, the variability of the risk estimates was high, the number of cases was low, there were multiple endpoints calculated with two modelling approaches (geographical and individual), and risk of exposure misclassification bias (the lack of residential history information to account for duration of exposure, latency, migration, and other issues regarding timing of exposure

relative to cancer). The geographical analysis (testicular cancer findings in the Mid-Ohio study) shares the bias and risk of confounding inherent to ecological studies.

Cumulative exposure to PFOA (retrospective estimates of log serum concentration) was associated with an increased risk of self-reported testicular, kidney, and thyroid cancers in a large cohort (n = 32,254) of C8 Health Project participants and DuPont Teflon-manufacturing plant workers above 20 years old (mean of 53 years old), after adjusting for smoking, alcohol consumption, sex, and education, and stratifying by age (Barry et al., 2013). Some cases were included in both the Barry et al. (2013) and in the Vieira et al. (2013) studies. The associations less likely to have occurred by chance alone (lowest p-values) were the ones between PFOA cumulative log serum concentration and testicular cancer (using the geographical and the water district individual approaches) and kidney cancer (using the residential analysis, individual approach) risks; while the associations with thyroid cancer and melanoma were considered to have occurred by chance based on poor statistical support. However, the associations were inconsistent between exposure quartiles and scenarios (e.g., residential, geographical), after follow-up (with very few, or no reported cases since 2005 regarding testicular cancer while background rates indicated that 5 cases were expected), and lost for testicular, kidney, and thyroid cancer risks, when compared with rates in the general U.S. population. Moreover, the 95% CI of the hazard ratios were large, the trends for testicular, kidney, and thyroid cancer risks were likely to have occurred by chance in at least one exposure scenario, Barry et al. (2013) mentioned the likelihood of exposure and outcome misclassifications, and the trends reported for testicular cancers were based on 6 cases only in the high exposure group (C8 Science Panel, 2012b; Barry et al., 2013).

In another occupational study conducted on workers in Minnesota, increased risk of prostate cancer mortality was observed; however, uncertainty persists because of the low number of cases, leading to poor precision in the risk estimates (Lundin et al., 2009). No statistically significant excess death from kidney, liver, pancreas, testicular, thyroid or breast cancer was found in another occupational study in West Virginia (Leonard et al., 2008) nor in the six-year follow-up of this cohort, except for excess of mortality by kidney cancer (Steenland and Woskie, 2012). Caution in the interpretation of these results is required, because the results were based on a small number of cases, and there was a considerable risk of selection bias.

No increase in the incidence of prostate, bladder, pancreas or liver cancer was found in a prospective cohort study conducted in the general population of Denmark, although the PFOA plasma concentrations [plasma concentration in men with cancer: 6.8 ng/mL (5–95% percentiles: 3.1–14.0); women with cancer: 6.0 ng/mL (5–95% percentiles: 2.6–11.0)] tended to be lower than in the U.S. cohorts [mean of 76.5 ng/mL (SD = 208) in male serum concentration and 42.3 ng/mL (SD = 118) in women, in a community exposed population reported by Frisbee et al. (2009); and, as high as a mean of 2,210 ng/mL (SD = 6.4) in the serum of PFOA manufacture employees, as reported in Olsen and Zobel (2007)] (Eriksen et al., 2009). Also, no evidence of a relationship for PFOA and breast cancer was found in a small-case control study in Greenlandic Inuit (Bonefeld-Jorgensen et al., 2011).

The C8 Science Panel (2012b) provides an assessment of the probable link between PFOA exposure and cancer. The "probable link" defined by the Science Panel means that "given the available scientific evidence, it is more likely than not that among class members a connection exists between PFOA exposure and a particular human disease." Testicular and kidney cancers were the particular types of cancer on which the association was based. However, a causal relationship cannot be determined because there were inconsistencies in the dataset, and the cancer risks were found to be equivocal across studies (lack of coherence). Moreover, the interpretation of the observed increased risk in testicular and kidney cancers is limited by the risk

of residual confounding (because not all covariates and exposures to other contaminants were included in the model), the small case numbers, the uncertainties in exposure characterization (roughly estimated based on residency within a certain area), and the high number of outcomes included in the models, increasing the likelihood of chance findings. Similarly, a systematic and critical review of epidemiological studies on the association between cancer risk in humans and exposure to PFOA and PFOS concluded that the epidemiological evidence does not support a causal association between cancer in humans and exposure to PFOA and PFOS (Chang et al., 2014). Based on these considerations, it would be premature to base a guideline on a cancer risk in epidemiology studies, without a stronger understanding of the potential causality between PFOA and the observed cancers. It is suggested to continue monitoring the epidemiological evidence to understand better the relationship between PFOA and cancer risk.

9.1.4 Developmental and reproductive toxicity

9.1.4.1 Developmental toxicity

Based on data available for gestational age, birth weight and length, head and abdomen or chest circumference, developmental milestones, miscarriage, and birth defects, previous reviews of developmental epidemiology studies concluded that developmental effects are not expected in humans (Olsen et al., 2009). Although increases in the risk of some of these outcomes occurred in individual studies, there was a lack of consistency across studies. Newer environmental studies have shown a positive association between prenatal exposure to PFOA and obesity in female offspring at age of 20 years (Halldorsson et al., 2012), and a negative association between maternal serum PFOA and birth weight and related anthropometric parameters at birth (Apelberg et al., 2007; Fei et al., 2007; 2008b; Andersen et al., 2010; Maisonet et al., 2012; Whitworth et al., 2012a).

The obesogenic properties of PFOA and other ~~PFAAs~~PFAS were investigated in a prospective cohort study with long-term follow-up (20 years) among pregnant women recruited within the Danish National Birth Cohort (1988–1989) and their offspring (Halldorsson et al., 2012). At 20 years of age, the female offspring from mothers with elevated serum concentration of PFOA were more likely to be overweight and to have a high waist circumference, after adjusting for mother's education, BMI, smoking, age, and infant birth weight. This large longitudinal study also showed alteration in serum biomarkers with an increase in maternal PFOA (increase in serum insulin and leptin and decrease in serum adiponectin in female offspring), suggesting biological plausibility. However, important confounders, such as physical activity and diet, were not included in the analysis, which is likely to result in spurious associations. The authors also indicated that loss to follow-up was the main limitation of the study. In a trans-Canada cohort study, no association was found between first-trimester maternal plasma PFOA concentrations and cord blood concentrations of leptin and adiponectin using data on 1705 mother-infant pairs recruited as part of the Maternal Infant Research on Environmental Chemicals (MIREC) Study (Ashley-Martin et al., 2017). However, the study authors cautioned against generalizing these findings to other Canadian populations because on average the study participants were older, more educated, had higher incomes, and were less likely to smoke than other women giving birth in Canada. More studies with better adjustments and follow-up in different populations would be needed to confirm the observed associations.

The data currently available regarding an association between PFOA and reduced birth weight are not consistent. Positive associations were reported among the general population in some studies, whereas no association was reported in other studies in the general population and in communities highly exposed to PFOA through drinking water. Longitudinal studies conducted in Danish and British general populations have found inverse associations between plasma PFOA

levels and birth weight (Fei et al., 2007; Andersen et al., 2010; Maisonet et al., 2012). Similarly, PFOA exposure (measured as maternal PFOA plasma concentration) was inversely associated with birth weight in the MIREC Study (Ashley-Martin et al., 2017). A small unpublished study based on birth certificates for C8 Health Project Community Cohort follow-up participants found some level of association between serum PFOA and term low birth weight; however, results were inconsistent and significance was not provided for all results. These studies represent concerning findings; however, the validity of the results still need to be confirmed, because these studies presented risk of selection bias, recall bias, chance findings, uncontrolled covariates, and absence of dose–response pattern. Moreover, no significant association between serum PFOA levels or PFOA water concentrations and low birth weight was found in cross-sectional studies or highly exposed communities (Nolan et al., 2009; Stein et al., 2009; Savitz et al., 2012a; 2012b). The C8 Science panel concluded that there is no probable link between PFOA and low birth weight (C8 Science Panel, 2011). ~~However~~Similarly, a systematic review of the epidemiology data conducted by Bach et al. (2015) concluded that the existing data are insufficient to confirm or reject an association between PFAS exposure and fetal growth. However, application of a novel systematic review methodology (called the Navigation Guide methodology), to determine whether developmental exposure to PFOA affects fetal growth in humans, concluded that there is sufficient evidence that developmental exposure to PFOA reduces fetal growth (Johnson et al., 2014). Additionally, considering that PFOA was found to be obesogen in mice (Hines et al., 2009) and humans (Halldorsson et al., 2012), and that *in utero* exposure to low doses of obesogens are known to reduce weight at birth (and induce obesity later in life; Holtcamp, 2012), a link between PFOA and low birth weight cannot be ruled out and close monitoring of new studies is recommended.

Investigation of different fetal growth indicators in association with PFOA exposure gave equivocal results. PFOA levels in maternal blood from the Danish National Birth Cohort (1996–2002) demonstrated negative associations with abdominal circumference (with a dose–response relationship) and birth length, after adjustment for multiple relevant cofounders (Fei et al., 2008b). These associations were obtained from large databases, and errors in exposure and outcome measurements and coding is possible. There is also a risk of residual confounding, as stated by the authors. Small negative associations were observed with head circumference, ponderal index and birth weight in a cross-sectional study of the general population (n = 293 singleton births) in Maryland (Apelberg et al., 2007). These must be considered with caution due to the limits inherent to the study design. Also, no associations between maternal serum PFOA levels and birth weight were observed in other general population studies in Canada (Hamm et al., 2010) or Japan (Washino et al., 2009).

There was no conclusive evidence of attention deficit/hyperactivity disorder (ADHD), learning disorder, motor developmental milestones, or behavioral or motor coordination problems based on results of cross-sectional studies conducted within the C8 Health Project and in the general population with exposure to PFOA (Fei et al., 2008a; Hoffman et al., 2010; Fei and Olsen, 2011; Stein and Savitz, 2011).

9.1.4.2 Puberty and sex hormone disruption

Serum PFOA levels were associated with delayed puberty in girls (reduced odds for the 2nd, 3rd, and 4th quartiles vs. the lowest quartile: delay of 142, 163 and 130 days for menarche and delay of 155, 158 or 183 days for combined high estradiol or menarche) in a cross-sectional study within the C8 Health Project (Lopez-Espinosa et al., 2011). Serum PFOA levels were inversely associated with testosterone in boys aged 6–9 years from the same cross-sectional study but were not associated with any sex hormones in girls of the same age group (Lopez-Espinosa et al.,

2016). Further investigations are needed to establish the nature of the relationship, and identify the mechanisms behind these associations. No association was found between PFOA and serum estradiol levels in perimenopausal or menopausal age groups of women (n = 25,957) from the C8 Health Project (Knox et al., 2011a).

9.1.4.3 Reproductive toxicity

No clear pattern of pregnancy-induced hypertension was observed in cohort studies on residents of the Mid-Ohio Valley within the C8 Health project and a cross-sectional study based on Washington County (Savitz et al., 2012b; Nolan et al., 2010; C8 Science Panel, 2011). Conversely, an unpublished prospective study presented by the C8 Science Panel (2011) addressed pregnancies among participants enrolled in the C8 Health Project. The four highest quintiles had higher odds of pregnancy-induced hypertension; however, there was no clear dose–response pattern. Based on this dataset, it would be premature to conclude a link exists between PFOA and pregnancy-induced hypertension.

Overall, no definitive association between PFOA and preeclampsia has been established. No increased occurrence of preeclampsia was observed in a study conducted among Mid-Ohio Valley residents (pregnant in 2000–2006) exposed to PFOA-contaminated drinking water (Stein et al., 2009). In a second study, risk of preeclampsia was examined among C8 Health Project participants from 1990–2005 (Savitz et al., 2012a). Self-reported preeclampsia was weakly associated with estimated serum PFOA at the time of pregnancy, and there was no dose–response pattern. The association was strengthened when restricted to pregnancies occurring after 1999.

An association between PFOA exposure and a reduction in fecundity has been observed; however, the studies were not robust and the results are inconclusive. A reduction of fecundity (increased time to pregnancy and irregular menstrual periods) was found to be associated with the plasma PFOA levels in 1,240 parous/nulliparous women; however, the information for multiple confounders was omitted from the analysis (e.g., sperm quality, occurrences of intercourses; Fei et al., 2009). Relative increases in the odds of subfecundity (time to pregnancy greater than 12 months) were reported in a case–control study on parous women enrolled in the Norwegian Mother and Child Cohort Study (with no increased odds of subfecundity in nulliparous women) (Whitworth et al., 2012b). Time to pregnancy and fecundity were not associated with serum PFOA levels in nulliparous women in a longitudinal cohort study in Denmark (Vestergaard et al., 2012). The lack of adjustment for confounders and of consistency in the results generates doubt on the link between lower fecundity and PFOA.

Three epidemiological studies reported associations of maternal serum PFOA with decreased duration of breast-feeding. A prospective cohort study recruited 1,400 pregnant women (randomly out of 43,045) within the Danish National Birth Cohort (DNBC, 1988–1989) and measured PFOA concentration in their plasma (Fei et al., 2010b). Duration of breastfeeding was reported 6 and 18 months after birth by phone interviews. The risk of breastfeeding for a shorter period was higher with increasing plasma PFOA. For example, the risk (adjusted hazard ratio) of shorter breastfeeding duration (weeks) for women with plasma PFOA > 7.0 ng/mL was 1.4 (95% CI 1.2–1.7) times higher than for those with plasma PFOA < 3.9 ng/mL, after adjusting for maternal age at delivery, pre-pregnancy BMI, maternal socioeconomic status, alcohol consumption and smoking (the trend for an increase in risk with increasing four-quartile comparison was also significant). Also, the odds (adjusted odds ratio) of weaning before 6 months of age was 1.23 (95% CI: 1.1–1.3) times higher for each 1 ng/mL increase in plasma PFOA when restricting the model to multiparous women (not significant in primiparous women), after statistical adjustments. A similar association was observed with weaning before 3 months of age. However, more studies would be needed to support these results, since PFOA plasma

concentration was measured only one time, only 18% of eligible women participated in the DNBC study, there is a risk of outcome recall bias (mothers might not report accurately the date of weaning), and the authors did not rule out the possibility that reverse causation could explain the association (especially since not observed in primiparous women, and considering that women that have breastfed longer can be more likely to breastfed longer their next infants, and that PFOA is excreted in breast-milk, lowering the plasma concentration). In a longitudinal cohort study of 468 pregnant women, recruited as part of the prospective pregnancy and birth cohort called Health Outcomes and Measures of the Environment (HOME) Study in the Cincinnati, Ohio area, Romano et al. (2016) measured serum PFOA, PFOS, perfluorononanoic acid (PFNA) and PFHxS concentrations. The duration of breastfeeding was reported in telephone interviews every three months until breastfeeding was discontinued. An association between higher maternal PFOA serum concentration and shorter duration of any breastfeeding (defined as the duration of breastfeeding notwithstanding supplementation with formula, liquids, or solid food) was observed, even after controlling for previous breastfeeding. The women in the cohort had higher average PFOA serum concentrations compared to pregnant women in NHANES. Notably, no association was found between PFOA exposure and exclusive breastfeeding; the authors suggested that other factors are likely responsible for the low rates of exclusive breastfeeding in this cohort. In a larger study of 1130 mother-child dyads from two birth cohorts recruited in the Faroe Islands, Timmermann et al. (2016) measured maternal serum PFOA, PFOS, PFHxS, PFNA, and perfluorodecanoic acid (PFDA) concentrations. The duration of breastfeeding, defined as the sum of exclusive and mixed breastfeeding, was reported either in an interview at offspring age 5 years or 18 months. An association between higher maternal serum PFOA and duration of both total and exclusive breastfeeding was observed; however, although the authors adjusted for the influence of other environmental chemicals (i.e., p,p'-DDE and polychlorinated biphenyls) they did not collect sufficient information to control previous breastfeeding. Neither study measured PFOA in drinking water.

The studies on the associations between PFOA exposure and sperm quality or hormone levels are sparse, inconsistent, and need to be corroborated in larger studies to better inform the possibility of a relationship. In a cross-sectional study conducted in 256 men from Durham, NC, a positive correlation was found between plasmatic PFOA and serum luteinizing hormone levels. No association between PFOA and semen quality measurements was found (Raymer et al., 2012). A positive association between PFOA and semen motility was identified in a group of men from one country, but not in the two other countries studied (Greenland, Poland and Ukraine). The author indicated the positive result might be attributable to chance findings (Toft et al., 2012). A prospective study has suggested that *in utero* exposure to ~~PFAAs~~PFAS may affect adult human male semen quality and reproductive hormone levels; however, there are concerns about the selection of participants (Vested et al., 2013).

Considering the weight of evidence, it is not possible to rule out possible adverse effects of PFOA on development and reproduction. Large cohort studies of offspring of mothers with high serum PFOA have reported an increased risk of lower abdominal circumference, length and weight at birth, as well as being overweight and having a high waist circumference 20 years after birth. These results are supported by effects on serum biomarkers (insulin, leptin, and adiponectin). Moreover, some evidence of reproductive toxicity has been observed, although to a lower extent. Higher level of exposure to PFOA has been associated with an increased risk of pregnancy-induced hypertension, preeclampsia, shorter duration of breastfeeding, altered sperm quality and reduced fecundity in longitudinal studies. However, the dataset for each individual outcome remains relatively small and definitive conclusions on the relationship between reproduction and developmental outcomes and exposure to PFOA are mainly limited by a lack of

consistencies in the results and the possibility of confounding. These limitations do not allow determining the nature of the association for the moment.

9.2 Effects on experimental animals

The vast majority of animal studies stated that exposure to PFOA was through its ammonium salt (APFO). Studies that did not state the specific salt used in their study were assumed to have used the ammonium salt, as this was the only compound used in studies that stated the PFOA salt. No studies stated whether the administered dose referred to the APFO compound, or specifically to the PFOA ion, separate from the ammonium salt. The summaries described herein use the concentrations and doses stated by authors. This approach is also used for quantitative assessments; however, as the PFOA ion contributes to 96% of the molar weight of APFO and is released from the compound upon exposure, only minor quantitative differences would result from using APFO and PFOA doses interchangeably.

9.2.1 Acute toxicity

The acute toxicity studies for PFOA or APFO indicate oral LD_{50} values of >500 and 680 mg/kg bw for male Sprague-Dawley and CD rats, respectively (Glaza, 1997), 250–500 mg/kg bw and 430 mg/kg bw for female Sprague-Dawley and CD rats, respectively (Dean and Jessup, 1978; Glaza, 1997), and <1,000 mg/kg for Sherman-Wistar rats of both sexes (Gabriel, 1976).

No mortality was reported in Sprague-Dawley rats of both sexes following inhalation exposure to PFOA at 18,600 mg/m^3 for 1 hour (Rusch, 1979).

The dermal LD_{50} in rabbits was determined to be >2,000 mg/kg bw or 4,300 mg/kg bw (Glaza, 1995; Kennedy, 1985). Higher values were obtained in rats, with a LD50 at 7,000 mg/kg bw in males and at 7,500 mg/kg bw in females (Kennedy, 1985).

Acute developmental neurobehaviour studies are discussed in Section 9.2.5.5.

9.2.2 Short-term exposure

Studies documenting the toxicity of PFOA after short-term oral exposure identified three main targets, namely reproductive and developmental effects (summarized in Section 9.2.5), hepatic effects, and serum lipid effects. Delayed mammary gland development appears to be the most sensitive target, with a LOAEL of 0.001 mg/kg bw per day (serum PFOA: 74.8 ng/mL; no NOAEL) in mice (White et al., 2011) (see Section 9.2.5.1). The lowest LOAELs for hepatic effects were 0.15 mg/kg bw per day in adult mice (Kennedy, 1987; NOAEL of 0.05 mg/kg bw per day). Serum lipid effects were observed at ≥0.3 mg/kg bw per day in rats (Loveless et al., 2006, 2008). This section will focus primarily on these key effects observed at the lowest levels, and will only briefly discuss other types of changes observed in animals.

9.2.2.1 Hepatic effects

The hepatic effects observed at the lowest levels in short-term studies were hepatocellular hypertrophy in male rats and mice (Perkins et al., 2004; Loveless et al., 2008) and increased liver weight in rats (Kennedy, 1987) and mice (Loveless et al., 2006). These studies will be described in greater detail, and other hepatic effects observed at higher levels will be discussed only briefly.

The lowest LOAEL for liver weight was in pups exposed *in utero* to 0.1 mg/kg bw per day on gestational days (GD) 1–17; further details on this study are provided in Section 9.2.5.4. In adults, the studies that observed liver weight increases at the lowest levels were Loveless et al. (2006; LOAEL of 0.3 mg/kg bw per day) and Kennedy (1987; LOAEL of 0.15 mg/kg bw per day and NOAEL of 0.05 mg/kg bw per day). These studies are described below.

A LOAEL of 0.3 mg/kg bw per day (no NOAEL) was identified in male CD-1 mice (n=10/dose) after oral exposure to PFOA (0, 0.3, 1, 3, 10 or 30 mg/kg bw per day) for 14 days (Loveless et al, 2006). Different preparations of PFOA were used (branched, linear, or combined branched/linear APFO). The LOAEL refers to increased relative liver weight in mice treated with linear and with branched APFO (most studies expose animals to a mixture that is predominantly linear APFO). Liver weights were also increased in rats, but only at ≥1 mg/kg bw per day. Absolute liver weights were significantly increased in at least one APFO form at ≥1 mg/kg bw per day in both species. In both rats and mice, the overall liver weight responses to linear and branched forms of PFOA were similar. The same researchers performed a 29-day study with linear APFO, and found no increases in liver weight at 0.3 mg/kg bw per day—absolute liver weight was increased in both species at ≥1 mg/kg bw per day, and relative liver weight was increased at ≥1 mg/kg bw per day in mice and ≥10 mg/kg bw per day in rats (Loveless et al., 2008). The latter study contained a high-dose (i.e., 30 mg/kg bw per day) recovery group (with exposure cessation at test days 23 in rats and 24 in mice), with liver weight increases still present at termination of the study in both species.

In the study with the lowest LOAEL for the endpoint (Kennedy, 1987), male and female CD rats were exposed to APFO at 0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 30 ppm in food (using Health Canada default assumptions of 1 ppm in food = 0.05 mg/kg bw per day in rats [Health Canada, 1994], the approximate doses were 0.0005, 0.0015, 0.005, 0.015, 0.05, 0.15, 0.5, and 1.5 mg/kg bw per day) for 21 days. Increased absolute and relative liver weight was observed at ≥0.15 mg/kg bw per day in both males and females, with a NOAEL of 0.05 mg/kg bw per day. The same study also exposed rats for 14 weeks, and observed increases at the ~~lowest~~highest dose in the study (30 ppm in food, equivalent to 1.5 mg/kg bw per day).

A wide variety of short-term studies observed increases in liver weight in adult animals at higher doses. These effects were observed in rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Staples et al., 1984; Kennedy et al., 1986; Biegel et al, 2001; Perkins et al., 2004; Cui et al., 2009~~) and~~), in mice (Metrick and Marias, 1977; Liu et al., 1996; Yang et al., 2001, 2002; Lau et al., 2006; Abbott et al., 2007; Wolf et al., 2007; DeWitt et al., 2008; Son et al., 2008; Qazi et al., 2010; Yahia et al., ~~2010).~~2010) and in monkeys (Thomford, 2001a; Butenhoff et al., 2002). Increases in liver weight appear to be generally reversible, as they were no longer observed after the exposure period in most studies with a recovery period (Palazzolo, 1993; Thomford, 2001a; Butenhoff et al., 2002; Perkins et al., 2004). In contrast, in a study of mice exposed for 10 days, the effect was still observed 10 days after ceasing exposure (Yang et al., 2001). Increases in liver weight were also observed in mice exposed *in utero* or peripubertally to PFOA; descriptions of these results can be found in Section 9.2.5.4.

The study that observed hepatocellular hypertrophy at the lowest levels exposed male Sprague-Dawley rats (n=10 per group) and male CD-1 mice (n=19–20 per group) to 0, 0.3, 1, 10, or 30 mg/kg bw per day of PFOA by for 29 days (Loveless et al., 2008). Incidence and severity of hypertrophy increased with dose, with effects of greater severity in mice. In the high-dose recovery group, hypertrophy persisted at the end of the study, despite cessation of exposure on study days 23 (rat) or 24 (mouse).

The most robust study with an observed NOAEL for increased liver weight and hepatocellular hypertrophy exposed male Crl:CD rats (n=55 per dose) to 0, 0.06, 0.64, 1.94, and 6.5 mg/kg bw per day in food (Perkins et al., 2004). Two control groups were included in the study—one set of controls pair-fed with the high dose group, and one *ad libitum* feeding group. The rats were divided into sacrifice groups exposed for a duration of 4, 7, or 13 weeks (n=15 per dose per duration), and each dose (and the *ad libitum* controls) had a recovery group that was observed for 8 additional weeks after cessation of exposure at week 13 (n=10 per dose).

~~Dose~~Significant dose-related increases in incidence and severity of hypertrophy were observed (Table 3). Most rats exposed to ≥0.64 mg/kg bw per day had minimal-to-slight hypertrophy, which was most severe in the high-dose group exposed for 13 weeks; effects did not persist in recovery groups. Hypertrophy was not accompanied by degenerative lesions in the liver. Relative liver weight was increased at ≥0.64 mg/kg bw per day in the 4-week group and at ≥1.94 mg/kg bw per day at the longer durations; the effect did not persist in the recovery groups. Thus, a NOAEL of 0.06 mg/kg bw per day for lack of hepatocellular hypertrophy is derived.

Table 3: Incidence and severity of hepatocellular hypertrophy in Perkins et al. (2004)

Dose (mg/kg bw per day)	Duration of exposure (wk)	Grade of hypertrophy			
		None	Minimal	Slight	Moderate
Ad libitum control	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	10	0	0	0
Pair-fed control	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	N/A	N/A	N/A	N/A
0.06	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	10	0	0	0
0.64	4	3	12	0	0
	7	3	12	0	0
	13	2	13	0	0
	13 (recovery)	10	0	0	0
1.94	4	0	7	8	0
	7	0	14	1	0
	13	1	12	2	0
	13 (recovery)	10	0	0	0
6.5	4	0	5	9	0
	7	0	6	9	0
	13	0	3	12	0
	13 (recovery)	10	0	0	0

Higher dose studies also identified hepatocellular hypertrophy in mice (Yahia et al., 2010) and rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Cui et al., 2009).

Other histological effects observed in the liver at higher doses in short-term studies include single cell and focal necrosis in mice (Loveless et al., 2008; Yahia et al., 2010) and rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Loveless et al., 2008; Cui et al., 2009); increased mitosis in mice (Yahia et al., 2010); mild calcification in mice (Yahia et al., 2010); cytoplasmic enlargement of hepatocytes in rats (Metrick and Marias, 1977); and cytoplasmic vacuolation in rats (Cui et al., 2009). Histological effects were also observed in livers of rats exposed to PFOA for 2 years; these effects are described in Section 9.2.3.

Changes in serum levels of markers of liver damage were observed in mice at higher levels than the LOAELs for increased liver weight and hepatocellular hypertrophy. These effects

included increased ALT (Son et al., 2008; Yahia et al., 2010), increased AST (Son et al., 2008; Yahia et al., 2010), increased GGT (Yahia et al., 2010), and increased ALP (Yahia et al., 2010; Qazi et al., 2010). Increased ALP was also observed in rats (Kennedy et al., 1986).

Dietary fat content has been proposed to contribute to the increased risk for PFOA-induced hepatotoxicity (Tan et al., 2013). Male Balb/c mice on a regular diet or a high fat diet were dosed with 0, 5, 10 or 20 mg/kg bw per day PFOA for 40 days. High fat diet alone did not cause any liver damage; however, high fat diet exaggerated PFOA-induced hepatotoxicity, including increased plasma AST and ALT levels, more severe hepatocellular hypertrophy, lipid droplet accumulation and necrosis and inflammatory cell inflammation. These results were supported by gene expression and metabolomics analysis that showed that a combination of high fat diet and PFOA significantly perturbed hepatic metabolism with activation of PPARα and hepatic inflammation.

9.2.2.2 Serum lipid effects

Alterations in serum lipid parameters were some of the effects observed at the lowest PFOA exposure levels in adult animals in short-term studies. The effects include changes in HDL, total cholesterol and triglycerides. Total cholesterol and HDL were decreased in most studies of mice (Loveless et al., 2006, 2008; Qazi et al., 2010) and rats (Loveless et al., 2006, 2008), but total cholesterol (along with phospholipid and free fatty acid) was increased in one high-dose study in mice (Yahia et al., 2010). Triglycerides were observed in mice to be increased in certain studies (Loveless et al., 2006; Yahia et al., 2010) and decreased in another (Loveless et al., 2008). They were decreased in both rat studies (Loveless et al., 2006, 2008).

The studies in which serum lipid changes were observed at the lowest levels were both performed by Loveless et al. (2006, 2008), which are described in greater detail in Section 9.2.2.1. The lowest LOAELs were in rats, with values of 0.3 mg/kg bw per day for decreases in cholesterol and triglycerides (Loveless et al., 2006, 2008) and 0.3 mg/kg bw per day for decreases in HDL (Loveless et al., 2008; in the 2006 study by Loveless et al. the LOAEL was ~~only~~ 3 mg/kg bw per day). Most of the effects were only observed at higher levels in mice—in Loveless et al. (2008), the LOAELs were 1 mg/kg bw per day for decreased HDL and 10 mg/kg bw per day for decreased total cholesterol and triglycerides, and most of the LOAELs in Loveless et al. (2006) were 3 mg/kg bw per day. An exception was for triglyceride increases specifically in the linear/branched APFO-exposed mice, as effects were observed at ≥0.3 mg/kg bw per day.

The effects on cholesterol and HDL did not appear to be persistent upon cessation of exposure~~, because~~; total cholesterol and HDL levels returned ~~similar~~close to control levels when exposure to 30 mg/kg bw per day dose was ceased at days 23 (rat) or 24 (mouse) in the 29-day study (Loveless et al., 2008). Triglyceride levels in ~~both species~~mice continued to ~~be lower than controls after the recovery period,~~rise following cessation of exposure but ~~in mice the~~triglyceride levels ~~had increased enough~~in rats did not change following cessation of exposure relative to ~~be~~the rats with continuous exposure; in both species triglyceride levels following cessation of exposure were significantly ~~higher~~lower than ~~the 29-day high dose group~~controls.

Loveless et al. (2006) investigated different forms of PFOA (branched, linear, or combined branched/linear). The linear form (the form most commonly appearing in PFOA mixtures used in studies) appeared to have the lowest LOAELs in rats for all lipid endpoints. In mice, the PFOA form did not appear to have any effect on HDL or cholesterol, but the linear/branched mixture appeared to be the only form that had any effect on triglycerides.

Additional studies saw increases in triglyceride, total cholesterol, and free fatty acid at 10 mg/kg bw per day in ICR mouse dams (Yahia et al., 2010) and reduction in total serum cholesterol in male C57BL/6 mice (Qazi et al., 2010).

Dietary fat content has been proposed to contribute to the observed differences in effects of PFOA on serum lipids in rodents versus humans (Tan et al., 2013; Rebholz et al., 2016). Consistent with the studies above, Tan et al. (2013) reported decreases in both serum cholesterol and triglycerides in a dose-related fashion in mice on the regular fat content diet, whereas serum cholesterol and triglycerides were unaffected by PFOA in mice on a high fat diet. Also, male and female C57BL/6 and male BALB/c mice fed a high fat diet containing 3.5 ppm PFOA (equivalent to 0.56 mg/kg bw per day) had significant increased plasma cholesterol (Rebholz et al., 2016). The response in C57BL/6 mice was more exaggerated compared to BALB/c mice, which the authors explained as strain-specific effects.

9.2.2.3 Other effects

Other effects besides hepatic and serum ~~liver~~lipid effects in short-term studies of adult animals occurred at PFOA exposure levels of ≥1 mg/kg bw per day. The studies are described briefly below.

At ≥1 mg/kg bw per day, increased kidney weight was observed in several studies of mice (Yahia et al., 2010) and rats (Goldenthal et al., 1978; Butenhoff et al., 2004b; Cui et al., 2009). In many of the studies, the increases were only in relative, but not absolute, kidney weight. The effects were also often accompanied by histological effects (Butenhoff et al., 2004b; Cui et al., 2009; Yahia et al., 2010).

Changes in weight of neurologically-relevant organs occurred at ≥3 mg/kg bw per day in monkeys. These observations were an increased group mean weight of the pituitary gland and decreased absolute brain weight (Goldenthal et al., 1978). The only other neurological effect noted in adult animals exposed for a short-term duration was reduced activity and lethargy in rats (Cui et al 2009).

Indications of immunosuppression occurred at ~~≥3.75 mg/kg bw per day in mice. These included~~0.49 mg/kg bw per day in mice. More specifically, Son et al. (2009) reported decreased numbers of splenic lymphocyte populations ($CD4^-$ $CD8^+$, $CD4^+$ $CD8^+$) in ICR mice dosed with ≥0.49 mg/kg bw per day PFOA in drinking water for 21 days. No NOAEL was identified. Additionally, PFOA exposure has been shown to induce decreased immunoglobulin levels, changes in cellularity and subtypes of immune cells, and changes in cytokine expression (Yang et al., 2001, 2002; DeWitt et al., 2008; Loveless et al., 2008; Son et al., 2008, 2009; Qazi et al., 2009, 2010). Splenic and thymic atrophy were also observed in mice (Yang et al., 2001, 2002; Loveless et al., 2008; Son et al., 2009; Qazi et al., 2009), and histological changes were observed in these organs in rats (Cui et al., 2009; Qazi et al., 2009; Son et al., 2009). Studies in mice also indicated a possibility for hypersensitivity due to exposures to PFOA, with a dose-related increase of serum histamine levels at ≥1 mg/kg bw per day (Singh et al., 2012) and increased IgE after challenge with OVA in mice exposed dermally to ≥18.75 mg/kg bw per day (Fairley et al., 2007). The U.S. NTP (2016) concluded that there is high confidence that exposure to PFOA is associated with antibody response suppression in animals based on consistent suppression of the primary antibody response in mice.

Effects on other organs were observed at ≥10 mg/kg bw per day. These effects included hypertrophy and vacuolation of the zona glomerusa of the adrenal gland in rats (Butenhoff et al., 2004b); pulmonary congestion, thickening of epithelial walls, cell infiltration and vasodilation in rats (Cui et al., 2009); pulmonary edema in rats (Kennedy et al., 1986); and decreased heart weight in monkeys (Goldenthal et al., 1978).

~~The only study indicating~~ Two studies reported changes in thyroid hormone levels. Butenhoff et al. (2002) reported decreased free and total T3 and T4 in monkeys exposed for 6

months ~~(Butenhoff et al., 2002).~~ Decreases in total and free T4 were observed at most timepoints, including termination, for monkeys exposed to 10 or 20–30 mg/kg bw per day; at termination (and not earlier timepoints), a significant decrease was also observed for total (but not free) T4 at the 3 mg/kg bw per day dose. Decreased total and free T3 was observed at most timepoints (including termination) in monkeys exposed to 20–30 mg/kg bw per day; decrease in total (not free) T3 was also observed at two mid-study timepoints, but not at termination, in low-dose monkeys. The effects were accompanied by significant increases in TSH at study termination in monkeys exposed to 3 or 10 mg/kg bw per day (no effect at high dose). The 4-week range-finding study for the Butenhoff monkey study (Thomford, 2001b) did not note any effects on TSH, or in total or free T3 or T4. Martin et al. (2007) measured thyroid hormone (total and free T4, and total T3) levels in male Sprague-Dawley rats one day following daily administration of 20 mg/kg bw per day PFOA or vehicle control by oral gavage for one, three, or five days. Levels of free and total T4 and total T3 were significantly reduced at all three time points, although the magnitude of decreases was smaller for T3 compared to T4.

Decreased bodyweight or bodyweight gain was observed in many different studies. The effects were observed at LOAELs of 3 mg/kg bw per day in rats (Metrick and Marias, 1977; Goldenthal et al., 1978; Staples et al 1984; Kennedy et al., 1986; Butenhoff et al., 2004b; Cui et al., 2010), 3 mg/kg bw per day in mice (Christopher and Marias, 1977; Lau et al., 2006; Wolf et al., 2007; Asakawa et al., 2008; Son et al., 2008; White et al., 2009; Yahia et al., 2010; Suh et al., 2011), and 30 mg/kg bw per day in monkeys (Goldenthal et al., 1978). This effect was accompanied by a decrease in food consumption at ≥5 mg/kg bw per day in rats (Metrick and Marias, 1977; Butenhoff et al., 2004b; Cui et al., 2009) and at 20.7 mg/kg bw per day in mice (Asakawa et al., 2008).

Clinical signs observed in studies included soft stools, diarrhea, and frothy emesis in monkeys (Goldenthal et al., 1978) and roughed fur, muscle weakness, and cyanosis in mice (Christopher and Marias, 1977).

Few studies reported increased mortality in animals. The endpoint was observed at high levels in studies of rats (Metrick and Marias, 1977; Staples et al., 1984; Butenhoff et al., 2004b), mice (Christopher and Marias, 1977), and monkeys (Goldenthal et al., 1978b; Thomford, 2001a; Butenhoff et al., 2002).

9.2.3 Long-term exposure and carcinogenicity

Two chronic toxicity studies in laboratory animals were identified for the oral route. No inhalation or dermal study was located. As was observed in long-term carcinogenicity studies, the liver was the most sensitive target organ in the chronic studies (LOAEL = 1.3 mg/kg bw per day in male rats for increased serum liver parameters) (3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b). Other effects observed in rats after chronic exposure to PFOA include an increased incidence of hyperplasia and tumors in various tissues (mammary gland in females, Leydig cells, pancreas and liver in males) and alteration of serum hormone levels (3M, 1983; Sibinski, 1987; Biegel et al., 2001).

~~The only study including more than one dose identified a LOAEL of 1.3 mg/kg bw per day (no NOAEL) in male rats for liver toxicity (3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b).~~ Only one study included more than one dose – this study was conducted by 3M Company and the results were presented as part of laboratory reports (3M, 1983; Sibinski, 1987) and a peer-reviewed publication (Butenhoff et al., 2012b). A LOAEL of 1.3 mg/kg bw per day (no NOAEL) in male rats was identified for liver toxicity. Sprague-Dawley rats (50/sex/group) were given APFO at 0, 30 or 300 ppm in the diet for 2 years (0, 1.3 or 14.2 mg/kg bw per day for

males; 0, 1.6 or 16.1 mg/kg bw per day for females). The LOAEL of 30 ppm was based on significant increases in serum liver parameters in males (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and albumin at many timepoints, which were still elevated—although not significantly at the low dose—at termination) and a dose-related increase of chronic sialadentitis in the salivary gland of males. Hepatocellular hypertrophy was also elevated in both male treatment groups, with significance only being reached at the high dose (incidence was 0% in controls, 12% at the low dose, and 80% at the high dose). Other effects in males include a dose-dependent increased incidence of Leydig cell adenomas, statistically significant at 300 ppm (14.2 mg/kg bw per day). In female rats, the first data analysis indicated a dose-dependent increase in mammary fibroadenomas, statistically significant at ≥30 ppm; however, a more recent analysis was conducted by a pathology working group using current diagnostic criteria, which concluded that PFOA treatment did not result in proliferative lesions in the mammary tissues (Hardisty et al., 2010; Butenhoff et al., 2012b). Non-neoplastic changes in the liver (hepatocellular hypertrophy, portal mononuclear cell infiltrate or cystoid degeneration at the high dose) and the lungs (alveolar macrophages and hemorrhage at the high dose) were observed, and proliferative acinar cell lesions were observed in the pancreas of rats at the high dose. PFOA did not increase the incidence of neoplastic or non-neoplastic lesions in the other organs (thyroid, pituitary, adrenal gland, kidney, uterus).

A follow-up study was performed in male CD rats given APFO in the diet (0 or 300 ppm) for 2 years (average daily dose of 13.6 mg/kg bw per day) (Biegel et al., 2001). Two controls groups were used; the first was an *ad libitum* fed (AL) group, and the second was a pair-fed (PF) group in which the food intake was controlled to match the food intake of the PFOA exposed group. Rats were evaluated at 1 and 3 months and at every 3 months for hormone status, cell proliferation in liver, testis and pancreas and hepatic peroxisome proliferation. Treatment with PFOA increased the relative liver weight at all time points (except at 24 months) compared to both controls. Hepatic β-oxidation activity was significantly elevated at all times, but cell proliferation was not increased in the liver. Pancreatic acinar cell proliferation was increased at 15, 18, and 21 months. Serum estradiol was increased during the first year of the study, serum LH at 6 and 18 months, and serum FSH at 6 months; changes in serum testosterone did not show any consistent pattern. There was a significant increase in tumours in treated animals when compared with one or both of the control groups for Leydig cell adenomas, hepatic adenomas, acinar cell adenomas and combined pancreatic adenomas and carcinomas. An increased incidence of hyperplasia was also observed in Leydig cells and acinar cells (Biegel et al., 2001).

Although the LOAEL for liver endpoints was higher in chronic studies than in shorter-term studies, the comparisons are difficult to make, as the lowest dose used in the chronic study (1.3 mg/kg bw per day) is higher than the lowest LOAELs for liver effects in the shorter-term studies (i.e., 0.1–0.3 mg/kg bw per day). However, some endpoints observed at these low doses in shorter duration studies, most notably hepatocellular hypertrophy in male rats (Loveless et al., 2008) were not observed at the lowest doses used in the chronic studies (i.e., the chronic NOAEL for this endpoint is 1.3 mg/kg bw per day).

9.2.4 Genotoxicity

The genotoxicity database indicates that PFOA compounds are not mutagenic, and generally not genotoxic (U.S. EPA, 2005; UK HPA, 2009; Environment Canada and Health Canada, 2012).

9.2.4.1 In vitro *findings*

Testing of PFOA (or its ammonium or sodium salts) produced no evidence of genotoxic activity in several Ames bacterial mutation assays and in three *in vitro* chromosomal aberration tests (two in hamster cells and one in human cells) (Environment Canada and Health Canada, 2012). More recently, PFOA (tested up to 1,000 µM) had no mutagenic activity in the *umu* test (Oda et al., 2007) and in the Ames test, with or without S9 metabolic activation (Fernandez Freire et al., 2008). PFOA did not increase oxidative DNA damage (as measured in a comet assay) in rat testicular cells exposed to 100 and 300 µM for 24 hours (Lindeman et al., 2012). In human hepatoma HepG2 cells, PFOA (up to 400 µM for 24 h) did not induce ROS generation, DNA single strand breaks or micronucleus (Florentin et al., 2011). In another study using human HepG2 cells, PFOA induced slight ROS generation (0.4-2,000 µM) without generating detectable DNA damage (200 µM) (Eriksen et al., 2010).

In contrast, positive results were obtained in one chromosome damage test in hamster cells and one micronucleus assay in human cells *in vitro*, and PFOA caused oxidative DNA damage in human hepatoma cells in culture (Environment Canada and Health Canada, 2012). PFOA (200 µM) led to mutagenicity induction in human-hamster hybrid (A_L) cells and mitochondria-dependent ROS was shown to play an important role in this process (Zhao et al., 2011b).

9.2.4.2 In vivo *findings*

Testing of PFOA (or its ammonium or sodium salts) for genotoxic potential produced no evidence of activity in three *in vivo* bone marrow micronucleus tests in mice (up to 5,000 mg/kg bw per day). PFOA caused oxidative DNA damage in the liver of rats treated through the oral route (200 ppm in diet for 2 weeks) or the intraperitoneal route (100 mg/kg bw, once) (Environment Canada and Health Canada, 2012).

9.2.5 Reproductive and developmental toxicity

The reproductive and developmental database for PFOA is robust. Two ~~2~~multi-generational studies have been ~~developed~~conducted in rats (Butenhoff et al., 2004b/York et al., 2010; White et al., 2011), and reproductive and developmental parameters have been investigated in many one-generation studies in rats, mice, and monkeys. Furthermore, early life or peripubertal exposures were performed in mice (Johansson et al., 2008, 2009; Yang et al., 2009b; Zhao et al., 2010; Dixon et al., 2012).

The most sensitive effects identified are delayed mammary gland development in the offspring of mice (Macon et al., 2011; White et al., 2011), obesity in the female offspring of mice at adulthood (Hines et al., 2009), uterine effects in immature female mice (Dixon et al., 2012), liver weight changes in pups (Abbott et al., 2007; Macon et al., 2011; Onishchenko et al., 2011) and altered neurobehaviour (Johansson et al., 2008, 2009; Onishchenko et al., 2011). These effects were all observed at exposure levels of ≤0.3 mg/kg bw per day, and will be discussed in greater detail. Other reproductive and development effects occurred at higher doses, and will only be described briefly in this section.

9.2.5.1 Mammary gland effects

Changes in mammary gland development (MGD) have only been studied in mice. Delayed MGD was consistent in 1-generation (White et al., 2007, 2009; Wolf et al., 2007; Macon et al., 2011), 2-generation (White et al., 2011), and peripubertal (Yang et al., 2009; Zhao et al., 2010) studies, and has been observed to be significantly different than controls at every dose level studied (≥0.001 mg/kg bw per day) in maternal and F1 generations (both as offspring and dams). The studies primarily identified delayed MGD development (noted to be as long as 10 days in a

study that exposed mice to 5 mg/kg bw per day [White et al., 2007]) and lower MGD scores[1] at many different time points. The specific mammary gland structures that were affected included ducts (reduced and delayed ductal elongation and branching), terminal ducts (decrease in number of stimulated TDs), terminal end buds (delayed time of appearance, excess of and decrease in number of TEBs), and longitudinal epithelium (reduced and delayed growth). One study also noted higher densities of darkly staining foci, along with other histological changes, at 18 months (White et al., 2009).

Three studies investigated MGD at ≤1 mg/kg bw per day (Macon et al., 2011; White et al., 2011; Tucker et al., 2015) and will be more thoroughly described below because the LOAELs from these studies are the lowest of any endpoint, including those observed in subchronic and chronic studies. The other studies observing these effects will be summarized more concisely.

A two-generation study (White et al., 2011) found that exposure of mice to low levels of PFOA in drinking water (5 µg/L) delayed mammary gland development in both P0 and F1 dams and F1 and F2 offspring, which persisted until adulthood (at least PND 63). Parental (P0) female CD-1 mice (n = 7–12 per group) were placed into different treatment groups, receiving:

- daily doses of PFOA by gavage (0, 1 or 5 mg/kg bw per day: control, G1 and G5 groups, respectively) on GD 1–17,
- PFOA in drinking water only (5 µg/L, DW group) on GD7–17, or
- PFOA by both gavage (1 mg/kg bw per day on GD1–17) and drinking water (5 µg/L on GD7–17) (G1+DW group).

On PND 1, F1 litters were pooled randomly and redistributed to dams of their respective groups (n=12–13 neonates per litter). F1 female offspring from G1 and G5 groups were not exposed after birth while F1 female offspring from DW and G1+DW groups were exposed via drinking water throughout the rest of the study (n=2–10 F1 dams per group). F1 female offspring were mated with unexposed males to produce the F2 generation. F2 female offspring from DW and G1+DW groups were exposed through drinking water up to the end of the study. Necropsies were performed on F1 and F2 females at PND 42 and PND 63, and on F1 dams and F2 female offspring at PND 10 and PND 22 (White et al., 2011).

In the P0 (i.e., directly-exposed dams), a significant increase of MGD score was observed in all the treated groups on PND 22, even at the lowest dose (5 µg/L in drinking water on GD 7–17). These elevated scores reflect a delay in the normal weaning-induced mammary involution (on PND 22, the structure of the mammary gland in the treated P0 was similar to the structure normally observed at the lactation peak at PND 10). The authors only provided information on the amount of daily ingestion of PFOA in P0 dams consuming 5 µg/L drinking water (approximately 0.05 µg per day during gestation and 0.1 µg per day during lactation [PND 1–22]). Average daily doses are estimated to be approximately 0.001 mg/kg bw per day during gestation and 0.004 mg/kg bw per day during lactation (based on mean approximate weights of 62 g during gestation and 25 g during lactation; the average maternal weight gain during gestation was 25 g, and the initial body weight of dams was not reported by the authors but is assumed to be approximately 25 g for this strain of mice). The maternal LOAEL was therefore considered to be 0.001 mg/kg bw per day.

[1] MGD is scored on a 1–4 subjective, age-appropriate developmental scale based on the number of primary ducts and large secondary ducts, lateral side branching, appearance of budding from the ductal tree, and longitudinal outgrowth of the epithelia. For female offspring, a score of 4 refers to excellent development/structure and a score of 1 to poor development/structure. For dams, a value of 4 represents well-differentiated, functionally lactating tissue characterized by extensive epithelium, reduced adiposity, and presence of secretory alveoli, consistent with the peak of lactation (PND10). A value of 1 represents little or diminishing presence of lobuloalveoli and extensive involution and regression of the tissue, with the presence of apoptotic bodies, increasing adiposity, and regressing alveoli, as anticipated at weaning (PND22).

F1 pups from all treatment groups exhibited reduced MGD scores (reduced ductal elongation and branching, delays in timing of TEB appearance) until at least 9 weeks of age (PND 63, i.e., the last time point). In F1 dams (i.e., adult F1 pups), all of the PFOA-treated groups exhibited reduced MGD scores on PND 10; low score value persisted on PND 22 in the G1+DW, whereas in the G5 group, the score became higher than the control on PND 22 (i.e., normal involution was delayed). In the F2 females, MGD scores at PND 10 and PND 22 did not differ significantly from control; however, this result may be biased due to unusually low scores in the control group. At later times, significantly reduced scores were obtained in all treated groups (PND 42 for DW, G1+DW and G5, PND 63 for G1) and were characterized by an excess of terminal end buds (TEBs) (White et al., 2011).

In summary, White et al. (2011) demonstrated that ingested PFOA alters the development of mammary glands in both dams and offspring of CD-1 mice after exposure to low, human-relevant doses of PFOA (as low as 5 µg/L in drinking water) leading to human-relevant PFOA serum concentrations in pups and dams (range of approximately 20–90 ng/mL). The corresponding dose (LOAEL) was estimated at a maternal exposure of approximately 0.001 and 0.004 mg/kg bw per day during gestation and lactation, respectively. Effects in this study occurred independently of body weight changes, and the only adverse maternal effects observed at these levels were the mammary gland changes.

Macon et al. (2011) performed two separate studies of MGD in CD-1 mice—a late-gestation study and whole-gestation study. In the late-gestation study, dams (n=13 per group) were exposed to PFOA (0, 0.01, 0.1, and 1.0 mg/kg bw per day) by oral gavage on GD 10–17. The whole-gestation study exposed dams (n=13 per group) by gavage to PFOA at 0, 0.3, 1.0 or 3.0 mg/kg bw per day on GD 1–17.

Results of the late gestation study indicate significantly reduced MGD scores (in all treated groups, with a dose-dependent relationship) at PND 21. Other effects observed in the mammary gland at PND 14 (at 0.1 and 1.0 mg/kg bw per day, respectively) included reduced longitudinal epithelial growth by 14.4% and 37.3% compared to control (reduction by 27.4% and 56.5% compared to PND 1) and a statistically significant reduction of TEBs. In the whole-gestation study, the effects observed at all doses were dose-dependent and included reduced MGD scores in female offspring, which persisted until adulthood (PND 84). The LOAELs for the late and whole gestation studies were 0.01 and 0.3 mg/kg bw per day, respectively. No decreases in pup body weight were observed in these studies; therefore, MGD delays did not arise from decreased body weight.

Tucker et al. (2015) studied MGD in both CD-1 and C57Bl/6 female mouse pups that were exposed *in utero* to PFOA. Dams were exposed to PFOA via gavage at concentrations of 0, 0.01, 0.1, 0.3, and 1 mg/kg bw per day on GD 1–17. Significant dose-related trends in decreases in MGD scores were observed in pups of both strains. In CD-1 mice, the decreases were significant at ≥0.1 mg/kg bw per day when measured at PND21, which then decreased to ≥0.01 mg/kg bw per day at PND35 and PND56. The LOAEL for C57Bl/6 was slightly higher, with significant decreases at ≥0.3 mg/kg bw per day at PND21 and PND61. The authors also noted that average serum PFOA levels were lower in C57Bl/6 mice than in CD-1 mice.

Although the LOAEL for MGD scores was lower in CD-1 than C57Bl/6 mice, the results from this study are not sufficient to conclude that strain sensitivity occurs for the endpoint. Fewer pups were born in all C57Bl/6 groups, which resulted in a smaller sample size for the strain. This was particularly notable in the 0.01 and 0.1 mg/kg bw per day groups, which contained 8–22 CD-1 mice, but only 2–5 C57Bl/6 mice. As average MGD scores were similar between the strains at all doses, the lower sample size might have prevented statistical significance from being reached at these lower doses for C57Bl/6 mice. Moreover, the timing of MGD scoring was

different for the strains at later timepoints (CD-1 mice were studied at PND 21, 35, and 56, whereas C57Bl/6 mice were only studied at PND 21 and 61), which might also affect results; MGD scores in control C57Bl/6 mice at PND 61 were lower than in control CD-1 mice at PND 35 and 56.

Tucker et al. (2015) also investigated other sexual maturity effects. No treatment-related effects on estradiol or progesterone levels, or on timing of vaginal opening or first estrus, were observed in either strain.

Several other higher-dose studies have noted delays in MGD at many different time points in female CD-1 mice (dams and offspring) exposed to gavage doses of ≥3 mg/kg bw per day (White et al., 2007, 2009; Wolf et al., 2007). These delays in MGD development are supported by data indicating reduced placental mRNA expression for genes in prolactin family (at ≥2 mg/kg bw per day; Suh et al., 2011), and a delay in lactotransferrin expression at 5 mg/kg bw per day (White et al., 2007).

A peripubertal study in mice (dosing beginning at 21 days of age) noted strain differences, with significant MGD delays at ≥5 mg/kg bw per day in Balb/c, but only at 10 mg/kg bw per day in C57Bl/6 (no inhibition occurred in either strain at 1 mg/kg bw per day; rather, stimulation was observed at this dose in C57Bl/6 mice) (Yang et al., 2009b). An additional peripubertal study (Zhao et al., 2010) noted effects at the only dose in the study, 5 mg/kg bw per day.

Although mammary gland delays can sometimes be associated with decreased body weight, two studies specifically stated that the effects were observed in absence of bodyweight disparities (White et al., 2007, 2009). One study also noted that the effect was not entirely due to underdeveloped offspring and insufficient stimulation by suckling, as the alteration of the functional mammary gland differentiation occurred prior to parturition and lactation (i.e., prior to stimulation of the gland by offspring) (White et al., 2007; 5 mg/kg bw per day).

Other effects related to sexual maturity were accelerated puberty (≥1 mg/ kg bw per day in M mice & 20 mg/kg bw per day in F mice; Lau et al., 2006), delayed sexual maturation (preputial separation & vaginal patency in rats; only at 30 mg/kg bw per day; Butenhoff et al., 2004b), and increased age of vaginal opening (at ≥5 mg/kg bw per day in C57BL/6 mice, but not Balb/c mice; Yang et al., 2009b).

9.2.5.2 Uterine effects

Histological changes in the uterus have been observed in CD-1 mice exposed to low doses of PFOA (Dixon et al., 2012). In immature mice exposed PND 18–20 to 0.01 mg/kg bw per day of PFOA by gavage, endometrial edema, hyperplasia of endometrial mucosa and glands, edema, and hypertrophy and hyperplasia of myometrium were induced. No histological effects were observed at the two higher doses in the study (0.1 and 1 mg/kg bw per day). The study also saw a dose-related increase of mucification (significant at the high dose only) in the cervix and vagina.

Differential effects were observed in uterine weight in mice. Increases in uterine weight in the Dixon et al. (2012) study were only observed in the lowest (0.01 mg/kg bw per day) group. The only other study reporting changes in uterine weight was a 4-week gavage study that exposed peripubertal Balb/c and C57BL/6 mice to 0, 1, 5, or 10 mg/kg bw per day (Yang et al., 2009b). In Balb/c mice, uterine weight was decreased at all doses (≥1 mg/kg bw per day), whereas in C57BL/6 mice, uterine weight was increased at 1 mg/kg bw per day, with a dose-dependent decrease at higher doses, which became significant only at 10 mg/kg bw per day.

9.2.5.3 Obesity in adulthood

Obesity in adulthood was noted to occur in a non-monotonic dose-response fashion in mice, in the only study that investigated this effect (Hines et al., 2009). Dose-dependent effects on

body weight, appetite control (increased leptin and insulin blood concentration) and fat distribution were observed at adulthood in female CD-1 mice exposed *in utero* to PFOA. Pregnant mice (n=7–22 per dose group) were exposed daily by gavage on GD 1–17 (PFOA doses of 0, 0.01, 0.1, 0.3, 1, 3 and/or 5 mg/kg bw per day); offspring were weaned at 3 weeks and then female offspring were selected and received a standard diet for the rest of study.

At low doses (0.01, 0.1 and 0.3 mg/kg bw per day), data indicate an excessive weight gain in mice aged 20–29 weeks that coincided with increased blood levels of leptin and insulin (by approximately 2.5-fold) at 21–33 weeks of age (Hines et al. 2009). At higher doses, tissue weights at 18 months of age revealed a decreased relative weight of abdominal white fat at 1 and 5 mg/kg bw per day (no data at 3 mg/kg bw per day), and an increased relative weight of interscapular brown fat at 1 and 3 mg/kg bw per day (no effect at 5 mg/kg bw per day); overall bodyweight was decreased at the higher tested dose (5 mg/kg bw per day). No effects on bodyweight were observed at 1 or 3 mg/kg bw per day.

Similar experiments conducted in ovariectomized siblings of the exposed offspring (ovariectomy performed at PND 21/22) indicated no effect on body weight and abdominal fat weight, but an increased relative weight of interscapular brown fat at 1 mg/kg bw per day (no effect at 5 mg/kg bw per day). Although the latter data were difficult to interpret, the authors concluded that the ovaries appeared to play an important role in the overweight effect in mid-life and proposed that potential dysregulation of PPAR and its signaling through ovarian hormones may be responsible for the low-dose effects observed (Hines et al., 2009). It should be noted that exposure of 8 week-old mice to the same doses for the same period (17 days) did not lead to any effect on the same endpoints (see Section 9.2.2.1), suggesting the timing of dosing was critical for latent effects (Hines et al., 2009).

9.2.5.4 Developmental hepatic effects

As described in Section 9.2.2.1, hepatic effects are the most sensitive non-developmental effect resulting from short-term exposure to PFOA. Likewise, increases in liver weight were also observed after *in utero* or peripubertal exposure to PFOA.

The lowest maternal exposure dose at which increases in liver weight were observed in pups exposed prenatally to PFOA was 0.1 mg/kg bw per day (Abbott et al., 2007). In this study, 129S1/SvImJ mice (n=5–22 dams/dose) were exposed by gavage to 0, 0.1, 0.3, 0.6, 1, 3, 5, 10, and 20 mg/kg bw per day on GD 1–17. Increased relative liver weight in pups was observed in all doses, and was worsened at higher doses.

In another study, Quist et al. (2015) reported significant increases in liver:body weight ratios at 0.3 and 1.0 mg/kg bw per day on postnatal day 21 in female offspring from pregnant CD-1 mice administered PFOA (0, 0.01, 0.1, 0.3, and 1 mg/kg bw per day) by oral gavage on GD 1-17; however, this was a transient effect as it was no longer observed at postnatal day 91. One other study observed slight but significant effects at <1 mg/kg bw per day; the study had only 1 dose group, 0.3 mg/kg bw per day (Onishchenko et al., 2011). The effect was observed at ≥1 mg/kg bw per day in other studies in mice exposed *in utero* (Wolf et al., 2007; White et al., 2009, 2011;Macon et al., 2011) or peripubertally (Yang et al., 2009b).

Filgo et al. (2015) exposed pregnant CD-1 mice, 129/SV mice, and PPARα-null mice (on 129/SV background) to PFOA by oral gavage throughout gestation. Doses administered differed depending on the mouse strain but ranged from 0.01 to 5.0 mg/kg bw per day. Livers from female offspring (exposed in utero and during lactation) were examined histologically at 18 months of age. In CD-1 pups, there was a significant increase in centrilobular hepatocyte hypertrophy and Ito cell hypertrophy at 5 mg/kg bw per day, as well as hepatocellular adenomas at 0.3 mg/kg bw per day only. Quist et al. (2015) similarly reported hepatocellular hypertrophy in pups exposed by

the same regime at postnatal day 91 with an increase in severity compared to controls at ≥0.01 mg/kg bw per day. Transmission electron microscopy of the liver slides showed cell damage and changes to mitochondrial morphology and numbers, which are not generally associated with PPARα-mediated effects. Filgo et al. (2015) reported a significant reduction in diffuse fatty change in 129/SV pups at 1 mg/kg bw per day, as well as a significant increase in bile duct hyperplasia at 3 mg/kg bw per day and significant decrease in Ito cell hypertrophy at ≥1 mg/kg bw per day in PPARα-null pup. Quist et al. (2015) reported no change in serum liver enzymes at postnatal days 21 and 91 in pups from dams fed control fat diets or high fat diets throughout lactation but did report a significant decrease in total cholesterol at ≥0.3 mg/kg bw per day in pups from dams fed high fat diet during lactation.

9.2.5.5 Neurodevelopmental effects

Neurobehavioural effects were observed in mice exposed *in utero* or shortly after birth, at the lowest doses applied in two studies—0.3 mg/kg bw per day (Onishchenko et al., 2011) and 0.58 mg/kg bw per day (Johansson et al., 2008). The effects manifested as changes in activity levels in mice.

Dietary exposure of C57BL/6/Bkl mice (n=6 dams/group) to 0 or 0.3 mg/kg (the only treatment group) of PFOA from GD 1 throughout pregnancy was found to induce gender-specific changes in offspring exploratory behaviour (first hour spent in a new environment), with an increased exploring activity in males and a decreased activity in females (Onishchenko et al., 2011). Prenatal exposure to PFOA also decreased the total number of inactive periods during the light phase in both males and females as well as in the dark phase of the circadian cycle in males. Motor coordination was slightly altered in females only. No effects were noted on locomotor activity, anxiety behaviour (elevated plus maze test), and immobility in the forced swimming test or muscle strength.

A LOAEL of 0.58 mg/kg for neurodevelopmental effects was identified in NMRI male mice administered a single gavage dose of PFOA (0.58 or 8.70 mg/kg) at the age of 10 days (Johansson et al., 2008). Mice were tested for spontaneous behavior and habituation at the age of 2 and 4 months, and the susceptibility of their cholinergic system was explored in a nicotine-induced spontaneous behaviour test at the age of 4 month (Johansson et al., 2008). Data indicate time-dependent and dose-related effects on the behaviour (deranged spontaneous behaviour, lack of habituation and increased susceptibility of the cholinergic system) reflecting the advance of a brain dysfunction process induced at the time of brain growth spurt in the neonatal mouse. At both doses, the exposed mice exhibited an altered spontaneous behaviour and a hypoactive response to nicotine. Any of the three variables of the behavioural test (locomotion, rearing and total activity) were altered, indicating hypoactivity during the first 20 minutes and hyperactivity in the last 20 min period (40–60 min after start of the test), and the effects worsened with age. These effects were supported by significantly increased levels of proteins that are important for normal brain development (CaMKII, GAP-43, and synaptophysin in the hippocampus, synaptophysin and tau in the cerebral cortex, and tau in the hippocampus) in mice under the same neonatal exposure conditions (Johansson et al., 2009).

9.2.5.5 Other effects

Reproductive and developmental effects other than those described earlier in this section were observed at higher doses; 0.6 mg/kg bw per day was the lowest LOAEL for delayed eye opening (Abbott et al., 2007), and all other effects were observed at ≥1 mg/kg bw per day.

The additional reproductive effects in mouse included a reduced number of implants (White et al., 2011), increased resorption, dead fetuses, post-implantation loss, or prenatal loss

(White et al., 2007; Suh et al., 2011; White et al., 2011;) including increases in full-litter resorption or loss (Lau et al., 2006; Wolf et al., 2007; White et al., 2009), decreased placental weight (Suh et al., 2011), increased time to parturition (Lau et al., 2006), reduced number of live fetuses (White et al., 2011), increase in number of stillborn pups (Yahia et al., 2010), decreased survival of pups (Lau et al., 2006; Wolf et al., 2007; White et al., 2009; 2011; Yahia et al., 2010) and histopathological changes in mouse placenta (Suh et al., 2011).

The additional developmental effects in mouse offspring included delayed eye opening at in 1-generation studies (Lau et al., 2006; Abbott et al., 2007; Wolf et al., 2007; White et al., 2009), skeletal effects in one-generational studies [one study observed altered ossification (enlarged fontanel, reduced ossification of sternebrae and calvaria; Lau et al., 2006), another found delayed ossification of phalanges, increased cleft sternum, and delayed eruption of incisor occurred; Yahia et al., 2010], decreased relative spleen weight, without a clear dose–response relationship (Hines et al., 2009), reduced fetal or pup weight (Staples et al., 1984; Lau et al., 2006; Abbott et al., 2007; White et al., 2007; 2009; Wolf et al., 2007; Yahia et al., 2010; Suh et al., 2011), and increased fetal weight (Yahia et al., 2010).

The only effects noted in a 2-generation study of rats included delayed growth (at ≥10 mg/kg bw per day in M and 30 mg/kg bw per day in F) and increased post-weaning mortality (in F only, at 30 mg/kg bw per day), with no effects on the F2 generation (Butenhoff et al., 2004b; York, 2002).

9.3 Mode of action

Mode of action analysis was considered for effects occurring at the lowest PFOA levels (i.e., Leydig cell tumours, hepatocellular hypertrophy, and changes in serum lipids in rats, and liver weight increases, hepatocellular hypertrophy, obesity, developmental delays, and delayed mammary gland development in mice). Only a preliminary evaluation of data could be performed for most of the MOAs; a MOA analysis using recent guidance (Meek et al., 2014) could only be performed for peroxisome proliferation effects on liver endpoints. Based on the MOA analysis, no endpoints were considered to be irrelevant to humans, and the results suggest that the TDI approach is the most appropriate method for cancer risk assessment. Results of the MOA evaluations are summarized in this section.

9.3.1 Direct-acting mutagenicity

Direct-acting mutagenicity and DNA reactivity was considered as a potential MOA for the development of Leydig cell tumours in rats. As discussed in Section 9.2.4, evidence predominantly indicates that PFOA is not mutagenic, with or without metabolic activation. PFOA was negative for genotoxicity in a wide variety of *in vitro* and *in vivo* assays. Positive results were obtained only in one chromosome damage test in hamster cells, one micronucleus assay in human cells, and mutagenicity was observed in human-hamster hybrid (A_L) cells, but mitochondria-dependent ROS was shown to play an important role in this process. The pattern of PFOA-induced tumours also did not follow that of typical mutagens. For example, mutagens are typically expected to cause tumours in many different organs, but PFOA only affected testicular Leydig cells, liver, and pancreas (i.e., organs associated with the PPARα tumour triad) in one study (Biegel et al., 2011), and only Leydig cells in another study at similar doses (Butenhoff et al., 2012b). Furthermore, mutagens often produce a high incidence of tumours, which occur at early timepoints and at low doses. In PFOA-exposed animals, the tumours were only observed after lifetime duration to high doses in PFOA studies, and at low incidences (10–14%).

Further support for non-mutagenic activity of PFOA is provided by a study that suggests that PFOA acts as a tumour promoter. Liver tumours—primarily hepatocarcinomas—were

observed in rats that underwent initiation protocols (i.e., were exposed to the mutagen diethylnitrosamine) and were exposed to feed containing 0.015% PFOA (equivalent to 7.5 mg/kg bw per day using the Health Canada [1994] assumption that 1 ppm in food is equivalent to 0.05 mg/kg bw per day in rats) on weeks 5–28 of the study (Abdellatif et al., 1990). Hepatic tumours were observed in 33% of animals (vs. 0% in controls that were initiated but not exposed to tumour promoters); therefore, effects were observed earlier (after 6 months of PFOA exposure and 7 months after initiation) and at a higher incidence than higher dose studies of rats exposed only to PFOA.

The weight of evidence for non-mutagenic MOAs of tumours (as discussed later in this section) is stronger than for direct-acting mutagenicity, which suggests that low-dose linear extrapolation is not appropriate for PFOA-induced tumours. No further MOA analysis is required for direct-acting mutagenicity, unless contradictory data are published.

9.3.2 Peroxisome proliferation

Peroxisome proliferation was considered as a potential MOA for hepatocellular hypertrophy in rats and mice, serum lipid changes and hepatocellular tumours in rats, and liver weight increase and obesity in mice. Some data exist for hepatic PPAR activity in rats and mice; therefore, this is the primary focus of the analysis. Because few studies directly measured PPAR impact on other outcomes, these could not be fully assessed; however, studies in PPAR-null mice indicate a decreased sensitivity to reproductive and developmental endpoints (including litter loss, delayed eye opening, and decreased body weight in pups [Abbott et al., 2007]) but not mammary gland development delays (Zhao et al., 2010). The evolved Bradford-Hill criteria were applied to evaluate the weight of evidence for the MOA of peroxisome proliferation for liver endpoints, which is summarized below.

Three main key events in the peroxisome proliferation MOA are considered to lead to liver histological effects and hepatocellular tumours. These key events are 1) the activation of hepatic PPARα receptors, which leads to 2) altered cell growth pathways that inhibit apoptosis and/or promote cell replication, eventually leading to 3) hepatocyte proliferation (Corton et al., 2014).

9.3.2.1 Key event 1 – PPARα activation

An absence of hepatic palmitoyl CoA oxidation was observed in rats exposed to 0.3 mg/kg bw per day of PFOA for 14 days (Loveless et al., 2006). The lowest dose at which the hepatic oxidation was observed in rats was 0.64 mg/kg bw per day after 4 weeks of exposure (Perkins et al., 2004), with the effect regularly occurring at higher doses (at ≥1 mg/kg bw per day for 14 days [Loveless et al., 2006], ≥1.94 mg/kg bw per day for ≥4 weeks [Perkins et al., 2004], ≥2 mg/kg bw per day for 14 days [Liu et al., 1996], 7.5 mg/kg bw per day for 23 weeks [Abdellatif et al., 1990], 13.6 mg/kg bw per day for ≥1 month [Biegel et al., 2011], and approximately 20 mg/kg bw per day for ≤28 days [Elcombe et al., 2010]). In mice, hepatic palmitoyl CoA oxidation was observed at lower PFOA doses than rats, with the effect measured at ≥0.3 mg/kg bw per day after 14 days of exposure (Loveless et al., 2006) and higher doses in other studies (Yang et al., 2002; Minata et al., 2010; Nakagawa et al., 2012); moreover, increased expression of PPAR-related genes was observed in wild-type mice, but not humanized PPAR or PPAR-null mice, exposed for 2 weeks to ≥0.1 mg/kg bw per day (Nakamura et al., 2009). In rats exposed to 13.6 mg/kg bw per day of PFOA for 2 years, no increase in palmitoyl CoA oxidation was observed in Leydig cells (Biegel et al., 2011); however, the same study did not measure an increase in the effect in a model peroxisome proliferator (Wyeth-14,643 [WY]).

9.3.2.2 Key event 2 – altered cell growth

No studies of markers of altered cell growth pathways could be found.

9.3.2.3 Key event 3 – cell proliferation

An absence of hepatocyte proliferation was noted in rats exposed to 13.6 mg/kg bw per day for 1–24 months, when it was observed in positive controls (i.e., WY-exposed mice) at the same time periods (Biegel et al., 2001), but the effect was observed in rats exposed to approximately 20 mg/kg bw per day for 2–29 days (Elcombe et al., 2010). A dose-related increase in labelling index was observed in both wild-type and PPAR-null mice exposed for 7 days, with significance reached at 10 mg/kg bw per day (but not 1 or 3 mg/kg bw per day) in both strains (Wolf et al., 2008).

Cell proliferation was measured in pancreatic acinar cells, but not Leydig cells, in rats exposed to 13.6 mg/kg bw per day for 2 years (Biegel et al., 2011).

9.3.2.4 Assessment of Bradford-Hill considerations

Biological concordance — PPAR activation, leading to increased replication in hepatocytes and increased hepatic tumours, is a well-recognized MOA. Increases were observed in testicular (Leydig cell), pancreatic, and hepatocellular tumours in rats (Biegel et al., 2011), which is a recognized tumour triad for the peroxisome proliferation MOA (Corton et al., 2014); pancreatic acinar cell proliferation and hyperplasia were also observed to be increased in rats (Biegel et al., 2011). However, inconsistencies in this observation arise as the tumour triad was not observed at a similar dose in another two-year study in rats (Butenhoff et al., 2012b). Studies of peroxisome proliferation and tumour development in these cells in mice (which are more sensitive to peroxisome proliferation than rats) would potentially provide more useful information for the MOA analysis.

Essentiality of key event — Studies of PPAR-null mice (Yang et al., 2002; Abbott et al., 2007; Wolf et al., 2008; Nakagawa et al., 2012) provided information to evaluate the essentiality of the key events for hepatic effects; no studies of PPAR-null rats exposed to PFOA could be found. In the Abbott et al. (2007) study, PPAR-null mice had decreased sensitivity to liver weight effects, which lends some support to the MOA for this adverse outcome; however, liver weight effects still occur (albeit at higher doses) in PPAR-null mice, and hepatomegaly is induced to the same extent in wild-type and PPAR-null mice in other studies (Yang et al., 2002; Wolf et al., 2008; Nakagawa et al., 2012). Similarly, Filgo et al. (2015) observed significant increases and significant trends in the development of neoplastic and non-neoplastic hepatic lesions in the female offspring from PPARα-null mice. The increase hepatocyte proliferation (as measured by increase in labelling index) was also similar between wild-type and PPAR-null mice (Wolf et al., 2008). Moreover, despite an absence of increased expression of PPAR-related genes in PPAR-null and humanized PPAR mice, increases in liver weight were similar among these strains and wild-type mice (i.e., mice with increased PPAR expression) (Nakagawa et al., 2012). Despite these quantitative similarities between strains for non-cancer liver effects, qualitative differences were observed—including differences in microscopic appearance and ultrastructure of hepatic cells (Wolf et al., 2008; Minata et al., 2010). Further studies that expose PPAR-null mice at lower doses and investigate other adverse outcomes, as well as studies of PPAR-null rats, would help to better evaluate the MOA.

Temporal and dose–response concordance — Some dose–response concordance was observed for the MOA, as PPAR activation precedes hepatocyte proliferation in rats; however, hepatocyte proliferation was absent at tumour-relevant doses in rats (Biegel et al., 2001), and occurred only at higher levels than those resulting in hepatocellular hypertrophy and increased

liver weight (Elcombe et al., 2010). The sole study of hepatocyte proliferation in mice indicates its occurrence only at doses above those at which increases in hypertrophy and liver weight were observed (Wolf et al., 2008). Moreover, the absence of data on altered cell growth pathways precludes the evaluation of whether this key event is triggered by PPAR activation and is a precursor for hepatocyte proliferation.

The first key event (PPAR activation) does not appear to precede the adverse hepatic outcomes in rats. Both increased liver weight and hepatocellular hypertrophy were observed either at or below doses where an absence of PPAR activation was observed.

Consistency (across species, strains, organs, and test systems) — PPAR activation begins at lower doses in mice than rats and monkeys, as is expected, based on knowledge of PPAR biology (Corton et al., 2014). However, in monkeys, PPAR activation is not consistent, is not accompanied by cell proliferation, and occurs only at higher doses than adverse liver effects.

Analogous compounds — The tumour triad observed in male rats, along with an increase in serum estradiol, was observed similarly in both PFOA and a model peroxisome proliferator, WY. However, hepatic effect in PFOS-exposed rats appears to occur in absence of peroxisome proliferation, and the tumour triad was not observed in PFOS-exposed rats.

Some evidence in rats and mice supports the occurrence of peroxisome proliferation as a mode of action for hepatocellular hypertrophy. The characteristic tumour triad of peroxisome proliferators (cancers of the testes, pancreas, and liver) was observed in rats, and the doses at which hepatocellular tumours are observed are higher than earlier key events in the peroxisome proliferation MOA. However, increases in liver weight and hepatocellular hypertrophy appear to occur at lower doses than PPAR activation in rats; therefore, although PPAR activation does occur in rats, it does not appear to be the sole driver for these two effects. Studies of PPAR-null mice indicate that peroxisome proliferation might play a role in observed hepatocellular hypertrophy and liver weight increases, but despite qualitative (i.e., appearance) differences between the strains, the quantitative similarities in the changes in PPAR-null vs. wild type mice indicate that other MOAs play a large role in the development of the effects. Because the peroxisome proliferation MOA does not seem to be the sole MOA involved, human relevance of PFOA-induced non-carcinogenic hepatic effects cannot be ruled out. Conversely, a detailed MOA analysis has concluded that the weight of evidence for the peroxisome proliferation MOA for PFOA-induced liver tumours was strong. The relevance of these tumours to humans is limited, as PPARα activation by PFOA is weaker in humans than in rats. Moreover, PPARα activation by various compounds in does not appear to result in hepatocellular proliferation and tumours (Corton et al., 2012; Klaunig et al., 2012).

9.3.3 Sex hormone disruption

Sex hormone disruption is a potential MOA that should be considered for mammary gland development delays in mice, obesity in prenatally exposed mice, and Leydig cell tumours in rats. Insufficient data exist to be able to perform a quantitative analysis of sex hormone disruption; however, a few different observations that could be relevant to the sex hormone MOA have been reported, including the muting of uterine effects when PFOA was co-administered with estradiol (Dixon et al., 2012), an enhancement of the effects of 17β-estradiol in a variety of *in vitro* assays, but with an absence of direct estrogenic activity (Sonthithai et al., ~~2015~~2016), the reversal of mammary gland development delays with the supplementation of physiological levels of estradiol or progesterone (Zhao et al., 2012), an increase in serum estradiol concentrations in male rats exposed for 1–12 months (Biegel et al., 2001), changes in estradiol genesis (decrease at lower doses and increase at higher doses) in an *in vitro* steroidogenesis assay (Rosenmai et al., 2013), an absence of PFOA binding to or activating human estradiol receptors *in vitro* (Ishibashi et al.,

2007), and decreases in cholesterol levels, which might disrupt testosterone synthesis (Li et al., 2011). If more in-depth studies on the effect of PFOA on sex hormone disruption are performed, this potential MOA could be further investigated.

9.3.4 Other MOAs

Insufficient data exist to allow for the assessment of other potential MOAs considered in the MOA analysis. Some data—particularly in regards to PPAR activation/peroxisome proliferation—exist for other endpoints that were not included in the MOA analysis (i.e., effects that were observed only at higher PFOA exposure levels).

9.4 Additivity

The application of an additive approach for PFAS was considered using the World Health Organization /International Programme on Chemical Safety (WHO/IPCS) framework for risk assessment of combined exposure to multiple chemicals (Meek et al., 2011). This section focuses on the evaluation of additivity for PFOS and PFOA, which are the predominant PFAS detected in Canadian water samples.

Considerations relevant to the additivity analysis are addressed within four over-arching questions (Meek et al., 2011):

1. What is the nature of exposure?
2. Is co-exposure likely, taking into account the context?
3. Is there a likelihood of co-exposure within a relevant time-frame?
4. What is the rationale for considering compounds in an assessment group?

Additionally, evidence demonstrating the toxic effects of mixture exposure can be used as supporting information in an additivity analysis (Meek et al., 2011). Based on analysis of these considerations, the application of an additive approach for PFOS and PFOA in drinking water is the most appropriate method for the protection of human health. The results are summarized below.

What is the nature of exposure?

PFOS and PFOA are highly fluorinated synthetic organic chemicals that consist of a straight-chain hydrocarbon backbone with a carbon chain length of eight. Structurally, they differ only in their terminal functional groups (i.e., PFOS has a sulfonic acid moiety and PFOA has a single carboxylate moiety). This class of chemicals has numerous uses, including stain/water resistant coatings and in fire-fighting foams, which is of particular concern for water (see section 4.1). Their elevated water solubility and the negligible volatility of ionized species suggest that PFOS and PFOA will partition primarily to the aquatic environment, supporting their occurrence in water. Additionally, they are persistent compounds that do not undergo biodegradation and are thus stable in water. Many studies have confirmed the presence of PFAS in drinking water sources and tap water (see Sections 4.1, 5.1, and 5.1.1).

Is co-exposure likely, taking into account the context?

Yes. Routine monitoring programmes to test drinking water for PFOS and PFOA have not been implemented; however, available studies have reported co-exposure in Canadian drinking water sources and tap water (see Section 5.1.1). As discussed in Section 5.1.1, PFOS and PFOA are the predominant PFAS detected in Canadian water samples.

Is there a likelihood of co-exposure within a relevant time-frame?

Yes. Co-exposure to PFOS and PFOA is likely – through ingestion of contaminated food and water, inhalation of dust, and use of consumer products. PFOS and PFOA are persistent compounds that do not undergo biodegradation, thus they compartmentalize into similar media, making the temporal aspects of external co-exposure likely. Additionally, they do not undergo biotransformation and have relatively long half-lives in humans (i.e., 3.9-6.9 years for PFOS and 2.5-4.4 years for PFOA (Olsen et al., 2007; Brede et al., 2010; Bartell et al., 2010)), thus their toxicokinetics make internal co-exposure likely. Additionally, biomonitoring data indicate co-occurrence of PFOS and PFOA in human serum in Canadian studies, as well as International studies.

What is the rationale for considering compounds in an assessment group?

Grouping of PFOS and PFOA is appropriate at the level of structure, application/use (as described above), and toxicology. The human health and toxicological effects, and modes/mechanisms of action induced by PFOS and PFOA are discussed below.

Human health and/or toxicological effects are similar. The available information on PFOS and PFOA toxicokinetics indicates a high degree of similarity (reviewed in section 8 of both documents). Oral uptake of PFOS and PFOA results in rapid and almost complete resorption (>90%) within 24 hours in male rats (Gibson and Johnson, 1979). PFOS and PFOA are weakly lipophilic, very water soluble, and bind preferentially to proteins, such as serum albumin. However, differences in their tissue distribution have been reported - whereas PFOA is mainly present in the serum/plasma (Johnson and Ober, 1999; Han et al., 2003; Kudo et al., 2007), PFOS is primarily distributed to the liver (Beskin et al., 2009; De Silva et al., 2009). Both PFOS and PFOA are highly resistant to biotransformation and are not metabolized in mammals, which accounts for their relatively long half-lives. Additionally, because of their resistance to biotransformation, the toxicity of the parent compound and not that of a metabolite is of concern for both PFOS and PFOA.

As reviewed in section 9.1 of this document and the PFOS document, studies in humans (including the general population and workers) have demonstrated similarities in health outcomes associated with elevated levels of serum PFOS and PFOA, including liver effects, immune suppression, lipidemia, thyroid effects, kidney effects, cancer, and some reproductive and developmental toxicities (i.e., reduced fecundity, reduced birth weight, changes in the onset of puberty). However, elevated serum PFOS is additionally associated with delays in developmental milestones, thyroid hormone levels, and immune system effects in offspring, while elevated serum PFOA is associated with decreased duration of breastfeeding.

Similarities and dissimilarities in health outcomes in experimental animals have also been demonstrated. Studies in experimental animals have demonstrated similarities in adverse effects of treatment with PFOS and PFOA on the liver (including increased liver weight, hepatocellular hypertrophy, changes in serum enzymes), immune system effects, serum lipids, thyroid effects, neurotoxicity, reduced body weight, and tumor formation (i.e., liver), and the induction of reproductive and developmental toxicities (including neurobehaviour, liver weight changes and histopathology, reduced survival/viability of pups, and increased mortality in pups). Additionally, neither PFOS nor PFOA are considered to be direct-acting genotoxic chemicals. However, discordant results are observed in some outcomes following treatment with PFOS and PFOA. For example, chronic administration of PFOA causes hepatocellular adenomas and Leydig cell adenomas in rats; yet while an increase in the incidence of hepatocellular adenomas is observed following chronic administration of PFOS, no significant dose-responsive changes in the

incidence of Leydig cell tumours were found. Furthermore, the most sensitive developmental effects observed following exposures to PFOA (i.e., delayed mammary gland development in the offspring of mice, uterine effects in immature female mice, and obesity in female offspring in mice at adulthood) are not observed following exposure to PFOS. Collectively, although some toxic effects appear to be compound-specific, there is a large degree of concordance in adverse toxicological effects induced by PFOS and PFOA in experimental animals.

There is similarity in their modes of action. The modes of action for PFOS and PFOA are not fully understood and it is likely that multiple pathways are involved in their toxic effects. The largest body of evidence points to PPARα ligand-dependent activation by PFOS and PFOA as a key initiating event in the development of liver toxicities (described in section 9.3 of each document). However, although some toxicity by PFOS and PFOA is attributable to PPARα activation, PPARα-independence has also been proposed. For example, PFOS-induced hypertrophy and lipid vacuolization occurred in the absence of peroxisome proliferation or increase in palmitoyl-CoA-oxidase activity in monkeys (Seacat et al., 2002) and transmission electron microscopy of liver sections with hepatocellular hypertrophy and hepatic inflammation observed in pups exposed to PFOA *in utero* revealed cellular damage and mitochondrial abnormalities with no evidence of peroxisome proliferation (Quist et al., 2015). Additionally, PFOS and PFOA have been shown to alter fatty acid metabolism, lipid transport, cholesterol synthesis, proteasomal activation and proteolysis, cell communication, and inflammation processes in experimental animals. Thus, although the mode of action for PFOS and PFOA-induced toxicities has yet to be elucidated, the similarity in the mechanisms activated by each compound is sufficient to suggest similar modes of action are at play.

In addition to the evaluation of data for additivity using the WHO/IPCS framework (Meek et al., 2011), evidence demonstrating the toxic effects of combined exposures were evaluated to strengthen support for the use of an additive approach for PFOS and PFOA. Only one *in vivo* mammalian study was found. Tatum et al. (2010) reported in a conference proceeding that a binary mixture of PFOS and PFOA (6 mg/kg bw per day and 4 mg/kg bw per day, respectively) behaves additively by dose addition (also known as concentration addition) on reproductive and developmental toxicity endpoints (i.e., maternal weight gain, pup body weight, maternal and neonatal liver weight) in CD-1 mice exposed to the mixture and to PFOS and PFOA individually by oral gavage on gestational days 1-17. The authors additionally reported less than additive behaviour for neonatal mortality (i.e., the mixture of PFOS and PFOA caused less neonatal mortality compared to PFOS and PFOA alone).

This finding is in general agreement with *in vitro* studies on the combined action of PFOS and PFOA (and other PFAS). In studies of binary mixtures of PFOS and PFOA, additivity has been observed at the level of apoptotic potential in mouse HEPG2 liver cells (Hu and Hu, 2009), mortality in zebrafish embyros (Ding et al., 2013), and PPARα activation in Cos-1 cells (Wolf et al., 2014). The additive effects reported by Wolf et al. (2014) and Ding et al. (2013) were observed at low exposure concentrations but deviations from additivity were observed at higher doses. Similarly, deviations from additivity showing less than additive effects (i.e., the mixture response is less than would be expected under conditions of additivity) have been observed at the level of PPARα activation in Cos-1 cells (Carr et al., 2013) and toxicity in cyanobacteria (Rodeo-Palomares et al., 2012) in studies of binary mixtures of PFOS and PFOA, as well as on cellular viability in human liver HL-7702 cells exposed to a simple mixture of 11 PFAS, including PFOS and PFOA. Greater than additive effects on cellular viability have also been reported in human liver HL-7702 cells (Hu et al., 2014) and in rare minnow hepatocytes (Wei et al., 2009) in studies of binary mixtures of PFOS and PFOA, and in human U2OS bone osteosarcoma cells exposed to a simple mixture of five PFAS, including PFOS and PFOA (Wilson et al., 2016). Wilson et al.

(2016) further investigated glucocorticoid receptor transactivation but the mixture responses were too weak to report, as were the estrogen receptor and androgen receptor activities in human MVLN breast cancer cells and hamster CHO-K1 ovary cells, respectively, exposed to a mixture of seven PFAS including PFOS and PFOA (Kjeldsen and Bonefeld-Jorgensen, 2013). Gene expression changes measured following exposure to PFOS and PFOA alone or in a binary mixture demonstrated that mechanisms activated following exposure to mixtures and individual chemicals are complex and can differ depending on the treatment (Wei et al., 2009). The differences reported among studies are largely attributable to the biological model, the concentrations used, and the particular composition/complexity of the mixtures.

The absence of *in vivo* studies investigating the additivity of PFAS was identified as a major data gap. However, based on the evaluation of the exposure and toxicological data for PFOS and PFOA in consideration of the WHO / IPCS framework for the risk assessment of combined exposures (Meek et al., 2011), an additive approach for PFOS and PFOA is the most appropriate in the interest of human health protection.

10.0 Classification and assessment

PFOA and its salts have been classified as possibly carcinogenic to humans (Group 2B) by IARC, based on limited epidemiological evidence demonstrating associations between PFOA and testicular and renal cancers, and on limited evidence in experimental animals (Benbrahim-Tallaa et al., 2014). When evaluated under the *Canadian Environmental Protection Act*, PFOA, its salts and its precursors met the criteria for persistence and immediate or long-term harmful effect on the environment or its biological diversity, but were not deemed to be bioaccumulative, nor entering the environment under conditions that constitute or may constitute a danger in Canada to human life or health (Environment Canada and Health Canada, 2012).

The benchmark dose (BMD) approach was used wherever possible to calculate potential PODs, because it is derived on the basis of data from the entire dose-response curve for the critical effect rather than from the single dose group at the NOAEL (IPCS, 1994). A lower confidence limit of the benchmark dose (BMDL) has been suggested as an appropriate replacement of the NOAEL (Crump, 1984). More specifically, a suitable BMDL is defined as a lower 95% confidence limit estimate of dose corresponding to a 1–10% level of risk over background levels. Definition of the BMD as a lower confidence limit accounts for the statistical power and quality of the data (IPCS, 1994). Benchmark dose values representing a 10% increase in adverse effect over background rates (BMD_{10}) and their lower 95% confidence limits ($BMDL_{10}$) were calculated using the U.S. EPA Benchmark Dose Software (BMDS Version 2.6.0.86; U.S. EPA, 2015).

Large pharmacokinetic differences exist between animals and humans, with lower clearance (i.e., higher half-life values) in humans than in rats, mice, and monkeys. These differences result in higher target tissue doses in humans when exposed to the same external doses as animals. Default approaches for interspecies extrapolation (e.g., interspecies uncertainty factor of 10, allometric scaling) are therefore not considered to be sufficiently protective of humans. As described in Section 8.6, AK_{UF} values (i.e., the component of the CSAF reflecting interspecies toxicokinetic differences) were calculated with a PBPK model to address pharmacokinetic differences between animals and humans. As different AK_{UF} values were calculated for various doses, the values can also address non-linearity in pharmacokinetics. Weaknesses still exist with this approach, as outlined in detail in Section 8.6, including the use of the steady-state plasma concentration as a dose metric, rather than selecting organ-based values or exploring whether other dose metrics (e.g., peak concentrations) are more appropriate. However, despite the

weaknesses, the approach was determined to be the best of the available options. This approach was selected over the use of serum concentrations as points-of-departure (PODs), because human PBPK models were determined to not be sufficiently robust for precise estimates of human exposure levels corresponding to serum-based PODs.

10.1 Cancer risk assessment

Epidemiological evidence has shown an association between exposure to PFOA and increased risk of incidence of testicular and kidney cancers (see Section 9.1.3). The associations were observed in large-scale epidemiology studies in a community with elevated PFOA concentrations in water (C8 project). However, causality and a point-of-departure cannot be determined from these studies due to the lack of consistency between studies (no association found in some prospective studies in Denmark and the U.S.). Limitations were also observed in the studies that found a positive association, including the risk of residual confounding (because not all covariates and exposures to other contaminants were included in the model), the small case numbers, the uncertainties in exposure characterization (rough estimates based on residency within a certain area), and the high number of outcomes included in the models, increasing the likelihood of chance findings.

Two chronic duration studies identified testicular Leydig cell adenomas in male Crl:CD BR (CD) rats exposed to PFOA for 2 years. The first study observed these adenomas at 13.6 mg/kg bw per day (the only dose tested in the study; Biegel et al., 2001); the other study observed a dose-related increase in incidence of adenomas, with significance achieved at the high dose (14.2 mg/kg bw per day; 3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b). The Leydig cell adenomas were accompanied by hyperplasia of Leydig cells and proliferation and adenomas of pancreatic acinar cells in the Biegel et al. (2001) study. Dose-dependent increases in mammary fibroadenomas was observed in female rats in the Butenhoff et al. (2012b) study, but were not considered proliferative lesions using current diagnostic criteria.

Although the mode of action for PFOA-induced tumours has not yet been elucidated, the weight of evidence more strongly suggests that PFOA is a non-mutagenic compound (see Sections 9.2.4 and 9.3). For this reason, the tolerable daily intake (TDI) approach is the most appropriate method for deriving a health-based value (HBV) for cancer.

The selected key study for the cancer risk assessment is Butenhoff et al. (2012b), as it is the only chronic study with more than one dose level. Incidence of Leydig cell tumours was 0, 2, and 7, in rats exposed to 0, 1.3, and 14.2 mg/kg bw per day, respectively. As significance was only observed at the high dose, the NOAEL and LOAEL for Leydig cell tumours in this study are 1.3 and 14.2 mg/kg bw per day, respectively. The use of benchmark dose modelling is not typically recommended for studies containing only two dose groups (U.S. EPA, 2012b); however, the approach was performed for comparison with the NOAEL. Three models (Log Logistic, Log Probit, and Multistage) had the best fit (all models had the lowest Akaike information criterion [AIC] among all considered models). The $BMDL_{10}$ values for these three models ranged from 1.06 to 1.26 mg/kg bw per day, and were therefore similar to the NOAEL of 1.3 mg/kg bw per day, which is used as the POD for the analysis.

To reflect the large interspecies differences in pharmacokinetics, the human-equivalent point-of-departure (POD_{HEQ}) can be calculated by dividing the ~~$BMDL_{10}$~~NOAEL by the AK_{UF}, as follows:

$$POD_{HEQ} = \frac{1.3 \text{ mg/kg bw per day}}{17}$$

$$= \quad 0.076 \text{ mg/kg bw per day}$$

where:

- 1.3 mg/kg bw per day is the ~~$BMDL_{10}$~~NOAEL for Leydig cell tumours in male rats (Butenhoff et al., 2012b); and
- 17 is the dose-specific AK_{UF} for rats in the 1 mg/kg bw per day range (as described in Section 8.6.2).

Using the calculated POD_{HEQ}, the cancer TDI was calculated as follows:

$$\text{TDI} = \frac{0.076 \text{ mg/kg bw per day}}{25}$$

$$= \quad 0.003 \text{ mg/kg bw per day}$$

where:

- 0.076 mg/kg bw per day is the POD_{HEQ} associated with the NOAEL for Leydig cell tumours in male rats (Butenhoff et al., 2012b); and
- 25 is the composite uncertainty factor, as described below.

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (×2.5) and intraspecies uncertainty factor (×10). A value of 2.5 is used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. A default value of 10 was applied for the intraspecies uncertainty factor. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOA excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. Average half-life values calculated from longitudinal data for different populations previously exposed to PFOA were similar (averages for each population ranged from 2.3–3.8 years; Olsen et al., 2007; Bartell et al., 2010; Brede et al., 2010); however, studies providing ranges indicated that there was approximately a 10-fold difference between the lowest and highest estimates of half-life. If further studies of PFOA consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed.

Using this TDI, the HBV for drinking water can be calculated as follows:

$$\text{HBV} = \frac{0.003 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= \quad 0.028 \text{ mg/L}$$

$$\approx \quad 0.03 \text{ mg/L (30 µg/L)}$$

where:

- 0.003 mg/kg bw per day is the TDI derived above;

- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7).

10.2 Non-cancer risk assessment

Although epidemiological evidence has shown an association between the exposure to PFOA and multiple health outcomes, such as dysfunctions of the immunological system and alterations in birth weight and lipid levels (see Section 9.1.3), a POD cannot be derived from these studies due to limitations, including in terms of study design, bias and confounders.

The lowest LOAELs for PFOA were for reproductive and developmental effects in mice, with effects observed at levels as low as 0.001–0.01 mg/kg bw per day for delayed mammary gland development (Macon et al., 2011; White et al., 2011; Tucker et al., 2015), at 0.01 mg/kg bw per day for estrogenic effects in the uterus (Dixon et al., 2012) and weight changes in adult females exposed prenatally (Hines et al., 2009), and at 0.6 mg/kg bw per day for delayed eye opening (Abbott et al., 2007). These endpoints were not used as the basis of the risk assessment for several reasons. Estrogenic effects in the uterus (endometrial edema, hyperplasia of endometrial mucosa and glands, hypertrophy and hyperplasia of myometrium, and increase in weight in the uterotrophic assay) were excluded from the assessment because they did not occur in a dose–related manner—significant increases were observed in mice exposed only to 0.01 mg/kg bw per day, and not at higher levels (0.1 or 1 mg/kg bw per day; Dixon et al., 2012). A non-monotonic response was also observed for body weight changes in adult female mice exposed *in utero*, with increased body weight at 0.01–0.3 mg/kg bw per day (not 1 mg/kg bw per day) and in serum leptin and insulin at 0.01 and 0.1 mg/kg bw per day (not 0.3 or 1 mg/kg bw per day; Hines et al., 2009). Moreover, slight changes (although significant) in mammary gland development and bodyweight are indicative of treatment-related changes, but not necessarily adversity—there was no evidence of insufficient milk intake or inability to thrive in pups of dams with MGD changes, and weight changes were low (measured at <10%). The observation of delayed eye opening at ≥0.6 mg/kg bw per day in mice (Abbott et al., 2007) was not corroborated in other studies, as the effect had a LOAEL of 3 mg/kg bw per day (NOAEL=1 mg/kg bw per day; Lau et al., 2006), and was not observed at 3 mg/kg bw per day in another study (Albrecht et al., 2013). Mammary gland development effects might also be affected by strain sensitivity—the majority of the low-dose effects have only been observed in CD-1 mice exposed *in utero*, and other strains were typically only studied at higher doses and in peripubertal mice. A recent *in utero* study comparing MGD in both CD-1 and C57Bl/6 mice at doses of 0.01–1 mg/kg bw per day potentially provided support for low dose effects in a second strain of mice, albeit at slightly higher doses (LOAEL = 0.01 vs. 0.3 mg/kg bw per day in CD-1 and C57Bl/6 mice, respectively); however, a small sample size at low doses for C57Bl/6 mice (as few as two pups) might have precluded the observation of significant changes at similar doses to CD-1 mice. Finally, species sensitivity might be occurring for these effects, as one- and two-generation studies in rats identified similar effects only at much higher doses, if at all; the NOAELs for body weight changes and delayed sexual maturation in pups were around 3 mg/kg bw per day (Staples et al., 1984; Butenhoff et al., 2004b) and 10 mg/kg bw per day (Butenhoff et al., 2004b), respectively, and no effects on lactation index were observed up to 30 mg/kg bw per day (Butenhoff et al.,

2004b). Further support for the potential for species sensitivity is provided in studies using PPARα-knockout mice, which were less sensitive to body weight changes and eye opening (Abbott et al., 2007) and MGD delays (Zhao et al., 2012~~);~~). PPAR activation is more sensitive in mice than in other species, including rats and humans (Corton et al., ~~2014).~~2014); note that this study is specific to the mode of action of liver tumours and its conclusions are not necessarily applicable to other effects. Although the data from the studies described above provide indication of some reproductive and developmental effects at low doses, the data are not currently considered to be an appropriate basis for quantitative risk assessment; however, if further studies demonstrate consistency of these effects in other species or their relevance to humans, the endpoint could become a more appropriate basis for the PFOA evaluation.

Few epidemiological studies have investigated the developmental effects described above, which limits the ability to conclude on the relevance of these effects in humans. The human observations related to weight gain in adulthood after developmental PFOA exposures were increased odds of women being overweight and having increased biomarkers of adiposity at 20 years of age after *in utero* exposures (with maternal serum levels of 5.8 ng/mL, as compared with levels of 2.3 ng/mL) (Halldorsson et al., 2012). Estrogenic observations were limited to delayed puberty in girls, and slight associations between PFOA concentration and shorter duration of breastfeeding. As previously discussed, care should be taken before concluding on health effects based on these epidemiological studies. The nature of the observed associations between PFOA exposure and the developmental outcomes need to be investigated further because of the lack of consistency across studies, the non-specificity of the outcomes, the misunderstanding of the mechanism of action, the borderline significance and lack of strength and dose-response of many results, and the presence of various limitations inherent to the study design, such as the possibility of residual confounding, biases due to errors in outcome measurements, and chance.

Hepatic effects were observed at slightly higher levels than reproductive effects, but observations of changes were still made at PFOA doses of ≤0.3 mg/kg bw per day. Increased relative liver weight was observed at ≥0.1 mg/kg bw per day in prenatally-exposed mouse pups (Abbott et al., 2007; Macon et al., 2011) and at ≥0.15 mg/kg bw per day in adult mice (Kennedy, 1987; Loveless et al., 2006, 2008). Dose-related increases in incidence and severity of hepatocellular hypertrophy were observed at ≥0.3 mg/kg bw per day in rats (Perkins et al., 2004; Loveless et al., 2008) and mice (Loveless et al., 2008) exposed subchronically to PFOA. Although increases in hepatocellular hypertrophy and liver weight were observed at slightly lower levels in other studies, Perkins et al. (2004) was selected as a key study that was representative of the database for the endpoint. Hepatocellular hypertrophy was observed in male rats in the Perkins study at ≥0.64 mg/kg bw per day, which is on the same order of magnitude as the studies demonstrating LOAELs of 0.1–0.3 mg/kg bw per day. A major advantage presented by the Perkins study is that a NOAEL was observed (0.06 mg/kg bw per day), whereas the LOAELs in the majority of other low dose studies were the lowest administered doses. A similar NOAEL of 0.05 mg/kg bw per day can be obtained from Kennedy et al. (1987) when Health Canada (1994) assumptions for food intake and bodyweight in rats (Health Canada, 1994) are used, but the authors did not provide actual values of measured doses. A further advantage of the Perkins study over the other low-dose studies is that the study duration was longer, with exposure durations of up to 13 weeks; moreover, in addition to *ad libitum* controls, the study provided pair-fed controls to ensure that effects did not result from food consumption quantities. Finally, PPAR-α activity was measured in the Perkins study, and was only increased at ≥1.94 mg/kg bw per day; because this suggests that hepatocellular hypertrophy was not resulting from peroxisome proliferation, human relevance of this endpoint cannot be excluded. A NOAEL of 0.06 mg/kg bw per day is also supported by the most conservative NOAEL for hepatic biochemical effects, which was

estimated at 0.055 mg/kg bw per day in male rats demonstrating increased alkaline phosphatase levels in conjunction with increased liver weight (Kennedy et al., 1986), using default assumptions for bodyweight and inhalation rates (Health Canada, 1994), and linearly scaling from periodic to continuous exposure. The NOAEL is also approximately 10-fold lower than the NOAEL and 30-fold lower than the LOAEL for hepatic necrosis (0.56 and 1.72 mg/kg bw per day, respectively) observed in rats exposed for 90 days (Goldenthal et al., 1978a).

Although increased liver weight and hepatocellular hypertrophy can sometimes be considered effects that are adaptive rather than adverse in their own right, evidence of other histological effects in the liver at higher concentrations provide an indication of their progression upon continued exposure (ECETOC, 2002; Hall et al., 2012). An adverse histological effect (portal mononuclear cell infiltrate) was observed in livers of male rats at the same dose where significant increases in hepatocellular hypertrophy were observed (14.2 mg/kg bw per day of PFOA for 2 years; Butenhoff et al., 2012b). Although this dose is much higher than the lowest points of departure for increased liver weight and hepatocellular hypertrophy observed in subchronic studies, the latter effects are proposed as critical effects for this assessment, as they might be sensitive indicators of the potential for the progression of adverse histological effects. Additional histological effects observed in rats in studies of shorter duration included necrosis at ≥1.72 mg/kg bw per day (Goldenthal et al., 1978a; Loveless et al., 2008), cytoplasmic vacuolation at ≥5 mg/kg bw per day (Cui et al., 2009), and fatty change, angiectasis, congestion, and acidophil lesion at 20 mg/kg bw per day (Cui et al., 2009). Therefore, increased liver weight and hepatocellular hypertrophy are considered in the dose–response assessment—despite their potential to be adaptive, rather than adverse, effects—as a means of preventing the more serious histological effects observed in other studies or at higher doses. The use of conservative endpoints for liver effects is also somewhat supported by epidemiology studies, in which some associations between PFOA exposure and increases in liver enzymes (including AST, ALT, and GGT) were observed; however, the associations between serum PFOA levels and liver effects cannot be used to draw definitive conclusions in humans because of limitations. These limitations include the lack of consistency and specificity of the outcomes, the weakness of the effects, and the study designs presenting many limitations (e.g., do not allow for verification of temporality). Serum levels at which these effects were observed in humans were on the order of 1,000 ng/mL in occupational studies and <10 ng/mL in environmental studies, which were lower than serum concentrations associated with the NOAEL and LOAEL for the 13-week Perkins study (7,100 and 41,000 ng/mL, respectively).

Changes in serum lipid levels were also observed around the levels at which hepatic effects occur. The lowest dose at which serum lipid changes were observed was 0.3 mg/kg bw per day in rats exposed for 14 days (decreased total cholesterol; Loveless et al., 2006) or 29 days (decreased total and HDL cholesterol; Loveless et al., 2008). Typical observed changes were decreases in total cholesterol, HDL, and triglycerides. These effects are important for consideration during the assessment of PFOA risks, as epidemiology studies generally demonstrated positive associations between PFOA and serum cholesterol levels. Inconsistencies in effect were observed not only in between the two databases, but also within both the toxicology (see Section 9.2.2.2) and epidemiology (see Section 9.1.2.2) databases. Clear dose–response relationships also tended to be absent in the animal studies. Due to these weaknesses, quantitative assessments were not performed for serum lipid effects; however, based on the present database, a TDI based on liver effects is assumed to be sufficiently protective of lipid changes.

Benchmark doses (BMD_{10}) and their 95% lower confidence limits ($BMDL_{10}$) were calculated for hepatocellular hypertrophy for male rats (Perkins et al., 2004). The analysis was performed using the U.S. EPA's BMDS (version 2.6.0.1) and BMD models were selected based

on visual inspection of the curve, goodness of fit p-value ≥0.1, and BMD/BMDL ratios <10. Eight models were selected according to these criteria. The logprobit model provided the best fit (i.e., lowest Akaike information criterion). Estimated BMD values were BMD_{10} of 0.13 mg/kg bw per day and $BMDL_{10}$ of 0.05 mg/kg bw per day.

To reflect the large interspecies differences in pharmacokinetics, a human-equivalent point-of-departure (POD_{HEQ}) was calculated for hepatocellular hypertrophy as follows:

$$POD_{HEQ} = \frac{0.0605 \text{ mg/kg bw per day}}{96}$$

$$= 0.000625 \text{ mg/kg bw per day}$$

where:

- 0.0605 mg/kg bw per day is the ~~NOAEL~~$BMDL_{10}$ for hepatocellular hypertrophy in rats from Perkins et al. (2004), which was selected to represent the hepatocellular hypertrophy and liver weight increase database; and
- 96 is the dose-specific AK_{UF} for rats in the 0.01 mg/kg bw per day range (as described in Section 8.6.2).

Using the calculated POD_{HEQ}, the non-cancer TDI was calculated as follows:

$$TDI = \frac{0.000625000521 \text{ mg/kg bw per day}}{25}$$

$$= 0.000025000021 \text{ mg/kg bw per day}$$

where:

- 0.000625000521 mg/kg bw per day is the POD_{HEQ} calculated for hepatocellular hypertrophy in rats, as described above; and
- 25 is the composite uncertainty factor, as described below.

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (×2.5) and intraspecies uncertainty factor (×10). An interspecies uncertainty factor of 2.5 was used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. Likewise, a default value of 10 was applied for the intraspecies UF. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOA excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. Average half-life values calculated from longitudinal data for different populations previously exposed to PFOA were similar (averages for each population ranged from 2.3–3.8 years; Olsen et al., 2007; Bartell et al., 2010; Brede et al., 2010); however, studies providing ranges indicated that there was approximately a 10-fold difference between the lowest and highest estimates of half-life. If further studies of PFOA consistently indicate a 10-fold difference in pharmacokinetics

within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed. No uncertainty factor was used for subchronic-to-chronic extrapolation, as liver effects were investigated in a chronic study (Butenhoff et al., 2012b), and increasing duration of exposure did not appear to worsen the effects in the key study (Perkins et al., 2004).

Using this TDI, the HBV for drinking water can be calculated as follows:

$$\text{HBV} = \frac{0.\cancel{000025}000021 \times 70\ \text{kg}}{\times\ 0.2 \over 1.5\ \text{L/day}}$$

$$= 0.\cancel{00023}00019\ \text{mg/L}$$

$$\approx 0.0002\ \text{mg/L}\ (0.2\ \mu\text{/L})$$

where:

- 0.\~~000025~~000019 mg/kg bw per day is the TDI derived above,;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7).

10.3 Comparison of cancer and non-cancer risk assessment

The HBV for the non-cancer assessment, which was 0.0002 mg/L for hepatocellular hypertrophy in rats, is more conservative than the HBV for Leydig cell tumours of 0.03 mg/L. The ~~proposed~~ HBV of 0.0002 mg/L that was derived for non-cancer effects is therefore considered to be sufficiently protective of the carcinogenic effects of PFOA.

10.4 Application of additive approach

In keeping with a precautionary approach, the currently available data support the implementation of an additive approach for PFOS and PFOA when evaluating situations where PFOS and PFOA co-occur in drinking water. Given that PFOS and PFOA are the predominant PFAS detected in Canadian water samples and the lack of toxicological data on PFAS besides PFOS and PFOA, the additive approach was not extended to other PFAS. Of the existing additivity approaches for risk assessment (i.e. hazard index, point of departure index, combined margin of exposure index, toxic unit summation, and relative potency factors/toxic equivalency factors; Meek et al., 2011; SCHER, 2012), the hazard index approach was deemed to be the best choice for PFOS and PFOA that is health protective. The hazard index is the sum of the hazard quotients (i.e., the ratios between exposure and the reference value) for each component to be evaluated (SCHER, 2012). When the hazard index is less than 1, the combined risk is considered acceptable; values greater than 1 indicate potential health concern. This approach is the preferred approach for chemicals with high quality toxicology data (e.g., dose-response data, health hazard information), reflecting the scientific knowledge and toxicity associated with each chemical, and

it is transparent and easy to apply (Meek et al., 2011; SCHER, 2012), although it is likely to overestimate risk (Boobis, 2009; Meek et al., 2011). Additionally, the value of this approach has been demonstrated for the combined risk assessment of PFOS and PFOA (Ludwicki et al., 2015) and for 17 perfluoroalkylated substances (Borg et al., 2013). Borg et al. (2013) noted that their assessment of 17 perfluoroalkylated congeners should be looked upon as conservative, given that the use of the hazard index approach is likely to overestimate risk (Boobis, 2009; Meek et al., 2011) and that the majority of congeners lack toxicological data, requiring the use of read-across extrapolations to the closest congeners with longer carbon chain lengths (assuming that potency is proportional to carbon chain length). Similarly, Ludwicki et al. (2015) cited the lack of toxicological data on other congeners besides PFOS and PFOA as a reason for not including them in any cumulative risk assessments of perfluoroalkylated substances. The differences between PFOS and PFOA described above (in section 9.4), in particular the lack of evidence demonstrating that a single receptor is required to mediate the toxicities of PFOS and PFOA and the ability of PFOS and PFOA to induce a multitude of toxicities, preclude the use of a scaling system analogous to the toxicity equivalence factor system used for polychlorinated biphenyls and polycyclic aromatic hydrocarbons (Scialli et al., 2007; Peters and Gonzalez, 2011). Therefore, in employing the additive approach for PFOS and PFOA, the addition of the observed concentration to MAC ratios for PFOS and PFOA should be kept below the value of 1. This approach can be expressed as:

$$\frac{\text{PFOA concentration}}{\text{MAC}_{\text{PFOA}}} + \frac{\text{PFOS concentration}}{\text{MAC}_{\text{PFOS}}} < 1$$

Field Code Changed

Or

$$\frac{\text{PFOA concentration in } \mu g/L}{0.2\ \mu g/L} + \frac{\text{PFOS concentration in } \mu g/L}{0.6\ \mu g/L} < 1$$

Field Code Changed

10.5 International considerations

~~A memorandum published in 2009 by the~~ The U.S. EPA ~~Office of Water indicates a Provisional Health Advisory (PHA~~(2016) has established a lifetime health advisory (LHA) of 0.~~4~~07 µg/L (0.~~000~~4000 07 mg/L) for PFOA ~~(U.S. EPA, 2009b).~~ This ~~PHA~~LHA was derived from a ~~$BMDL_{10}$~~LOAEL of 1.0~~.46~~ mg/kg bw per day for ~~increased~~reduced ossification and accelerated puberty (in males) in pups following maternal ~~liver weight at term in mice exposed~~exposure to PFOA on GD 1–17 by oral gavage (Lau et al., 2006). ~~This $BMDL_{10}$ is within the range of $BMDL_{10}$ values for increased liver weight in mice and rats (~~A reference dose (RfD) of 0.~~29–0.74~~000 02 mg/kg bw per day~~) (EFSA, 2008; U.S. EPA, 2009b).~~ (0.02 µg/kg bw per day) was derived by applying pharmacokinetic modeling to serum PFOA concentrations to calculate a human equivalent dose (HED) (equivalent to an uncertainty factor of 189 from the LOAEL to the HED to account for interspecies differences in toxicokinetics). An additional uncertainty factor of ~~2,430~~300 (10 for intraspecies differences, 3 for interspecies toxicodynamic differences ~~and 81,~~ and 10 for use of LOAEL) was applied to the HED (U.S. EPA, 2016). From the RfD, a health advisory of 0.07 µg/L was calculated assuming a drinking water exposure level of 0.054 L/kg bw per day (the 90th percentile drinking water intake for lactating women; a 3.78 L/day equivalent is calculated assuming 70 kg body weight). Additionally, when PFOA co-occurs with PFOS at the same time and location in a drinking water source, the U.S. EPA recommends comparing the sum of the concentrations of PFOS and PFOA to the LHA of 0.07 µg/L.

The Australia Department of Health (2017) has established a health-based drinking water quality value of 0.56 µg/L (0.000 56 mg/L) for PFOA based on a TDI calculated by Food Standards Australia and New Zealand (FSANZ, 2017). This drinking water quality value was derived from a NOAEL of 1 mg/kg bw per dayfor decreased body weight gain occurring at doses ≥ 3 mg/kg bw per day in mouse pups following maternal exposure to PFOA on GD 1-17 by oral gavage (Lau et al., 2006). A TDI of 0.000 16 mg/kg bw per day (1.6 µg/kg bw per day) was derived by applying pharmacokinetic modeling to serum PFOA concentrations to calculate a HED (equivalent to an uncertainty factor of 204 from the NOAEL to the HED to account for interspecies toxicokinetic differences~~) was applied to the $BMDL_{10}$, resulting in a reference dose rounded at 200 ng/kg bw per day (0.2 µg/kg bw per day) (U.S. EPA, 2009b). This reference dose (RfD) was also indicated in a memorandum emitted in 2009 by the U.S. EPA Office of Solid Waste and Emergency Response (U.S. EPA, 2009c). Based on U.S. EPA policy, the PHA (0.4 µg/L; 0.0004 mg/L) was further derived for a 10-kg child consuming 1 L water per day using a default assumption that drinking water contributes 20% of total exposure to PFOA (U.S. EPA, 2009c).~~). An additional uncertainty factor of 30 (10 for intraspecies differences and 3 for interspecies toxicodynamic differences) was applied to the HED. From the TDI, a drinking water quality value of 0.56 µg/L was calculated using a body weight of 70 kg, water consumption of 2 L/day, and an allocation factor of 0.1.

~~The New Jersey Department of Environmental Protection derived a preliminary health-based guidance for PFOA in drinking water of 0.04 µg/L (0.00004 mg/L) from the NOAEL of 1.6 mg/kg bw per day obtained in rats exposed chronically (Sibinski, 1987). At the higher dose (16.1 mg/kg bw per day), decreases in body weight gain, hematocrit, erythrocyte counts and hemoglobin concentration were observed in female rats. Using pharmacokinetic modelling, it was determined that a dose of 1.6 mg/kg bw per day was equivalent to a mean serum PFOA concentration of 1,800 ng/mL in rats. An uncertainty factor of 100 for inter- and intraspecies variation was applied, resulting in a target maximum human serum PFOA concentration of 18 ng/mL. Using data from an epidemiology study (Emmett et al., 2006a), which noted that ingestion of PFOA in drinking water resulted in a blood PFOA concentration approximately 100 times greater than the water concentration, it was estimated that a water concentration of 0.18 ng/mL (0.18 µg/L or 0.00018 mg/L) would result in the target serum PFOA concentration. Using a default assumption that drinking water contributes 20% of total exposure to PFOA, the preliminary health-based guidance for PFOA in drinking water was set at 0.04 µg/L (State of New Jersey, undated).~~

~~The Minnesota Department of Health derived a health risk limit (HRL) of 0.3 µg/L (0.0003 mg/L). This value was based on the increased liver weight observed in monkeys exposed to ≥ 3 mg/kg bw per day (Thomford, 2001a; Butenhoff et al., 2002). More precisely, the benchmark dose ($BMDL_{10}$) for these effects was estimated at 23,000 ng/mL PFOA in monkey serum. A human equivalent dose (HED) of 2,300 ng/kg bw per day (2.3 µg/kg bw per day) was calculated based on the elimination of PFOA in humans (using human half-life data to estimate clearance). An uncertainty factor of 30 (10 for human variability and 3 for interspecies toxicodynamic differences) was applied to the HED, resulting in a reference dose of 77 ng/kg bw per day (0.077 µg/kg bw per day). Steady-state uptake/elimination was estimated to occur after 19 years of exposure, therefore a time-weighted 95th percentile intake for the first 19 years of life (0.053 L/kg bw per day) was used as the daily water ingestion. This, along with a relative source contribution of 20%, resulted in a HRL rounded at 0.3 µg/L (MDH, 2008c, 2008d).~~

A drinking water guideline of 10 µg/L (0.01 mg/L) was derived by the UK Health Protection Agency (UK HPA, 2007, 2009) based on a TDI of 3,000 ng/kg bw per day (3 µg/kg bw per day) previously derived by the UK Committee on Toxicity of Chemicals in Food,

Consumer Products and the Environment (UK COT, 2006). This TDI was based on a POD of 0.3 mg/kg bw per day, corresponding to the lowest $BMDL_{10}$ for increased liver weights in rats exposed for 13 weeks (data from Palazzolo, 1993 and Perkins et al., 2004); this value was similar to the $BMDL_{10}$ (0.31 mg/kg bw per day) for hepatic necrosis in F0 and F1 male rats (data from Butenhoff et al., 2004b). An uncertainty factor of 100 (for intra- and inter-species variation) was applied. The drinking water guideline (10 µg/L) was derived from the TDI using an allocation factor of 50%, a body weight of 5 kg and a water ingestion rate of 0.75 L per day for bottle-fed infants (UK HPA, 2007).

In their scientific opinion document on contaminants in the food chain, the CONTAM panel under the European Food Safety Authority derived a TDI of 1,500 ng/kg bw per day (1.5 µg/kg bw per day) based on a $BMDL_{10}$ of 0.3 mg/kg bw per day in rats (EFSA, 2008). This value refers to the lowest $BMDL_{10}$ identified for effects on the liver (Palazzolo, 1993; Butenhoff et al., 2004b; Perkins et al., 2004) among those (0.3–0.7 mg/kg bw per day) derived from a number of studies in mice (Lau et al., 2006) and male rats (Sibinski, 1987; Palazzolo, 1993; Butenhoff et al., 2004b; Perkins et al., 2004). The $BMDL_{10}$ was divided by an uncertainty factor of 200 (10 for interspecies differences, 10 for intraspecies differences and 2 to compensate for uncertainties relating to the internal dose kinetics).

11.0 Rationale

PFOA is an anthropogenic compound used in the manufacture of stain/water-resistant coatings for various consumer products. Environmental concentrations, and therefore potential exposure levels, may be higher in areas near facilities using high amounts of PFOA and near locations with extinguished fires if PFOA-containing fire-fighting foams were used. Canadians can be exposed to PFOA in food, consumer products, dust, and drinking water. The major sources of PFOA are expected to be food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Based on its physico-chemical properties, exposure to PFOA via inhalation and dermal routes during showering or bathing is expected to be negligible.

Chronic exposure to PFOA has been associated with both cancer and non-cancer effects in animals and humans. HBVs for both endpoints have been calculated, with the non-cancer effects resulting in a lower, more conservative ~~HBV~~value.

Epidemiological studies have shown associations between exposure to PFOA and multiple non-cancer health outcomes, such as dysfunctions of the immunological system and alterations in birth weight and lipid levels. However, these studies cannot be used to derive the non-cancer HBV for PFOA due to limitations in terms of design, bias, confounding, and possibility of chance findings. In animals, non-cancer effects observed at the lowest levels of exposure include reproductive and developmental effects, liver effects and changes in serum lipid levels. For various reasons described in section 10.2, the most appropriate endpoint to derive a HBV for PFOA is hepatocellular hypertrophy (liver effects) in rats, occurring at the same levels as the changes in serum lipid levels. Using a TDI approach, a HBV of 0.0002 mg/L (0.2 µg/L) has been calculated for the non-cancer effects of PFOA based on liver effects in rats. This HBV is considered to be sufficiently protective of both cancer and non-cancer effects of PFOA.

A MAC of 0.0002 mg/L (0.2 µg/L) is ~~proposed~~established for PFOA in drinking water. ~~The proposed~~This MAC for PFOA can be measured by available analytical methods and is achievable by municipal and residential treatment technologies.

However, when detected in drinking water, PFOA is often found with other PFAS, including PFOS. Although current science does not justify the use of this approach for other

PFAS, it does support additivity for PFOA and PFOS, based on the similarity of the health effects used to establish their respective MACs, and the extensive characterization of their toxicity and toxicokinetics. Thus, when PFOS and PFOA are found together in drinking water, the best approach to protect human health is to consider both chemicals together, by ensuring that the sum of the ratios of the observed concentration to the MAC for PFOA and PFOS does not exceed 1. As part of its ongoing guideline review process, Health Canada will continue to monitor new research and recommend any change to the guideline that is deemed necessary.

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Appendix A: Reported full-scale drinking water treatment plant PFOA removal data

Developed from table 3 in Rahman et al. (2014)

Water Source	Treatment Train[2]	Influent concentration[3] (ng/L)	Effluent concentration[3] (ng/L)	% Removal of PFOA	Reference
Groundwater	DBF, UV, Cl_2	10	9.4	6	Quinones and Snyder, 2009
Surface water	O_3, COA/FLOC, DBF, Cl_2	1.4	1.4	0	Quinones and Snyder, 2009
Surface water	PAC, CHLM, DBF	1.7	1.9	-12	Quinones and Snyder, 2009
Surface water	Cl_2, COA/FLOC, DBF, UV	22	22	0	Quinones and Snyder, 2009
Planned potable indirect reuse facility	MF/RO, UV/H_2O_2, SAT	41	ND	100	Quinones and Snyder, 2009
Planned potable indirect reuse facility	Cl_2, DL, SAT	29	57	-97	Quinones and Snyder, 2009
River water	RSF, O_3, GAC, Cl_2	1.0 (summer)	0.93 (summer)	7	Takagi et al., 2008
River water	RSF, O_3, GAC, Cl_2	0.87 (summer) 3.2 (winter)	2.8 (summer) 1.6 (winter)	-222 (summer) 50 (winter)	Takagi et al., 2008
River water	RSF, O_3, GAC, Cl_2				Takagi et al., 2008
Lake water	RSF, GAC, Cl_2	4.6 (summer) 4.5 (winter)	0.16 (summer) <0.1 (winter)	97 (summer) >98 (winter)	Takagi et al., 2008
River, lake, subsoil and groundwater (7 plants)	RSF, Cl_2	0.56 – 22 (sum) 0.54 – 4.2 (win)	0.45 – 22 (sum) 0.37 – 4.5 (win)	20 – 0 (summer) 31 to -7 (winter)	Takagi et al., 2008
River water	Membranes, Cl_2	0.37 (summer) 0.26 (winter)	0.29 (summer) 0.20 (winter)	22 (summer) 23 (winter)	Takagi et al., 2008
Lake water	SSF, Cl_2	2.7 (summer) 1.8 (winter)	2.3 (summer) 1.9 (winter)	15 (summer) -6 (winter)	Takagi et al., 2008
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.3 (summer) 3.3 (winter)	3.7 (summer) 1.3 (winter)	-185 (summer) 60 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.6 (summer) 3.3 (winter)	2.3 (summer) 1.7 (winter)	44 (summer) 48 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.2 (summer) 2.8 (winter)	1.6 (summer) 1.9 (winter)	-33 (summer) 32 (winter)	Takagi et al., 2011
River water	SED, O_3, GAC, Cl2, SF	1.4 (summer) 3.3 (winter)	2.2 (summer) 2.0 (winter)	-57 (summer) 39 (winter)	Takagi et al., 2011
Lake water	COA/FLOC/SED, SF, GAC (reactivated), Cl_2	4.4 (summer) 4.1 (winter)	<0.5 (summer) <0.5 (winter)	>89 (summer) >88 (winter)	Takagi et al., 2011
Ground water	UF, Cl_2	16	16	0	Atkinson et al., 2008
Ground water	GAC (not in operation), super chlorination and dechlorination	135	130	3	Atkinson et al., 2008

Water Source	Treatment Train[2]	Influent concentration[1] (ng/L)	Effluent concentration[1] (ng/L)	% Removal of PFOA	Reference
Ground water	GAC (2 parallel GAC trains each having 6 beds; contactors are mature and act as biological contactors; not been regenerated for some years), Cl_2	42	45	-7	Atkinson et al., 2008
Ground and surface water (60:40)	SSF, O_3, GAC (6 beds-no regeneration for several years), Cl_2using NaOCl	20.6	25	-21	Atkinson et al., 2008
Ground water	Cl_2 using NaOCl				Atkinson et al., 2008
River water	COA/FLOC/SED, O3, GAC, RSF	5.3 (Aug) 5.8 (Oct)	9.4 (Aug) 6.4 (Oct)	-77 (Aug) -10 (Oct)	Shivakoti et al., 2010)
River water	COA/FLOC/SED, O3, GAC, RSF	5.8 (Aug) 8.8 (Oc)	3.9 (Aug) 4.2 (Oct)	33 (Aug) 53 (Oct)	Shivakoti et al., 2010)
Treated wastewater	De-nitrification, pre-O_3, OA/FLOC/SED, DAF, O_3, GAC (acts as biological contactor), O_3	2,2 (Oct) 3.7 (Nov) 3.6 (Nov)	<LOR (0.3) (Oct) 0.6 (Nov) 0.7 (Nov)	100 (Oct) 84 (Nov) 81 (Nov)	Thompson et al., 2011b
River water	COA/FLOC/SED, RSF, Cl_2	5.02	0.73	85	Kunacheva et al., 2010)
Treated wastewater	Clarifier/lamellar settler ($FeCl_3$&$(NH_4)_2SO_4$, NaOCl addition), UF, RO, UV+H_2O_2, stabilization/disinfection (addition of lime, CO_2, NaOCl)	38 39 23	<LOR (0.5) ND <LOR (0.2)	100 100 100	Thompson et al., 2011
River water	COA/FLOC, RSF, O_3, GAC, SSF	8.2	<0.23	<97	Eschauzer et al., 2012
River water	Cl_2, COA/FLOC, RSF, O_3, GAC	116	33	69	Flores et al., 2013
River water	Cl_2, COA/FLOC, RSF, O_3, GAC, UF, RO	86	13	86	Flores et al., 2013

[1] COA/FLOC/SED = coagulation/flocculation sedimentation; DAF = dissolved air flotation; DL=dilution, GAC = granular activated carbon; O_3 =ozonation; RSF = rapid sand filtration; SSF = slow sand filtration; SF = sand filtration; NaOCl = sodium hyochlorite; Cl_2 = chlorine; RO = reverse osmosis; UF = ultrafiltration; IX = ion exchange; UV/H_2O_2 = ultraviolet irradiation/hydrogen peroxide; SAT = soil aquifer treatment; CHLM = chloramines;

[2] LOR = limit of reporting; ND = not detected

Appendix B: List of acronyms

AFFF	aqueous film-forming foam
ALT	alanine transaminase
APFO	ammonium perfluorooctanoate
BMD	benchmark dose
BMDL	lower confidence limit on the benchmark dose
$BMDL_{10}$	lower 95% confidence limit on the benchmark dose for a 10% response
BV	bed volume
CAS	Chemical Abstracts Service
CI	confidence interval
CSAF	chemical specific adjustment factor
DI	direct injection
DL	detection limit
EBCT	empty bed contact time
EPA	Environmental Protection Agency (U.S.)
ESI	electrospray ionization
GAC	granular activated carbon
GD	gestational day
GM	geometric mean
HBV	health-based value
HED	human equivalent dose
HPLC	high performance liquid chromatography
ISO	International Standard Association
IT	ion-trap
LC	liquid chromatograph
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantitation
LLE	liquid-liquid extraction
MAC	maximum acceptable concentration
MDL	method detection limit
MGD	mammary gland development
MG/D	million gallons per day
MOA	mode of action
MRL	minimum reporting level
MS/MS	tandem mass spectrometry
NF	nanofiltration
NHANES	National Health and Nutrition Excamination Survey (U.S.)
NOAEL	no-observed-adverse-effect level
NOM	natural organic matter
PAC	powdered activated carbon
PBPK	Physiologically-based pharmacokinetic
PEFT	polytetrafluoroethylene
PFA	perfluoroalkyl
PFAA	perfluorinated alkyl acid

PFAS	perfluoroalkyl substance
PFCA	long-chain perfluorocarboxylic acids
PFDA	perfluorodecanoic acid
PFHxS	perfluorohexanesulfonate
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PND	postnatal day
POD	point of departure
POD_{HEQ}	human-equivalent points-of-departure
PTFE	polytetrafluoroethylene
RBF	river bank filtration
RO	reverse osmosis
SPE	solid phase extraction
TDI	tolerable daily intake
TDS	total diet study
UCMR3	third Unregulated Contaminant Monitoring Rule (U.S.)
WAX	weak anion exchange

Public Consultation Comments - PFOA in Drinking Water

General comments:

#	Comments	Response
1	Je dois dire que j'ai trouvé ce document très bien fait, exhaustif. Du beau travail de professionnel.	Thank you. No change to the document.
2	Although we do not object to the establishment of a MAC of 0.0002 mg/L (0.2 µg/L) for PFOA, we ask that it be clear inthe final guideline that it applies to tap water and to explicitly state that the MAC is not applicable to foods or beverages such as bottled water, etc.	Thank you. No change to the document.
3	The case for investing significant resources into the expensive monitoring for PFOAis weak. The limited amount of occurrence data in raw and treated drinking water provides little evidence that this contaminant is a threat to drinking water safety.	PFOA has been identified as a concern in drinking water in several locations in Canada, thereby meeting our criteria for guideline development. No change to the document.
4	The occurrence of problematic concentrations of PFOA in raw or treated drinking water would be remarkably site-specific, with characteristics driven by unique features (manufacture, use or spilling of these compounds in substantial quantities) that would point to a site-specific need for expensive monitoring.	Agree. The issue is already discussed in the document. No change to the document.
5	We concur with the proposed MAC, but would suggest that water quality testing for raw and treated water for a few select vulnerable communities should be conducted before implementing the new guideline.	This is outside Health Canada's mandate, and outside the scope of the document. Provinces and territories are responsible for the adoption and/or implementation of guidelines. No change to the document.
6	We would recommend that the MAC for PFOA be lowered based on the U.S. EPA's analysis for their health advisory.	Health Canada derives health based values based on the latest science for the protection of human health, using the Canadian context and assumptions. Other international assessments are considered in our approach. No change to the document.
7	We would recommend that Health Canada, working with its provincial counterparts if necessary, identify Canadian communities and vulnerable populations of Canadians at risk of exposure to elevated PFOA and PFOS in drinking water, and develop and implement a plan to ensure safe drinking water is provided to those communities and populations of Canadians.	This is outside Health Canada's mandate, and outside the scope of the document. Provinces and territories are responsible for the adoption and/or implementation of guidelines. No change to the document.
8	Il serait pertinent que le document précise si des composantes d'un réseau de distribution (ex. conduites) peuvent être une source potentielle de cette substance.	PFOA salts are used as a processing aid in the production of fluoropolymers which are used in joining and sealing materials. Some of these materials may be used in distribution systems and may contain trace amount of PFOA. This information has been added to section 3.0 of the document.
9	Le document détaille bien les données scientifiques disponibles, et plus particulièrement l'approche spécifique au contaminant utilisée pour l'extrapolation de l'animal vers l'humain. La lecture de la description des effets à la santé des humains et des animaux serait grandement facilitée par l'ajout de tableaux synthèses.	Due to limitations on web publishing of the documents, the use of tables in our documents is kept to a minimum. No change to the document.

10	Enfin, puisque les effets critiques du SPFO et de l'APFO sont les mêmes et que ces derniers sont susceptibles d'être présents simultanément dans l'eau potable, le GSE considère qu'il serait approprié de discuter de la pertinence ou non de présenter une recommandation commune à la fois pour l'APFO et le SPFO.	The text has been modified to include an additive approach for PFOS and PFOA.
11	In summary, the available scientific information from both human and animal studies indicates that a drinking water concentration for PFOA of 0.2 µg/L is not sufficiently health protective. Health Canada does not acknowledge that a PFOA drinking water concentration of 0.2 µg/L and the resulting blood serum levels are well above levels that are consistently associated with health effects in humans. Additionally, well-established toxicological effects that occur at doses far below the dose used as the basis for the proposed MAC were not considered. I strongly suggest that these additional endpoints, circulating blood levels and most sensitive individuals and endpoints within the exposed population be considered.	Health Canada employs the best science with conservative estimates to derive health based values that are protective of human health with lifetime exposure to PFOA in drinking water at the MAC. No change to the document.
12	In preparation for review of the documents on PFOS and PFOA, we undertook sampling of raw and treated water for surface water sources and had the samples analyzed. The sample analysis costs were a staggering $540 per sample for both PFOS and PFOA. If this guideline is adopted and utilities are required to monitor for these compounds, it will likely be a financial challenge for many utilities, especially where it is unlikely that many source waters would be considered high or even medium risk for the presence of these compounds.	The cost of analysis is beyond the scope of the document. The adoption and implementation of guideline is under PT jurisdiction. No change to the document.
13	Having a MAC of 0.6 µg/L, while perhaps a commendable goal from a health standpoint, provides some challenges from a laboratory and treatment perspective. At the present time very few, if any, analytical laboratories in Canada, public or private, seem to be able to measure to this level of MAC and be ISO 17025 accredited for it in drinking water. Consequently, we're not sure what is being achieved by having such a stringent target, notwithstanding the ability of water utilities to obtain a representative drinking water sample and access a Canadian laboratory accredited for this analysis cost effectively.	Thank you for the comment. No change to the document.

Section 2.0: Executive summary

#	Comments	Response
14	2.2 - La dernière phrase de cette section fait état des concentrations susceptibles d'être retrouvées dans l'eau potable à l'aide d'une valeur exprimée en nanogrammes. Il serait plus approprier d'exprimer ces concentrations en milligrammes.	The document has been modified to address this comment.

Section 3.0: Application of the guideline

#	Comments	Response
15	3.1 - L'abréviation SPFO est utilisée pour la première fois dans cette section sans que le nom de la substance ait été indiqué au long auparavant.	Thank you for the comment. The text has been modified accordingly.
16	3.1 Le sens de l'expression « de l'application de sols modifiés par des biosolides » n'est pas clair. Il faudrait reformuler.	Change made to the document to clarify the meaning of this phrase
17	3.1 - La section recommande une vérification ponctuelle des concentrations d'APFO dans l'eau brute, et un suivi trimestriel ou semestriel si la CMA est dépassée à l'eau brute. Il n'est cependant pas fait mention qu'une détection à l'eau brute devrait amener à instaurer un suivi dans l'eau distribuée.	The information in the document has been updated and now indicates that if treatment is required, paired samples of source water and treated water should be taken semi-annually to confirm the efficiency of the treatment.
18	3.1 - Une mention relative aux dépassements transitoires devrait être ajoutée, comme c'est le cas dans les documents relatifs aux substances organiques publiés dans les dernières années.	Text added to section 3.0
19	3.1 - "*Utilities should characterize their source water to assess PFOA concentrations*" should be accompanied by a caution that analysis for PFOA is a highly specialized analytical capability. A routine water quality laboratory without explicit experience in analysis of perfluorinated compounds and documented QA/QC for such methods is likely to be subject to either or both false positives or false negatives.	We agree. The document has been modified to include this information in sections 3.1 and 6.2.

Section 4.0: Identity, use and sources in the environment

#	Comments	Response
20	4.0 - "*The main producers of PFOA are located principally in the United States, Europe and Asia. Industrial information obtained in 2004 indicates no known manufacturers of perfluoroalkyl and fluoroalkyl substances in Canada; however, APFO was imported into Canada in quantities ranging between 100 and 100,000 kg (EC&HC, 2012). APFO is mainly used as a commercial polymerization aid for fluoropolymer manufacturing*" highlights how unlikely any Canadian water utility is to be affected by PFOA unless there is some identifiable connection with PFOA use.	We refer the reviewer to section 4.1, which describes in detail scenarios that result in PFOA entering Canadian waters. In addition, PFAS are being found in Canadian drinking water supplies near point sources (e.g., airports) in several regions of the country. No change to the document.
21	4.1 - "*PFOA was detected in effluent wastewater treatment facilities at concentrations ranging from 0.007 to 0.055 µg/L in Canada (EC&HC, 2012) and at average concentrations ranging from 0.080 to 0.12 µg/L in effluents of seven different locations in the U.S. (Quinones and Snyder, 2009)*" shows that no reported analyses of wastewater for PFOA exceed the proposed MAC for PFOA of 0.2 µg/L in drinking water.	As the reviewer is aware, PFOA is not routinely monitored and the limited Canadian data support the low levels of PFOA in source and tap water. However, it is important to remember that there are point sources of PFAS (e.g., airports) and that PFOA does not biodegrade, has the potential to accumulate in drinking water sources, and is not removed using existing treatment methods. The MAC has been established In the interest of protecting human health from the serious health effects associated with exposure to this man-made chemical. No change to the document.

Section 5.0: Exposure

#	Comments	Response
22	5.0 - The statement: "*The estimated total daily intake of PFAAs (estimates not provided for individual PFAAs) in Canadians was reported to be 410 ng/day for the general population of Canada (Tittlemier et al., 2007). Drinking water ingestion contributed only a minor amount to the overall estimated exposure (estimated at 0.3 ng/day)*" for total PFAAs, not just PFOA should be compared with the proposed MAC for PFOA alone that would yield 300 ng/day of PFOA for consumption of 1.5 L of drinking water. As low as is this proposed MAC, the foregoing comparison suggests that from an exposure perspective alone, excessive PFOA exposure via drinking water is a very unlikely possibility, certainly not one of national or even province-wide relevance.	Canadian exposure to PFOA and PFAS is not limited to drinking water. Considering the bioaccumulative nature of PFOA and its long half-life in humans, cumulative exposure from various sources may have an impact on health of Canadians across the country. Data from the CHMS survey show that PFOA is found in the blood of most Canadians. As PFOA is not routinely monitored in Canadian drinking water, it cannot be assumed that it is not a concern. No change to the document.
23	5.1 Il serait utile de préciser si les échantillons d'eau brute prélevés lors des différentes campagnes d'échantillonnages mentionnées provenaient d'eau souterraine ou d'eau de surface.	The text has been modified to indicate that the samples were sourced from groundwater and surface water (rivers and lakes) in the national survey.
24	5.1 - Des concentrations moyennes d'APFO sont présentées dans cette section. Il serait intéressant de rapporter également les concentrations maximales observées.	The text has been modified to include maximum levels where available.
25	5.1 The meaning of the findings – "*In Quebec, raw and treated water samples were obtained monthly between April 2007 and March 2008 from seven sites (a total of 84 raw and treated water samples each). PFOA was detected in 75% of treated samples (MDL of 0.3–0.6 ng/L), with a median value of 2.5 ng/L. The detection rate and median concentrations were higher in treated water than in raw water, for which the detection rate and median were 55% and 2.0 ng/L, respectively (Ministère du Développement durable, de l'Environnement, de la Faune et des Parcs, 2012)*" need to be viewed with extreme caution. The April 2016 U.S. EPA UCMR3 summary of the 2013-2015 program shows a Minimum Reporting Level (MRL) based on current analytical capability of 0.02 µg/L (20 ng/L), more than 33 fold higher than the MDL in this study. The summary for PFOA, based on 36,148 analytical results from 4,864 water utilities found 354 samples (at 108 locations) with results above the MRL and 31 samples (at 13 locations) above 0.07 µg/L. The comparatively high percentage of PFOA detections in Quebec is at best a reflection of an extremely low MDL and may be no more than a large number of false positives. The median PFOA level detected of 2.5 ng/L is 600 fold below the proposed MAC. No other percentiles or maximum values found in Quebec have been reported.	The limit of detection stated in the document is what was reported in the published report. Maximum levels in Quebec have been added to the document to address such concerns.

#	Comments	Response
26	5.1 - The USEPA UCMR3 results show much lower levels of PFOA than were reported for Canada using a MDL about 1000 fold lower than UCMR3. Even though the Canadian results have higher proportions of PFOA detections, they do not provide a compelling case for PFOA monitoring in drinking water in Canada. These results should also report medians and/or geometric means to reflect the likely skewed results obtained that will be poorly represented by an arithmetic mean. Publication of a MAC for PFOA that may drive water utilities to spend even more on contaminant monitoring than currently done is not justified. This is important because the analytical methods required for the perfluorinated compounds are not needed for other current MAC monitoring purposes.	The section on PFOA in water highlights how infrequently PFOA in drinking water has been investigated. PFOA has been detected in biomonitoring of the Canadian population and due to its properties discussed in the guideline technical document, it is likely to occur in water. Median results are reported where available. The text has been modified to include median values for the national survey.
27	5.2 - : « *L'APFO a rarement été détecté (9% sur 68 échantillons au total)...* » À 9% de détection, il serait plus approprié que l'APFO est peu fréquemment détecté.	Thank you for the comment. The recommended change to the wording has been made.

Section 6.0: Analytical methods

#	Comments	Response
28	6.1 - "*The MDL for PFOA is 1.7 ng/L (0.0017 µg/L) and the Lowest Concentration Minimum Reporting Level (LCMRL) is 5.1 ng/L (0.0051 µg/L) (U.S. EPA, 2009a). PFOA has been included in the third Unregulated Contaminant Monitoring Rule (UCMR3), which stipulates that using Method 537 ver. 1.1, an MRL of 20 ng/L (0.02 µg/L) for PFOA must be achieved and reported by the utilities during monitoring (U.S. EPA, 2012b)*" captures the difference between what is possible as a method detection limit (MDL) and what is specified as a minimum reporting level (MRL) for a large survey.	Thank you for the comment. No change to the document.

Section 7.0: Treatment technology

#	Comments	Response
29	Our water treatment plant does not currently test for these two substances. They have been added to our quarterly testing program. We do not believe they are prevalent in our raw water; however, if they are detected in significant quantities (near or above the MAC), our current treatment process may be inadequate. If our treatment process needs to be upgraded, this will require significant increases in both capital and operational costs.	Cost is beyond the scope of the document. The adoption and implementation of guideline is under PT jurisdiction. No change to the document.

#	Comments	Response
30	While most utilities will likely have no difficulty meeting the proposed MACs for PFOS and PFOA in drinking water, for those that do, the cost to remove them will be substantial. These substances are resistant to most conventional treatment and even some advanced processes. In some cases a full system redesign or replacement may be necessary to meet the MAC, which could be beyond the financial capacity of a utility. Would it be possible to propose a higher MAC, or delay the publication of this guideline until the treatment and standardized analytical technologies are less expensive, more readily available and, in the case of the treatment, more effective.	Cost is beyond the scope of the document. The adoption and implementation of guideline is under PT jurisdiction.No change to the document.
31	7.1.2.1 The statement: "*Close monitoring of PFOA breakthrough (treatment objective) is necessary for efficient operation of GAC unit. Studies indicated that PFOA was successfully removed from drinking water when a frequent regeneration or replacement (3 to 6 months) of the GAC was performed (e.g., Wilhelm et al., 2008; Rumsby et al., 2009; Takagi et al., 2011). Takagi et al. (2011) observed that GAC regenerated over periods greater than one year were not effective in removing PFOA and PFOS and suggested regenerating the carbon 2 to 3 times per year*" illustrate how expensive and impractical it would be to operate an expensive unit process like GAC strictly for the purpose of achieving the MAC for PFOA.	GAC treatment is well established and the most widely used technology for small systems because of general ease of use. Cost-effectiveness is beyond the scope of the document. The adoption or implementation of guidelines is under PT jurisdiction. No change to the document
32	Employing appropriate equipment for adequate removal of these substances, if present in the water, will impose additional cost on water systems. The review of the proposed guideline documents shows that treatment such membrane filtration and GAC systems effectively remove 95% and 99% of PFOS and PFOA, respectively. We also have noticed that exhausted GAC system does not achieve 99% removal.	The effectiveness of GAC to remove PFOA in drinking water is dependent on the regeneration frequency and/or replacement of the carbon. Cost-effectiveness is beyond the scope of the document. No change to the document.

Section 8.0: Kinetics and metabolism

#	Comments	Response
33	8.2 - « *Les cinétiques d'APFO ne sont pas linéaires des doses élevées probablement en raison de la saturation des transporteurs d'anions organiques (TAO) qui sont responsables de la réabsorption rénale des doses importantes ce qui entraîne un taux d'excrétion plus élevé à des doses élevées qu'à de faibles doses* (Andersen et coll., 2006). » Quelles sont les valeurs de doses faibles et élevées dont il est question ici? Est-ce que cela implique que la cinétique est linéaire à faible dose?	The text has been modified to specify the high and low doses, and to clarify that first order processes are linear.
34	8.2 - « *Peu de données ont été recueillies sur les tissus humains vers lesquels l'APFO est généralement distribué.*» Qu'en est-il de la distribution tissulaire chez les animaux? Par exemple, vers quel compartiment est-il majoritairement distribué?	The text has been modified to include information on the tissue distribution in experimental animals.

#	Comments	Response
35	8.2 - « *On a de plus mesuré le transfert de l'APFO par l'allaitement chez différentes espèces de mammifères, dont les humains, les rats, les souris et les moutons (Hinderliter et coll., 2005; Fenton et coll., 2009; Kim et coll., 2011; Needham et coll. 2011). Les concentrations d'APFO dans le lait maternel étaient constamment inférieures à celles du plasma maternel (Hinderliter et coll., 2005; Fenton et coll., 2009); chez les humains, un examen des concentrations sériques chez la mère et dans le lait a démontré que les ratios sériques de lait maternel indiqués dans plusieurs études étaient d'environ 0 11–0,12 (Liu et coll., 2011). En outre, les concentrations d'APFO dans le lait maternel humain diminuent de façon importante pendant l'allaitement (Thomsen et coll. 2010) et un nom re croissant de bébés sont nourris au sein (Tao et coll., 2008; Kadar et coll., 2011).* » Qu'en est-il de la différence entre les concentrations sériques des nourrissons allaités et celles des mères?	Thank you for your comment. The text has been modified to mention differences in serum concentrations of breastfed infants and mothers.
36	8.2 - « *Chez les souris et les primates non humains, il ne semble pas y avoir de différences de concentrations d'APFO entre les sexes (Griffith et Long 1980; Butenhoff et coll., 2004a; Lou et coll., 2009).* » Selon le tableau 1, les intervalles de confiance à 95% associés aux demi-vies moyennes des souris ne se chevauchent pas, il semble donc y avoir une différence entre les sexes.	The text has been modified to include a sentence to indicate the possibility of sex differences in mice.
37	8.4 - Nous apprécions l'effort de synthèse présenté à l'intérieur des tableaux du document de consultation. Nous encourageons Santé Canada à poursuivre dans cette lancée.	No change to the document. For web publishing policy reasons we limit inclusion of tables in our documents.
38	8.4 - Commentaire: « *Conformément aux observations chez les animaux auxquels on a administré de fait les doses, la relation entre une dose externe et une dose interne (taux sérique) est linéaire chez les humains qui sont exposés l'APFO dans leur milieu (lewell 2009); une cinétique non linéaire – comme on le constate chez les animaux auxquels on a administré des doses plus élevées – pourrait toutefois survenir dans le cas d'expositions humaines plus importantes.* Quelles sont les valeurs de faibles doses et de doses plus élevées ?	The information requested was not available in the reference cited. No change to the document.
39	8.5 - « *En raison de la nature non linéaire de la pharmacocinétique de l'APFO selon laquelle l'élimination plus rapide est associée une dose bolus élevée les modèles physiologiques peuvent permettre d'améliorer les moyens d'examiner le paramètre de dose d'une voie d'élimination et d'une espèce l'autre en vue d'évaluer les risques.* » Est-ce que la cinétique non linéaire de l'APFO est seulement observée lors de l'administration de doses bolus uniquement ou bien si elle s'applique à d'autres modes d'administration? Les sections précédentes décrivant la cinétique non linéaire ne font pas mention du mode d'administration.	The text has been modified to specify that the administered doses were oral.
40	8.5 - Pourquoi le modèle de Wambaugh et coll. (2013) n'a-t-il pas été retenu?	We had also considered the Wambaugh et al. (2013) approach, which is also valid, and has some weaknesses. We chose to use a PBPK model approach whereas they used a PK model. Their model could not be fully validated either. This clarification has been added to the document.
41	8.6.1 - « *En outre l'utilisation de la clairance comme paramètre de dose constitue une hypothèse raisonnable pour les substances chimiques dotées d'une longue demi-vie.* » Qu'est-ce qu'on entend par une longue demi-vie? Selon les données du tableau 1, chez les animaux, la demi-vie se mesure en jours, voir en heures.	Thank you for the question. The text has been modified to indicate that a half-life ranging from days to years constitutes a long half-life.

#	Comments	Response
42	8.6.2 - « *Les données sur les humains que l'on peut vérifier sont limitées aux études de biosurveillance qui ne permettent de réaliser que des estimations approximatives des scénarios d'exposition, et pour lesquelles les mesures des concentrations sériques n'ont généralement été calculées qu'une seule fois (des mesures deux intervalles n'ont été prises que pour quelques populations).* » Aucune référence n'est fournie.	Thank you for your comment. The text has been modified to refer the reader to the section on human biomonitoring data.
43	8.6.2 - « *Comme autre approche que l'utilisation du modèle P P pour calculer les PDD les ratios des paramètres des doses prévus dans le modèle P P ont été utilisés afin de calculer les valeurs de FICA pour les doses pertinentes.* » Des organismes (ex : MDH, 2009; ATSDR, 205; US EPA, 2016) utilisent la concentration sérique chez l'animal (modélisée ou mesurée) puis font une extrapolation vers une dose externe chez l'humain à partir de la clairance chez l'humain. Il serait intéressant que Santé Canada compare son approche avec celle employée par ces autres organismes. En effet, des différentes importantes peuvent être observées entre les doses équivalentes chez l'humain (PDDEQH) issues de ces différentes approches. Par exemple, selon la US EPA (2016), la dose équivalente chez l'humain associée à l'étude de Lau et al. (2006), soit l'étude retenue par l'agence américaine, est de 0,0053 mg/kg-jour. Si on applique la démarche de Santé Canada au même LOAEL (1 mg/kg-jour), alors la dose équivalente chez l'humain est de 0,059 mg/kg-jour. Changement propose: Décrire l'approche d'extrapolation retenue par d'autres organismes et comparer les résultats avec ceux obtenus par Santé Canada.	It is beyond the scope of this document to directly compare this assessment to approaches used by other agencies. Because PFOA remains in the body for years in humans, compared to days/weeks in rodents, it can be difficult to extrapolate to humans using conventional methods. The EPA's approach used pharmacokinetic modeling and linear clearance-based scaling. HC considered this approach but identified key issues. In particular, it does not account for potential non-linear pharmacokinetics in humans, which makes this approach less accurate across different dose ranges. HC employed a PBPK-derived chemical-specific adjustment factor approach which used PBPK models to generate chemical- and species-specific clearance information for humans and animals, and accounts for PFOA's non-linear kinetics. This approach was supported by external PBPK experts and by external and internal peer-reviewers. No change to the document.
44	8.6.2 - « *En revanche, les valeurs de CAFI qui ont été calculées ci-dessus dépendent des doses spécifiques et des schémas de posologie utilisés dans des études pharmacocinétiques; des incertitudes découlent des valeurs obtenues dans ces études car on a administré uniquement des doses uniques aux animaux et les données sur les humains n'ont pas été obtenues partir d'études sur l'administration de doses contrôlées.* » Selon les données du tableau 1, des doses répétées ont été administrées aux singes pendant 6 mois. Il faudrait corriger la phrase.	Thank you for this comment that draws our attention to a point of miscommunication. The text has been modified to clarify that the method of using CSAF calculated AK_{UF} values for single dose points, and as such cannot account for non-linear kinetics.
45	8.6.2 - « *En outre, comme les valeurs de CAFI fondées sur la clairance constituent des rapports entre les faibles doses chez les humains et les doses élevées chez les animaux les expositions entre les espèces ne sont pas du même ordre de grandeur; l'utilisation de la modélisation P P afin de calculer la valeur de CAFI permet de comparer de façon plus appropriée des doses du même ordre de grandeur.* » Dans ce cas, les valeurs calculées à la section 8.6.1 apparaissent non pertinentes. Les retirer faciliterait grandement la compréhension du document	No change to the document. The approach taken for interspecies extrapolation uses the AK_{UF} component of the CSAF, as described in section 8.6.3. The information in 8.6.1 is necessary to understand the calculations used in the approach.

#	Comments	Response
46	8.6.2 - « *En outre l'utilisation de concentrations plasmatiques comme mesure approximative d'une variété d'organes simplifie l'application des valeurs de AFI dans l'évaluation qui est déj complexe en raison de l'utilisation de valeurs de FICA propres aux espèces et aux doses.* » Plusieurs études épidémiologiques et toxicologiques rapportent les concentrations sériques plutôt que plasmatiques. Pourquoi avoir utilisé les concentrations plasmatiques?	Plasma concentrations were used instead of serum concentrations because the Loccisano et al. (2011) model included plasma as a parameter. No change to the document.
47	8.6.3 - « *L'état d'équilibre n'a également pas été atteint dans le modèle utilisant des humains à des doses inférieures à 0,1 mg/kg p.c. par jour.* Quel est l'impact sur les valeurs de CAFI calculées? Sont-elles sous-estimées ou surestimées?	The impact of not achieving equilibrium below 0.1 mg/kg bw per day cannot be predicted and it is therefore a source of uncertainty (which is the context within which this information is stated in the text). No change to the document.

Section 9.0: Health effects

#	Comments	Response
48	9.0 - Santé Canada se base sur une revue fait par un contractuel (Sanexen Environmental Services Inc) qui n'a pas été publiée. Il serait mieux d'utiliser des revues systématiques publiées dans des revues scientifiques.	The consultant's report is not a review, but a summary of the published data, and is available upon request. While published reviews are valuable (and cited in the document), they are not often comprehensive since the authors have criteria for inclusion of studies, such that the breadth of the literature is not always represented. Please note that the source document for each cited study was consulted.
49	9.0 - « *Ce résumé comprend seulement les études directement pertinentes au calcul de la valeur basée sur la santé.* » Quels sont les critères qui font qu'une étude est considérée comme «*directement pertinentes au calcul de la valeur basée sur la santé* »?	The text has been modified to indicate that the summary includes reports, reviews, and original papers published concerning PFOA in order to understand toxicity in humans exposed to PFOA via drinking water.
50	Increase in human blood serum PFOA from ongoing exposure to 0.2 µg/L in drinking water should be considered. The document does not consider the large increase in human blood serum PFOA levels that will result from ongoing exposure to the proposed.	This is accounted for in the document. By using a PBPK-based CSAF approach, Health Canada considered the difference in clearance between rodents and humans. The longest regularly reported half-life of 3.8 years was used as this would result in the lowest predicted water concentrations, as compared with the ½ life of 2.3 years employed by the reviewer in his calculations. No change to the document.

#	Comments	Response
51	The increase in serum PFOA level, on average, expected from ongoing consumption to the proposed MAC for PFOA of 0.2 µg/L in drinking water can be predicted using the clearance factor, 0.00014 L/kg/day, and an assumed drinking water ingestion rate (L/kg/day).	The proposed approach to calculate the increase in serum PFOA level expected from consumption to the proposed MAC is overly simplistic. The approach taken by Health Canada accounts for plasma concentrations of PFOA, addresses the non-linear kinetics of PFOA, and uses PBPK models to derive clearance rates. Furthermore, due to the use of the more conservative ½ life of 3.8 years by Health Canada, the suggested clearance factor of 0.00014 L/kg-day is less conservative than the approach taken by Health Canada (which is 0.0001 L/kg-day). No change to the document.
52	The mean daily water ingestion rate in the U.S. is 0.016 L/kg/day, and the daily water ingestion rate based on the upper percentile factors (2 L/day water consumption; 70 kg body weight) used USEPA and several U.S. states to derive health-based drinking water values is 0.029 L/kg/day. For each 10 ng/L in drinking water, ongoing exposure at the mean ingestion and upper percentile ingestion rates are predicted to increase serum PFOA by 1.2 ng/ml and 2.0 ng/ml, respectively. Drinking water exposure values used by Health Canada can be used to develop similar predictions (Table 1 – please see Appendix).	This simplistic analysis is not reflective of human exposure scenario. The % increase from drinking water (columns 4 and 7 of table 1) are based on the assumption of 2.1 ng/ml in serum based on NHANES from non-drinking water exposures; however, while the presence of PFOA in human serum is not desired, that alone does not imply the development of adverse health effects. The calculations employed by Health Canada resulted in a health-based value for PFOA, with consideration of the increases in serum PFOA levels, that is protective of human health. Additionally, the USEPA health advisory was not based on 2 L/day and 70 kg body weight; rather it was calculated assuming a drinking water exposure level of 0.054 L/kg bw per day (the 90th percentile drinking water intake for lactating women; a 3.78 L/day equivalent is calculated assuming 70 kg body weight). The text in section 10.5 has been updated to mention this.
53	Ongoing exposure to the proposed MAC is expected to result in about a 10-fold increase in serum PFOA levels with average drinking water consumption and about a 20-fold increase with upper percentile consumption. These drinking water and serum concentrations are well above those associated with human health effects.	The published human data have limitations that preclude their use as a primary quantitative basis for health based drinking water levels. Comparison of the MAC and the serum concentrations derived by the reviewer using simplistic mathematical calculations with the serum levels reported in the literature to be associated with adverse health effects is not scientifically sound. No change to the document.

#	Comments	Response
54	Importantly, both breast-fed infants whose mothers ingest contaminated drinking water and infants consuming formula prepared with contaminated drinking water receive much greater exposures to PFOA than older individuals from drinking water with the same PFOA concentration. These higher exposures are of concern because infants are a sensitive subpopulation for the developmental effects of PFOA (Post et al., 2012).	The exposure of breast-fed infants whose mothers ingest contaminated drinking water and infants consuming formula prepared with contaminated water has been thoroughly described in the document. The selected POD is protective of both infants and children because all reproductive/ developmental effects (except mammary gland development and estrogenic changes in the uterus described in detail in section 10.2) occur at much higher doses. Further, the complex modeling used in the document to account for differences in clearance also considers PFOA's long half-life following repeated high exposure in a population of retired workers. This half-life is comparable to the upper limit half-life calculated in Faroese children (Mogensen et al., 2015a). Thus, the HBV is protective of infants and children. No change to the document.
55	Serum PFOA levels (Figure 2) were measured in umbilical cord blood at delivery and at 6 month and 19 months of age in infants from the German general population (Fromme et al., 2010). Serum levels were increased, typically by several-fold, from birth to 6 months by exposure through breast milk. Levels declined between 6 months and 19 months, a time point at which breast feeding had stopped or was decreased, but remained higher at 19 months than at birth (Figure 2). It is important to note the variability in the individual infants for their internal doses. In summary, both breast-fed and formula-fed infants receive much greater exposures to PFOA from contaminated drinking water (directly or indirectly) than older individuals. Serum PFOA levels peak during the first year of life and remain elevated for several years. These elevated exposures during early life are of particular concern because effects from neonatal exposure are sensitive endpoints for the reported toxicity from PFOA exposures.	No change to the document. After six months of age, dramatic changes in dietary habits of infants occur. Unfortunately, Fromme et al. (2010) did not characterize the dietary exposure during this period (between 6 months to 18 months). Thus, the decline in PFOA levels to levels higher than at birth could be the result of ongoing exposure to PFOA or the study did not continue for long enough to see a discernable difference. Mogensen et al. (2015a) similarly saw that the decline in serum PFOA levels did not reach levels at birth up to age 5 years (although the difference was not as dramatic). The authors speculated that this could be due to dietary exposure to PFOA, in particular through traditional intake of pilot whale meat (>2/3 of children had eaten it by age 5 years). Additionally, although large differences in internal doses are shown, the range between the lowest and highest is less than 10-fold. The available information does not warrant deviating from the default (which is considered to be conservative). This approach was supported by peer reviewers.
56	9.1 - Aucune donnée sur l'ampleur de l'exposition des populations humaines étudiées n'est présentée, constituant une importante lacune de la section.	The extent of human exposure is discussed in Section 5. No change to the document.
57	9.1 - Aucune mesure d'exposition et pratiquement aucune donnée sur la taille des populations étudiées n'est fournie. Il est difficile pour le lecteur d'apprécier les résultats rapportés.	In order to make the document concise, we do not provide comprehensive descriptions of all studies in order to provide the reader with as much information as possible on the key study. The information presented in section 9.1 was used to verify the relevance of animal to human extrapolation and as such the inclusion of such details was deemed to be unnecessary. No change to the document.

#	Comments	Response
58	9.1.2 - Increases in serum liver enzymes should be added to the list of clinical biomarkers in the first paragraph. Consistent associations have been observed between PFOA exposure and increased levels of ALT in the general population and in communities with drinking water exposure.	The text has been modified to include serum liver enzymes in the list of clinical biomarkers associated with exposure to PFOA.
59	9.1.2.2 - «*Dans l'ensemble malgré une incohérence sur le plan de l'exposition et des effets observés les données de l'étude transversale et de l'étude longitudinale indiquent un certain niveau d'association entre les concentrations sériques d'APFO et le taux de cholestérol total ou de cholestérol LDL observé chez différentes populations.* » De quelle étude transversale et de quelle étude longitudinale s'agit-il?	This paragraph has been modified to indicate that it is a summary of all the longitudinal and cross-sectional studies described in the previous two paragraphs.
60	9.1.2.2 - "*The strength of association [for serum PFOA with cholesterol and/or LDL] was generally higher in the general population than in workers.*" This observation may be explained because the steepest dose-response for associations of PFOA with some health endpoints, including serum cholesterol, is observed within the lower range of serum PFOA concentrations. In the absence of data from the lower range of serum PFOA concentrations, increases in serum cholesterol with increasing serum PFOA concentration may not be detected. In occupational studies, associations may not be observed because even the lowest exposed group used as the comparison may have PFOA exposures high enough to fall on the flatter "plateau-like" portion of the dose response curve.	The text has been modified to explain that this observation can be explained due to the absence of lower ranges in serum PFOA levels in workers and thus prevents the observation of associations at lower doses.
61	9.1.2.5 - « *L'étude n'a pas pu par ailleurs s'appuyer sur les résultats d'une autre étude de cohorte non publiée menée dans la même région.* » De quelle autre étude de cohorte s'agit-il?	The document has been modified to add the appropriate reference.
62	9.1.2.8 - « *Le C8 Science Panel (étude non publiée) a découvert qu'une exposition cumulative accrue l'APFO augmentait le risque de développer une maladie intestinale inflammatoire une constatation qui a été alimentée par l'établissement d'associations avec la colite ulcéreuse.* » Il serait intéressant de donner plus de détail sur cette étude.	A full description of the C8 study is already provided in Section 9.1.2. No change to the document.
63	9.2.2 - « *Le retard du développement des glandes mammaires semble être la cible la plus sensible avec une LOAEL de 0,001 mg kg p.c. par jour (concentration sérique d'APFO : 74,8 ng mL; aucune NOAEL) chez les souris (voir la section 9.2.5.1).* » Quelles sont les études auxquelles ce LOAEL réfère?	Thank you for your comment. The text now includes the references.
64	9.2.2.1 - Pourquoi mettre l'emphase sur les résultats de l'étude de Perkins et al. (2004), laquelle a été sélectionnée pour dériver la VBS pour les effets non cancérigènes? Cela crée un déséquilibre dans la section par rapport aux autres résultats issus des autres études clés potentielles, car ces derniers ne sont pas décrits autant.	In order to keep the document as concise as possible, we do not provide comprehensive descriptions of all studies except for the one selected for HBV calculation in order to provide the reader with as much information as possible on the key study.
65	9.2.2.1 - « *Dans le cadre de la même étude on a également exposé les rats à l'APFO pendant 14 semaines et observé des augmentations à la dose minimale (30 ppm dans la nourriture, ce qui équivaut à 1,5 mg/kg p.c. par jour).* » Devrait se lire « *à la dose maximale* ».	The text has been modified to correct this sentence.

#	Comments	Response
66	9.2.2.1 - «*Ces effets ont été observés chez les rats* (refs) *et chez les souris* (refs)*. Les augmentations de poids du foie semblent généralement réversibles, puisqu'on ne les observait plus après la période d'exposition dans la plupart des études comportant une période de récupération (Palazzolo, 1993; Thomford, 2001a; Butenhoff et coll., 2002; Perkins et coll., 2004)*» Les études de Thomford et de Butenhoff, citées dans la dernière phrase, ont été menées chez des primates non humains. Or, dans la deuxième phrase, on mentionne que les effets ont été observés seulement chez les rats et les souris.	Thank you for your comment. The text has been modified to mention that the increased liver weight is also observed in monkeys exposed to PFOA.
67	9.2.2.1 - « *L'étude la plus fiable révélant une NOAEL pour ce qui est du poids du foie et de l'hypertrophie hépatocellulaire a exposé des rats Crl:CD mâles (n =55 par dose) à des doses de 0, 0,06, 0,64, 1,94 et 6,5 mg/kg p.c. par jour dans la nourriture (Perkins et coll., 2004).* » Quelle est la NOAEL?	The text has been modified to add the NOAEL to the paragraph.
68	9.2.2.1 - «*Des augmentations liées à la dose de l'incidence et de la gravité de l'hypertrophie ont été observées (tableau 3). La plupart des rats exposés à ≥0,64 mg/kg p.c. par jour présentaient une hypertrophie jugée minime à légère, dont la gravité était supérieure dans le groupe exposé à des doses élevées pendant 13 semaines;…* » Est-ce les effets étaient statistiquement significatifs?	The text has been modified to mention that the effects were statistically significant.
69	9.2.2.2 - «*Les taux de triglycérides chez les deux espèces continuaient d'être inférieurs à ceux des témoins après la période de récupération, mais, chez les souris, les taux avaient augmenté de manière assez importante pour en venir à être supérieurs à ceux du groupe exposé à des doses élevées pendant 29 jours.*» La dernière portion de cette phrase n'est pas claire, de quels groupes de souris est-il question?	The text has been modified for clarity.
70	9.2.2.2 - Two studies not cited in the document suggest the possibility that differences in dietary fat content may contribute to the observed differences in effects of PFOA on serum lipids in rodents versus humans. Tan et al. (2013) and Rebholz et al. (2016) should be added to the document.	The text has been modified to include the studies that suggest that dietary fat content may contribute to differences in the effects of PFOA on serum lipids in rodents vs humans (Tan et al., 2013; Rebholz et al., 2016) as well as an increased risk of hepatic toxicity (Tan et al., 2013).
71	9.2.2.3 - « *D'autres effets que les effets hépatiques et hépatiques sériques ont été observés dans des études à court terme menées sur des animaux adultes exposés à l'APFO à des doses de 1 mg/kg p.c. par jour.* » Devrait se lire « *sur les lipides sériques* »	The text has been modified to correct this error.
72	9.2.2.3 - "*the only study indicating changes in thyroid hormone levels reported decreased free and total T3 and T4 in monkeys exposed for 6 months (Butenhoff et al., 2002).*" An additional study evaluating these endpoints (Martin et al., 2007) should be mentioned.	The text has been modified to include the Martin et al. (2007) reference.
73	9.2.2.3 - It is stated that immune effects of PFOA in mice occur at doses of > 3.75 mg/kg/day. However, Son et al. (2009), not cited in the document, reported a lower LOAEL for immune effects of PFOA. They found decreased numbers of splenic T cell subpopulations (CD4-CD8+, CD4+CD8+) in male ICR mice dosed with > 0.49 mg/kg/day PFOA in drinking water for 21 days, with no NOAEL identified.	The text has been modified to indicate that immunosuppression occurs at doses as low as 0.49 mg/kg bw per day and to include this reference (Son et al., 2009).

#	Comments	Response
74	9.2.3 - « *En ce qui concerne la voie orale nous avons ciblé deux études sur la toxicité chronique menées sur des animaux de laboratoire.* », mais 4 publications sont citées dans cette sous-section. Est-ce que les publications de 3M (1983); Sibinski (1987); Butenhoff et coll. (2012b) traitent de la même étude, laquelle a été réalisée dans les années 1980? Si oui, le mentionner.	The text has been modified to explain that these three publications refer to the same study.
75	9.2.3 - It is suggested that additional information be added about the chronic rat study reported by Sibinski et al. (1987) and Butenhoff et al. (2012).	While the information suggested to be added is interesting, it does not add to the derivation of the health based value nor does it add to the weight of evidence. The information currently included in the document is a thorough and detailed description of the most relevant findings from these studies. Thus, with the goal of maintaining a concise document, no change was made to the document.
76	9.2.5 - The mouse study conducted by White et al. (2011) is not a standard two-generation study, but was rather a "multi-generational" study. Males were not dosed with PFOA as is done is a standard two-generation study.	The text has been modified to indicate that this study was a "multi-generational" study rather than a two-generation study.
77	9.2.5 - When discussing developmental effects in rats, it is important to mention that female rats excrete PFOA very rapidly. Steady-state is not reached in female rats from once daily gavage dosing, and exposures to the developing fetus are much lower than in other species given the same administered doses.	This information is discussed in detail throughout Section 8. Considering that the studies discussed in Section 9.2.5 are primarily in mice, it is not necessary to re-mention the differences in PFOA excretion in female rats. No change to the document.
78	9.3 - I agree with the conclusion that the mode of action information indicates that the toxicological effects of PFOA should be considered relevant to humans. However, I disagree with the statement that "the TDI approach is the most appropriate method for cancer risk assessment."	Section 9.4 explains that the weight of evidence for a non-mutagenic mode of action is stronger than for direct-acting mutagenicity, which suggests that low dose linear extrapolation is not appropriate for PFOA-induced tumours. No change to the document.

Section 10.0: Classification and assessment

#	Comments	Response
79	10.0 - «*Nous avons sélectionné celle-ci plutôt que l'utilisation de concentrations sériques comme PDD, parce que nous avons déterminé que les modèles humains PBPK n'étaient pas suffisamment solides pour obtenir des estimations précises des niveaux d'exposition correspondants aux PDD fondés sur le sérum.* » Cette information devrait se trouver à la section 8.6. Y-a-t-il un impact sur les valeurs de CAFI calculées? Sont-elles sous-estimées ou surestimées?	This information is important here to remind the reader of the rationale behind our approach. Further discussion about the use of plasma over serum is provided in response to previous comment in section 8.
80	10.1 - « *L'utilisation d'une modélisation des doses de référence n'est généralement pas recommandée pour les études comportant seulement deux groupes de doses.* » Alors pourquoi l'avoir modélisé?	The text has been corrected to reflect that the POD selected was indeed the NOAEL. Additionally, as already stated in section 10.1, BMD modeling was done for comparison purposes as described in the text.
81	10.1 - The cancer risk assessment assumes that PFOA causes tumors through a threshold MOA, because the MOA for tumors caused by PFOA has not been established, and most studies indicate that PFOA is not genotoxic. The HBV is based on a TDI instead of a cancer potency factor. Studies showing associations of increased incidence of cancer in humans with PFOA drinking water concentrations well below 30 µg/L were not considered. Kidney and testicular cancer were associated with exposure to PFOA in drinking water at concentrations much lower than 30 µg/L in the C8 Health Study. Although these data have limitations which preclude their use as the primary basis for risk assessment, they strongly suggest that the HBV of 30 µg/L is not sufficiently protective for carcinogenic effects. The cancer risk assessment is based on Leydig cell testicular tumors from a chronic rat study (Butenhoff et al., 2012). Although the mode of action for testicular Leydig cell tumor induction by PFOA is unknown, a non-threshold mode of action cannot be dismissed.	Although the weight of evidence indicates that PFOA exposure is associated with human health effects, the existing epidemiology studies do not support direct causality and cannot be used as a basis for the HBV for drinking water. The approach used to derive HBVs uses the best science with conservative estimates to be protective of health from lifetime exposure to PFOA in drinking water at the MAC. The mode of action analysis presented in section 9.4 explains that the weight of evidence for a non-mutagenic mode of action is stronger than for direct-acting mutagenicity, which suggests that low dose linear extrapolation is not appropriate for PFOA-induced tumours. Therefore, the use of a threshold approach is appropriate for the cancer risk assessment. No change to the document.
82	10.1 - «*1,3 mg/kg p.c. par jour représente la BMD_{10} associée aux tumeurs des cellules de Leydig chez les rats mâles (Butenhoff et coll., 2012b)*» BMD_{10} devrait se lire NOAEL.	The text has been modified to correct this error.

#	Comments	Response
83	10.2 - Plusieurs doses sont rapportées et comparée dans cette section afin de justifier le choix du PDD pour les effets non cancérigènes. Or : 1) Puisque les différences dans la toxicocinétique de l'AFPO entre les humains et les animaux de laboratoire sont spécifiques aux espèces et aux doses administrées, les facteurs d'incertitude pour l'extrapolation inter espèce (composant cinétique) sont très variables et sont passsablement supérieures au facteur par défaut de 4 (soit entre 17 et 97 pour le rat et le singe). C'est pourquoi il serait préférable que les comparaisons entre les PDD potentiels dont il est question dans cette sous-section s'effectue sur la base des points de départ équivalents chez l'humain (PDDEQH) et non sur celle des doses administrées à l'animal. 2) la lecture est particulièrement ardue en l'absence d'un tableau synthèse qui permet de comparer, d'une étude à l'autre, les espèces étudiées, les doses administrées, le(s) mode(s) d'administration, les durées d'exposition, les effets critiques observés et les PDDEQH associés ainsi que le raisonnement ayant permis de rejeter et ou de retenir les PDDEQH pour le calcul de l'AQT.	In fact, in selecting the lowest POD, we did compare the external human doses (and the TDIs) for each study. The outcome of the comparisons were the same as that described in the text. The justification for not using the studies with lower PODs was included in the text based on biological plausibility and human relevance. Health Canada limits the use of tables in their documents for web publishing policy reasons.
84	10.2 - « *En outre, de légers changements (bien que significatifs) dans le développement des glandes mammaires et le poids corporel démontrent que ceux-ci sont liés au traitement, mais pas nécessairement au caractère nocif du composé – il n'y avait aucune preuve de consommation de lait insuffisant ou d'incapacité de se développer chez les petits des mères démontrant des changements dans le DGM, et les variations de poids étaient faibles (mesurées à <10 %).* » À quelle(s) étude(s) fait-on référence ici? À la sous-section 9.2.5.1, il est question de trois études pour lesquelles les effets au DGM ont été observés à des doses inférieures à 1 mg/kg-jour (et aussi faible que 0,001 mg/kg-jour). Aussi, que veut-on dire par « *pas nécessairement au caractère nocif du composé* »? Même s'il y a absence d'effets sur la lactation ou le poids corporel des portées, l'étude démontre tout de même un effet sur le développement (DGM). Pourquoi ne pas avoir considérer cet effet, d'autant plus que, selon la section 9.2, l'une des trois études, soit l'étude de White, est la seule pour laquelle les auteurs ont administré le PFOA par l'eau potable *ad libitum* (et non par la diète ou par gavage). Il serait pertinent de meiux justifier le fait de ne pas avoir considéré le retard de DGM dans la détermination de la VBS pour les effets non cancérigènes, d'autant plus que, comme les VBS pour les effets au développement s'appuient sur un scénario pour le nourrisson ou la femme enceinte, celles-ci sont susceptibles d'être moins élevées que les VBS fondées sur d'autres effets systémiques comme les effets hépatiques.	The justification for not using the delayed mammary gland development for HBV calculation has been very thoroughly explained in section 10.2. The necessary references are included in the 3rd line of that same paragraph so a repetition a few lines later is unnecessary. Regarding the question as to why it matters if an effect is adverse or not: Adversity of an outcome must be demonstrated for it to be used for HBV calculation. Some physiological changes occur as a result of adaptive changes in response to a stressor that have no deleterious or long-term consequences. Based on the current available information, the observed delayed mammary gland development is a non-adverse response to exposure. This conclusion was also reached by our colleagues at the EPA and was supported by external and internal peer reviewers. No change to the document.
85	10.2 - Sensitive toxicological endpoints were not considered in developing the proposed MAC. Increased liver weight and hepatocellular hypertrophy, the endpoints used as the basis for the MAC, are not the most sensitive well-established toxicological effects of PFOA. Multiple toxicological effects (delayed mammary gland development, persistent hepatic structural changes, and others such as obesity) result from developmental exposures to PFOA at doses far below those that cause increased liver weight in adult animals, suggesting that the MAC based on the increased liver weight is not sufficiently protective.	These toxicological endpoints were considered in deriving the proposed MAC. Section 9 extensively describes these health effects associated with exposure to PFOA in humans and animals. No change to the document.

#	Comments	Response
86	10.2 - A NOAEL was used as the POD for the TDI for hepatocellular hypertrophy and increased liver weight in Perkins et al. (2004). However, use of a benchmark dose approach is preferable to use of a NOAEL because a benchmark dose uses data from the entire dose-response curve for the critical effect rather than from the single dose group at the NOAEL. It is not clear why a Benchmark Dose for increased liver weight and hepatocellular hypertrophy from Perkins et al. (2004) was not developed.	The text has been modified to replace the NOAEL of 0.06 mg/kg bw per day with a $BMDL_{10}$ of 0.05 mg/kg bw per day. The final health based value does not change.
87	10.2 - «*0,06 mg/kg p.c. par jour représente la NOAEL pour l'hypertrophie hépatocellulaire de l'étude Perkins et coll. (2004), qui a été choisie pour représenter la base de données sur l'hypertrophie hépatocellulaire et les augmentations du poids du foie;* » Est-ce que les données de cette étude ne permettaient pas une modélisation de la dose de référence? Si oui, le mentionner.	The text has been modified to replace the NOAEL of 0.06 mg/kg bw per day with a $BMDL_{10}$ of 0.05 mg/kg bw per day. The final health based value does not change.
88	Nous appuyons l'utilisation de facteurs d'incertitude spécifiques à l'APFO pour la composante toxicocinétique de l'extrapolation inter-espèce. Toutefois, il serait intéressant que Santé Canada compare les facteurs d'incertitude obtenus avec ceux publiés par les organismes de référence ayant eu recours également à un facteur d'incertitude spécifique, d'autant plus que des différences entre les facteurs calculés par Santé Canada et ceux calculés par d'autres organismes sont observées (MDH, 2009, ATSDR, 2015, US EPA, 2016).	It is beyond the scope of this document to directly compare this assessment to approaches used by other agencies.
89	Nous questionnons l'argumentaire utilisé pour rejeter les effets sur le développement mammaire, d'autant plus qu'il semble que les auteurs de l'une des études concernées sont les seuls à avoir eu recours à l'eau potable comme mode d'administration (White et al., 2011). Une justification plus appuyée à cet effet serait appropriée dans le contexte où la plus récente recommandation de la US EPA s'appuie sur des effets aux développement.	The justification for not using the delayed mammary gland development for HBV calculation has been very thoroughly explained in section 10.2 of the document. No change to the document. As more scientific information on this endpoint becomes available, Health Canada will revisit the assessment.
90	Toutefois, puisque la justification entourant le choix de l'effet critique retenu par Santé Canada est incomplète, nous ne sommes pas en mesure de nous prononcer sur ce dernier. Dans cette optique, il serait utile de mieux appuyer le choix de l'effet critique au regard des autres effets critiques potentiels, plus particulièrement ceux retenus par la US EPA.	It is beyond the scope of this document to directly compare this assessment with approaches used by other agencies. Health Canada used hepatocellular hypertrophy, which is the most sensitive (lowest) adverse effect POD of all studies in the literature, increases in a dose-related manner, is observed consistently across species and sexes, is considered to be a sensitive indicator and precursor of adverse liver effects, and is supported by human studies that show changes in liver enzymes; mode of action analysis supports human relevance of this endpoint. The reproductive/developmental effects used by EPA occurred at higher doses (> 1 mg/kg bw per day). EPA used the 90th percentile drinking water intake for lactating women of 0.054 L/kg bw per day (i.e., 3.78 L/d assuming 70 kg body weight), almost twice the volume of water assume used to derive their MCLs. No change to the document.

#	Comments	Response
91	10.2 - «*Nous n'avons utilisé aucun facteur d'incertitude pour l'extrapolation de l'exposition subchronique à chronique, puisque les effets hépatiques ont fait l'objet d'un examen dans une étude sur l'exposition chronique (Butenhoff et coll., 2012b) et que l'augmentation de la durée d'exposition n'a pas semblé aggraver les effets dans la principale étude sur le sujet (Perkins et coll., 2004).*» Sur quelle base s'appuie-t-on pour conclure que «*l'augmentation de la durée d'exposition n'a pas semblé aggraver les effets*»?	The justification for not using a sub-chronic to chronic uncertainty factor is already in the document and was supported by expert peer reviewers. Briefly, the liver effects observed in the chronic studies occurred at higher doses compared to the sub-chronic studies, indicating that the severity of the effect does not increase with time at the low exposure doses. No change to the document.
92	10.2 - Human health effects are consistently associated with drinking water concentrations below the proposed and blood serum levels below those that result from 0.2 µg/L. The document acknowledges that "*the human weight of evidence provides a strong argument in favor of detrimental health effects of the compound*". However, the drinking water concentrations and serum PFOA levels at which these effects occur are not considered. Multiple human health effects, some with evidence supporting multiple criteria for causality, are associated with exposures to PFOA drinking water concentrations well below 0.2 µg/L and with serum PFOA levels well below those resulting from exposure to this concentration in drinking water. These associations have been observed in communities exposed to PFOA through drinking water and at the lower serum PFOA levels in the general population without known exposure through drinking water. Although the human data have limitations that preclude their use as the primary quantitative basis for health-based drinking water levels such as the MAC, the overall body of human evidence indicates the need for caution about additional exposures from drinking water.	The assertion that the human health studies provide evidence supporting multiple criteria for causality is misleading. As it stands, although the weight of evidence indicates that PFOA exposure is associated with human health effects, the existing studies do not support direct causality and cannot be used as a quantitative basis for deriving health based values for drinking water. Thus, comparing the MAC with the drinking water concentrations used in these studies is not scientifically sound. The approach Health Canada employed to derive health based values uses the best science with conservative estimates to be protective of human health with lifetime exposure to PFOA in drinking water at the MAC. No change to the document.
93	10.4 - De son côté, la US EPA a publié en 2016 un nouvel *Lifetime Health Advisory*, basé sur un AQT chronique de 0,02 µg/kg de p.c. par jour (ou VBS de 0,07 µg/L) sur les retards au développement osseux et sexuel des souris. Il serait particulièrement pertinent que cette évaluation soit au minimum présentée à la section 10.4 et accompagnée d'une analyse critique du document de l'agence américaine, puisque leur recommandation de 0,07 µg/L est la plus récente publiée sur le sujet et la plus faible publiée par un organisme reconnu.	Information on the U.S. EPA's 2016 Lifetime Health Advisory has been incorporated into section 10.4 of the document. Health Canada derives health based values based on the latest science for the protection of human health, using the Canadian context and assumptions. International assessments are considered in our approach, but it is not appropriate to include a critical analysis of another agency's assessment. No change to the document.
94	10.4 - « *Selon la politique de l'U.S. EPA, un APS (0,4 µg/L; 0,0004 mg/L) a également été calculé pour un enfant de 10 kg consommant 1 L d'eau par jour en utilisant l'hypothèse par défaut que l'eau potable constitue 20 % de l'exposition totale à l'APFO* ». Est-ce qu'une valeur pour les enfants a été calculée ? Si oui, la valeur correspondante devrait être précisée.	This short-term value was the only value available from the U.S. EPA when the consultation document was drafted, but it has not been published to date. This section has been updated with the more recent health advisory adopted by the U.S. EPA. No change to the document.

Section 11.0: Rationale

#	Comments	Response
95	11.0 - Puisque les effets critiques du SPFO et de l'APFO sont les mêmes et que ces derniers sont susceptibles d'être présents simultanément dans l'eau potable, il serait approprié de discuter de la pertinence ou non de présenter une recommandation commune à la fois pour l'APFO et le SPFO. C'est d'ailleurs l'avenue privilégiée par la US EPA (2016).	The text has been modified to indicate that Health Canada is recommending an additive approach for PFOS and PFOA in new sections (2.4, 9.4, 10.4, and 11.0). Thank you for your comment.

Section 12.0: References suggested for addition:

This guideline technical document is not meant to be a comprehensive review of the literature. All references submitted were reviewed, however only publications deemed to be relevant to the Canadian population and the MAC have been added to the document.

#	Comment	Response
	1. Alberta Health and Wellness (2010). The Alberta Biomonitoring Program: Chemicals in Serum of Children in Southern Alberta (2004 2006) – Influence of Age and Comparison to Pregnant Women. Alberta Health and Wellness. Edmonton.	Used pooled blood samples and reported levels by age group. No added value compared to existing information in 5.6. No change to the document.
	2. Alberta Health and Wellness (2008). Alberta Biomonitoring Program: Chemicals in Serum of Pregnant Women in Alberta. Surveillance and Environmental Health. Public Health Division. Edmonton.	Used pooled blood samples and reported levels by age group. No added value compared to existing information in 5.6. No change to the document.
	3. Beesoon, S., Martin, J.W. (2015). Isomer-specific binding affinity of PFOS and PFOA to serum proteins. Environ. Sci. Technol. 49: 5722–5731.	Added to document.
	4. Beesoon, S., Genuis, S.J., Benskin, J.P., Martin, J.W. (2012). Exceptionally high serum concentrations of PFOS in a Canadian family are linked to home carpet treatment applications. Environ. Sci. Technol. 46: 12960–12967	Added to section 5.5 of document.
	5. Bischel, H.N., MacManus-Spencer, L.A., Zhang, C., Luthy, R.G. (2011). Strong associations of short-chain perfluoroalkyl acids with serum albumin and investigation of binding mechanisms. Environ. Toxicol. Chem. 30: 2423–2430.	Not relevant. Only bovine serum albumin. No change to the document.
	6. Bloom, M.S., Jansing, R.L., Kannan, K., Rej, R., Fitzgerald, E.F., 2014. Thyroid hormones are associated with exposure to persistent organic pollutants in aging residents of upper Hudson River communities. Int. J. Hyg. Environ. Health. 217: 473–482.	No PFAS included in study. No change to the document.
	7. Chan, E., Sandhu, M., Benskin, J.P., Ralitsch, M., Thibault, N., Birkholz, D., Martin, J.W. 2009. Endogenous high-performance liquid chromatography / tandem mass spectrometry interferences and the case of perfluorohexanesulfonate (PFHxS) in human serum; are we overestimating exposure? Rapid Commun. Mass Spectrom. 23: 1405–1410.	No PFAS included in study. No change to the document.

	Comment	Response
	8. Ehresman, D.J., Froehlich, J.W., Olsen, G.W., Chang, S.-C., Butenhoff, J.L. 2007. Comparison of human whole blood, plasma, and serum matrices for the determination of perfluorooctanesulfonate (PFOS), perfluorooctanoate (PFOA), and other fluorochemicals. Environ.Res. 103:176–184.	Methods paper. No change to the document.
	9. Fisher, M., Arbuckle, T.E., Wade, M., Haines, D.A. 2013. Do perfluoroalkyl substances affect metabolic function and plasma lipids? – analysis of the 2007–2009, Canadian Health Measures Survey (CHMS) cycle1. Environ.Res. 121: 95–103.	Added to document.
	10. Glynn, A., Berger, U., Bignert, A., Ullah, S., Aune, M., Lignell, S., Darnerud, P.O. 2012. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends1996–2010. Environ.Sci.Technol. 46(16): 9071–9079.	Serum levels in Swedish pregnant women. No added value. No change to the document.
	11. Goosey, E., Harrad, S. 2011. Perfluoroalkyl compounds in dust from Asian, Australian, European, and North American homes and UK cars, classrooms, and offices. Environ. Int. 37(1): 86–92.	Added to document.
	12. Hanssen, L., Dudarev, A.A., Huber, S., Odland, J.O., Nieboer, E., Sandanger, T.M. 2013. Partition of perfluoroalkyl substances (PFASs) in whole blood and plasma, assessed in maternal and umbilical cord samples from inhabitants of Arctic Russia and Uzbekistan. Sci. Total Environ. 447: 430–437	No added value. Serum levels in Russian/Uzbekistan pregnant women. No change to the document.
	13. Hanssen, L., Roellin, H., Odland, J.O., Moe, M.K., Sandanger, T.M. 2010. Perfluorinated compounds in maternal serum and cord blood from selected areas of South Africa: results of a pilot study. J. Environ. Monit. 12:1355–1361.	No added value. Serum levels in South African pregnant women. No change to the document.
	14. Hebert, P.C., MacManus-Spencer, L.A. 2010. Development of a fluorescence model for the binding of medium-to long-chain perfluoroalkyl acids to human serum albumin through a mechanistic evaluation of spectroscopic evidence. Anal. Chem. 82:6463–6471.	Methods paper. No change to the document.
	15. Jones, P.D., Hu, W., De Coen, W., Newsted, J.L., Giesy, J.P., 2003. Binding of perfluorinated fatty acids to serum proteins. Environ. Toxicol. Chem. 22: 2639–2649.	Wildlife albumin (carp, avian, bovine). No change to the document.
	16. Kowalczyk, J., Ehlers, S., Oberhausen, A., Tischer, M., Fuerst, P., Schafft, H., Lahrssen-Wiederholt, M. 2013. Absorption, distribution, and milk secretion of the perfluoroalkyl acids PFBS, PFHxS, PFOS, and PFOA by dairy cows fed naturally contaminated feed. J. Agric. Food Chem. 61: 2903–2912.	Dairy cows. No change to the document.
	17. Moody CA, Martin JW, Kwan WC, Muir DCG, Mabury SA. 2002. Monitoring perfluorinated surfactants in biota and surface water samples following an accidental release of fire-fighting foam into Etobicoke Creek. Environ. Sci. Technol. 36: 545–551.	Added to document.
	18. Olsen, G.W., Lange, C.C., Ellefson, M.E., Mair, D.C., Church,T.R., Goldberg, C.L., Herron, R.M., Medhdizadehkashi, Z., Nobiletti, J.B., Rios, J.A., Reagen, W.K., Zobel, L.R. 2012. Temporal trends of perfluoroalkyl concentrations in American Red Cross adult blood donors,	No added value. No change to the document.

#	Comment	Response
	2000–2010. Environ. Sci. Technol. 46: 6330–6338.	
	19. Olsen, G.W., Huang, H.Y., Helzlsouer, K.J., Hansen,K.J., Butenhoff, J.L., Mandel, J.H. 2005. Historical comparison of perfluorooctanesulfonate, perfluorooctanoate, and other fluorochemicals in human blood. Environ. Health Persp. 113: 539–545.	No added value. Old study compared to what is already in document. No change to the document.
	20. Olsen, G., Church, T., Hansen, K., Burris, J., Butenhoff, J., Mandel, J., Zobel, L.R. 2004. Quantitative evaluation of perfluorooctanesulfonate (PFOS) and other fluorochemicals in the serum of children. J. Child. Health. 2(1): 53–76.	No added value. Old study compared to what is already in document. No change to the document.
	21. Pan, Y., Shi, Y., Wang, J., Cai, Y., Wu, Y. 2010. Concentrations of perfluorinated compounds in human blood from twelve cities in China. Environ. Toxicol. Chem. 29: 2695–2701.	No added value. Serum levels in China, No change to the document.
	22. Salvalaglio, M., Muscionico, I., Cavallotti, C. 2010. Determination of energies and sites of binding of PFOA and PFOS to human serum albumin. J. Phys. Chem. B. 114:14860–14874.	Outside scope of document. No change to the document.
	23. Yeung, L.W.Y., So, M.K., Jiang, G.B., Taniyasu, S., Yamashita, N., Song, M.Y., Wu, Y.N., Li, J.G., Giesy, J.P., Guruge, K.S., Lam, P.K.S. 2006. Perfluorooctanesulfonate and related fluorochemicals in human blood samples from China. Environ. Sci. Technol. 40: 715–720.	No added value. Blood levels in China. No change to the document.
	24. Zhang, Y., Jiang, W., Fang, S., Zhu, L., Deng, J. 2014. Perfluoroalkyl acids and the isomers of perfluorooctanesulfonate and perfluorooctanoate in the sera of 50 new couples in Tianjin,China. Environ. Int. 68:185–191.	No added value. Serum levels in China. No change to the document.
	25. Zhang,Y., Beesoon, S., Zhu, L., Martin, J.W. 2013. Biomonitoring of perfluoroalkylacids in human urine and estimates of biological half-life. Environ. Sci. Technol. 47: 10619–10627	No added value. Levels in Chinese population. No change to the document.
	26. Zhang,Y., Beesoon, S., Zhu, L., Martin, J.W. 2013. Isomers of perfluorooctanesulfonate and perfluorooctanoate and total perfluoroalkyl acids in human serum from two cities in North China. Environ. Int. 53: 9–17.	No added value. Levels in Chinese population. No change to the document.
	27. Zhang, T., Wu, Q., Sun, H.W., Zhang, X.Z., Yun, S.H., Kannan, K. 2010. Perfluorinated compounds in whole blood samples from infants, children, and adults in China. Environ. Sci. Technol. 44: 4341–4347.	No added value. Levels in Chinese population. No change to the document.
	28. Mondal et al., 2014	Added to document.
	29. Mogensen et al., 2015a	Added to document.
	30. Mogensen et al., 2015b;	Added to document.
	31. Verner et al., 2015	Does not provide added value to the document. No change to the document.

#	Comment	Response
	32. Verner et al., 2016a	Does not provide added value to the document. No change to the document.
	33. Verner et al., 2016b	Does not provide added value to the document. No change to the document.
	34. Gleason et al., 2015	The text has been modified to include the Gleason et al. (2015) study.
	35. Grandjean et al., 2016	Added to document.
	36. NTP, 2016	Added to document.
	37. Chang et al, 2016. A critical review of PFOA ad PFOS exposure and immunological health conditions in humans. Crit Rev Toxicol 2016; 46:279-231	The text has been modified to include a description of the Chang et al. (2016) study.
	38. Johnson PI et al., 2014. The navigation guide-Évidence based medicine meets environmental health : systematic review of human evidence for PFOA effects on fetal growth	Added to document.
	39. Bach CC et al. (2015). Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth : a systematic review. Crit Rev Toxicol, Jan;45(1) :53-67.	Added to document.
	40. Lopez-Espinosa et al., 2016	Thank you for your comment. The text now includes this reference.
	41. Romano et al., 2016	Thank you for your comment. The text now includes this reference.
	42. Timmermann et al., 2016	Thank you for your comment. The text now includes this reference.
	43. Filgo et al., 2015	Thank you for your comment. The text now includes this reference.
	44. Quist et al., 2015	Thank you for your comment. The text now includes this reference.
	45. Martin et al. (2007).	Thank you for your comment. The text has been modified in section 9.2.2.3 to include this reference.

4 Parameters - Chemical

4-D 1,4-Dioxane

Reference/Action:

- Oral presentation on the draft guideline technical document on 1,4-dioxane in drinking water
- Status: The work on the document was initiated in December 2014. The document went through an external peer-review process which ended in December 2016. The comments from the peer-reviewers were addressed and the document revised accordingly. The document is presented at this meeting for approval by CDW for a 2 month public consultation period.
- To be sent prior to meeting: Draft guideline technical document for 1,4-dioxane in drinking water
- For CDW discussion/approval

Notes:

4 Parameters - Chemical

4-E Chloramines

Reference/Action:

- Oral presentation on the draft guideline technical document on chloramines in drinking water
- Status: The work on the chloramines document was initiated in November 2014. The document is being drafted and will go through internal and external peer-review processes in summer 2017. The document is expected to be presented to CDW members at the fall 2017 meeting for approval for a 2-month public consultation period.
- For information only

Notes:

4 Parameters - Chemical

4-F Barium

Reference/Action:

- Oral presentation on the draft guideline technical document for barium in drinking water
- Status: The work on the barium document was initiated in January 2016. The document is being drafted and will go through internal and external peer-review processes in summer 2017. The document is expected to be presented to CDW members at the fall 2017 meeting for approval for a 2-month public consultation period.
- For information only

Notes:

4 Parameters - Chemical

4-G 2,4-D

Reference/Action:

- Oral presentation on the draft guideline technical document for 2,4-D in drinking water
- Status: The work on the guideline technical document on 2,4-D in drinking water was initiated in April 2012. The work on the document was postponed in late 2013 when PMRA announced a special review, expected be completed and posted by end of March 2017, but we are still awaiting PMRA's special review decision.
- For information only

Notes:

4 Parameters - Chemical

4-H Strontium

Reference/Action:

- Oral presentation on the draft guideline technical document on strontium in drinking water
- Status: The work on the document was initiated in November 2014. The document went through internal and external peer-review processes which ended in December 2016. The comments from the peer-reviewers were addressed and the document revised accordingly. The document is presented at this meeting for approval by CDW for a 2 month public consultation period.
- To be sent prior to meeting: Draft guideline technical document for strontium in drinking water
- For CDW discussion/approval

Notes:

4 Parameters - Chemical

4-I Microcystins (recreational)

Reference/Action:

- Verbal update on upcoming work on the recreational water quality guidelines
- For information only

Notes:

4 Parameters - Chemical

4-J Other chemical

Reference/Action:

- Other parameters /issues to discuss, including pesticides
- For information only

Notes:

5 Secretariat Projects

5-A Guidance for well owners

Reference/Action:

- Oral presentation on the guidance for well owners and discussion on path forward
- For CDW discussion

Notes:

5 Secretariat Projects

5-B EHSRB update

Reference/Action:

- Verbal update by Dr. Anca-Maria Tugulea (Exposure and Biomonitoring Division) on drinking water related research at the Environmental Health and Research Bureau (EHSRB)
- For information only

Notes:

5 Secretariat Projects

5-C INAC update

Reference/Action:

- Oral presentation by Karl Carisse from INAC (Indigenous and Northern Affairs Canada) on the status of the Safe Drinking Water for First Nations Act
- For information only

Notes:

6 Committee Liaison Reports

6-A FNIHB report

Reference/Action:

- Kristina Taracha will provide a verbal update on First Nations and Inuit Health Branch activities related to drinking water
- For information only

Notes:

6 Committee Liaison Reports

6-B WHO report

Reference/Action:

- Verbal update on WHO-related activities
- For information only

Notes:

6 Committee Liaison Reports

6-C CHE report

Reference/Action:

- Verbal update on CHE activities
- For information only

Notes:

6 Committee Liaison Reports

6-D CCME Report

Reference/Action:

- Verbal update on CCME activities by Philippa Cureton from Environment Canada
- For information only

Notes:

7 Member's Reports

Reference/Action:

- Verbal update by all CDW members

Notes:

8 Future Meetings

Reference/Action:

- Future meetings
- Status: fall 2017 meeting: November 7-9, 2017; spring 2018 meeting: May 1-3, 2018.
- Need to find date for fall 2018 meeting
- For CDW discussion/decision

Notes:

Perfluorooctanoic Acid (PFOA) in Drinking Water

Document for Public Consultation

Prepared by the Federal-Provincial-Territorial Committee on Drinking Water

Consultation period ends
Month, 201?

Perfluorooctanoic Acid in Drinking Water
Document for Public Consultation
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November, 2015

Perfluorooctanoic Acid in Drinking Water

Purpose of consultation

The Federal-Provincial-Territorial Committee on Drinking Water (CDW) has assessed the available information on PFOA with the intent of developing a drinking water guideline and guideline technical document on PFOA in drinking water. The purpose of this consultation is to solicit comments on the proposed guideline, on the approach used for its development and on the potential economic costs of implementing it, as well as to determine the availability of additional exposure data.

This document proposes a maximum acceptable concentration (MAC) of 0.0002 mg/L (0.2 µg/L) for PFOA in drinking water, based on liver effects in rats. The document is based on currently available scientific studies and approaches. It incorporates a detailed mode of action analysis and modelling to establish a proposed guideline for PFOA. It provides exposure information as well as analytical methods and treatment technologies that may be effective for PFOA removal at the municipal and residential scales.

The CDW has requested that this document be made available to the public and open for comment. Comments are appreciated, with accompanying rationale, where required. Comments can be sent to the CDW Secretariat via email at water_eau@hc-sc.gc.ca. If this is not feasible, comments may be sent by mail to the CDW Secretariat, Water and Air Quality Bureau, Health Canada, 3rd Floor, 269 Laurier Avenue West, A.L. 4903D, Ottawa, Ontario K1A 0K9. All comments must be received before XXX, 2016.

Comments received as part of this consultation will be shared with the appropriate CDW member, along with the name and affiliation of their author. Authors who do not want their name and affiliation shared with their CDW member should provide a statement to this effect along with their comments.

It should be noted that this guideline technical document on PFOA in drinking water will be revised following evaluation of comments received, and a drinking water guideline will be established, if required. This document should be considered as a draft for comment only.

November 2015

Perfluorooctanoic Acid

Part I. Overview and Application

1.0 Proposed guideline

A maximum acceptable concentration (MAC) of 0.0002 mg/L (0.2 µg/L) is proposed for PFOA in drinking water.

2.0 Executive summary

PFOA is a man-made compound that does not occur naturally in the environment. It is used in the manufacture of stain/water-resistant coatings for various consumer products and in specialized chemical applications, such as fire-fighting foams, hydraulic fluids, and carpet spot removers. Environmental concentrations, and therefore potential exposure levels, may be higher in areas near facilities using high amounts of PFOA and near locations with extinguished fires if PFOA-containing fire-fighting foams were used.

This guideline technical document reviews and assesses all identified health risks associated with PFOA in drinking water. It incorporates new studies and approaches and takes into consideration the availability of appropriate treatment technology. Based on this review, the proposed drinking water guideline for PFOA is a maximum acceptable concentration (MAC) of 0.0002 mg/L (0.2 µg/L), based on the general population.

During its fall 2015 meeting, the Federal-Provincial-Territorial Committee on Drinking Water reviewed the guideline technical document on PFOA and gave approval for this document to undergo public consultation.

2.1 Health effects

PFOA and its salts have been classified as possibly carcinogenic to humans (Group 2B) by IARC, based on limited epidemiological evidence demonstrating associations between PFOA and testicular and renal cancers, and on limited evidence in experimental animals. Non-cancer effects occurring at the lowest level of exposure to PFOA in animals include reproductive and developmental effects, liver effects and changes in serum lipid levels.

Both cancer and non-cancer endpoints were considered in the derivation of the proposed MAC for PFOA in drinking water. The non-cancer approach, based on liver effects in rats, was used to calculate a proposed MAC that is protective of human health from both cancer and non-cancer effects.

2.2 Exposure

Canadians can be exposed to PFOA in food, consumer products, dust, and drinking water. Exposure is mainly from food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Although PFOA is not regularly monitored at water treatment plants in Canada, the analysis has been performed for a few locations. When detected in drinking water, it is usually found below 2 or 3 ng/L.

2.3 Analysis and treatment

To date, the United States Environmental Protection Agency has not approved any analytical methods for the analysis of PFOA in drinking water. There are some methods that can be used to measure PFOA in drinking water at levels well below the proposed MAC. However, they require good quality control procedures to get accurate results.

The selection and effectiveness of a treatment strategy for PFOS removal is driven by several factors, including source water chemistry, concentration of PFOA and/or other perfluoroalkyl substances and pre-existing treatment processes. Conventional treatment is not effective for PFOA removal. Other treatment methods are promising, although full-scale studies are limited. Activated carbon adsorption can achieve treated water concentrations of PFOA below the proposed MAC. However, proper operation of the system is essential to ensure that the performance of GAC is not affected by the presence of natural organic matter in the source water. Membrane filtration techniques (reverse osmosis and nanofiltration) and anion exchange may also be effective. Although there are no residential treatment devices certified to remove PFOA, it is expected that the same treatment technologies would also be effective at the residential scale.

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

3.1 Monitoring

PFOA is typically found in groundwater and surface water contaminated by discharges from industrial facilities; discharge from wastewater treatment plants treating domestic and industrial waste; storm water runoff; land application of biosolid amended soils as well as groundwater and surface water sources that are or may have been impacted by aqueous film-forming foam (AFFF) (i.e., fire-fighting foams). Like other groundwater contaminants, PFOA can reach drinking water wells through migration of a contaminated groundwater plume. It can also reach groundwater from air emissions of industrial facilities. Particle-bounded volatile perfluoroalkyl substances (PFASs) may be carried by wind from disposal sites and deposited on the land or the surface water thus explaining the presence of these anthropogenic chemicals in remote locations and, in waters not impacted by a point source. PFOA migrates very slowly through the soil to groundwater and may not be detected in the source water for years.

Utilities should characterize their source water to assess PFOA concentrations. In source waters where PFOA is present at levels exceeding the proposed MAC, quarterly monitoring of surface water and semi-annual monitoring of groundwater should be conducted.

The monitoring frequency of the treated water depends on the treatment technology the utility employs. Utilities that use a granular activated carbon (GAC) system for PFOA removal may want to enhance monitoring of the treated water in order to assess the performance of the GAC system and to determine the timing of the regeneration. Utilities may consider reduced monitoring when they have data indicating that PFOA does not occur in the source water. However, if the main source of groundwater contamination is suspected to be from the use of AFFF, utilities may want to consider monitoring for other perfluorinated alkyl acids PFAAs (i.e., shorter chain compounds). These other PFAA compounds are likely to co-occur at AFFF-impacted sites and are typically more mobile. As such, they can serve as an early warning sign of PFOA and PFOS contamination of a groundwater source.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Perfluorooctanoic acid (PFOA) is an anthropogenic compound with a chain length of eight carbons, of which seven are perfluorinated. It belongs to the class of chemicals known as perfluorocarboxylic acids (PFCAs), one of a broader class of chemicals known as perfluoroalkyls (PFAs), which belong to the even larger class of perfluorinated alkyl acids (PFAAs) (Environment Canada and Health Canada, 2012). In this report, the term "PFOA" may refer to the free acid ($C_8HF_{15}O_2$; CAS number 335-67-1; 414.07 g/mol) or its conjugate base ($C_8F_{15}O_2^-$; CAS number 45285-51-6). The term APFO (ammonium perfluorooctanoate) refers to the ammonium salt ($C_8F_{15}O_2^- NH_4^+$; CAS number 3825-26-1), its principal salt, and K^+PFOA refers to the potassium salt (CAS number 2395-00-8). The main synonyms of PFOA are pentadecafluorooctanoic acid, perfluorooctanoate, C8, FC-143, pentadecafluoro1-octanoic acid, pentadecafluoro-n-octanoic acid, perfluorocaprylic acid, perfluoroctanoic acid, perfluoroheptanecarboxylic acid and octanoic acid.

PFOA is highly soluble in water, with estimates as high as 3,500 mg/L in neutral to alkaline pH and 9,500 mg/L in pure water, and as low as 0.7 mg/L at acidic pH (Kauck and Diesslin, 1951; Barton et al., 2007; Environment Canada and Health Canada, 2012). Solubility depends on the acid dissociation constant (pKa) of the acid form. Data for pKa indicate values ranging from –0.5 to 4 (Kissa, 1994; Burns et al., 2008; Goss, 2008; ATSDR, 2009; Goss and Arp, 2009; Environment Canada and Health Canada, 2012), and it was suggested that with such a low pKa value, the environmental partitioning of PFOA will be dominated by the anionic form (Goss, 2008).

PFOA has combined hydrophobic and hydrophilic properties over different portions of its molecule (Environment Canada and Health Canada, 2012). Due to this particularity, PFOA is thus expected to behave differently than traditional hydrophobic chemicals. The octanol:water partition coefficient (K_{ow}) cannot be determined directly (because multiple layers are formed in octanol/water) and the parameters usually estimated from the K_{ow} (e.g., K_{oc}, bioconcentration factor) cannot be calculated using this method (ATSDR, 2009; Environment Canada and Health Canada, 2012). The values of $LogK_{ow}$ estimated by modelling range from 3.62 to 6.30 (Arp et al., 2006; Jasinski et al., 2009; Environment Canada and Health Canada, 2012).

PFOA is essentially non-volatile, with a vapour pressure of 2.24×10^{-5} atm at 20°C (Barton et al., 2007; ATSDR, 2009; Environment Canada and Health Canada, 2012). Its Henry's law constant was estimated at 2.4×10^{-5} atm-m^3/mol (Barton et al., 2007).

Precursors of PFOA (polyfluoroakyl phosphate diesters, fluorotelomers, perfluorinated phosphonic acids) represent an indirect source of PFOA in the environment (Ellis et al., 2004; D'Eon et al., 2009; Lee, 2010).

The main producers of PFOA are located principally in the United States, Europe and Asia. Industrial information obtained in 2004 indicates no known manufacturers of perfluoroalkyl and fluoroalkyl substances in Canada; however, APFO was imported into Canada in quantities ranging between 100 and 100,000 kg (Environment Canada and Health Canada, 2012). APFO is mainly used as a commercial polymerization aid for fluoropolymer manufacturing. Fluoropolymers are used in the manufacture of stain/water-resistant coatings for textiles and carpets, hoses, cable and gaskets, non-stick coatings on cookware and personal care products. APFO is also used in aqueous fluoropolymer dispersions that are used in paints and in photographic film additives as well as within the aerospace industry (e.g., it may be a component of aqueous film-forming foams [AFFFs] for firefighting; Environment Canada and Health Canada, 2012). Fluorochemicals (potential PFOA precursors) are also used in the treatment of

food packaging materials (Environment Canada and Health Canada, 2012) such as microwaveable popcorn bags (Dolman and Pelzing, 2011). The term PFOA is not interchangeable with commercial mixtures containing PFOA, as these mixtures are often not well characterized and could include any product that contains even a small amount of PFOA (Environment Canada and Health Canada, 2012).

4.1 Sources to water

A source of PFAAs in water is the discharge of AFFF for extinguishing fires. Discharge of AFFF was presumed to have resulted in increased levels of PFAAs in water surrounding the Toronto International Airport, based on spatial and temporal trends of PFAAs in water (Awad et al., 2011). Although the study focused on PFOS contamination, as this was the primary PFAA in the AFFF used at the location, PFOA-containing AFFFs could plausibly also result in similar increased concentrations of PFOA in water near discharge sites. Data supporting the possibility of contamination in the vicinity of firefighting training areas include measurements of elevated PFOA concentrations in groundwater near a Michigan air force base (Moody et al., 2003), at a firefighting training ground in Australia (Baduel et al., 2015), and in private drinking water wells proximate to an industrial site in Cologne, Germany (Weiß et al., 2012).

Elevated PFOA concentrations measured in surface water downstream from fluorochemical manufacturing plants have also been used as indications of the potential for industrial sources of PFOA in water (Hansen et al., 2002; Frisbee et al., 2009).

Mass balance studies of PFAAs at wastewater treatment plants commonly report similar or higher PFOA concentrations in effluents in comparison to raw influents, suggesting that the degradation of other fluorinated organic compounds (i.e., fluoropolymers) into PFOA may take place during wastewater treatment (Clarke and Smith, 2011) and that conventional wastewater treatment plants are not effective in removing PFAAs (Ahrens, 2011). PFOA was detected in effluent wastewater treatment facilities at concentrations ranging from 0.007 to 0.055 µg/L in Canada (Environment Canada and Health Canada, 2012) and at average concentrations ranging from 0.080 to 0.12 µg/L in effluents of seven different locations in the U.S. (Quinones and Snyder, 2009).

Although measures are in place in North America and Europe to restrict the production, use and/or the major exposure risks to PFAAs (primarily PFOS, but to some extent PFOA), the ubiquitous use of PFAAs within the built environment still causes their transfer to biosolids (sludge) (Clarke and Smith, 2011). The use of biosolids as fertilizers may thus represent a source of soil and water contamination with PFOA (Clarke and Smith, 2011). Elevated concentrations of PFOA were found in surface and well water in Decatur, Alabama, after biosolids from a municipal wastewater treatment plant (at which waste from local fluorochemical facilities were received) were applied in agricultural fields (Lindstrom et al., 2011).

4.2 Environmental fate

The elevated water solubility of PFOA and the negligible volatility of its ionized species suggest that PFOA species will partition primarily to the aquatic environment (Environment Canada and Health Canada, 2012).

PFOA may be found in air, surface water, sediment, groundwater and soil around the world (including the Arctic). Two long-range transport pathways have been proposed to explain this ubiquity (Post et al., 2012). The first pathway involves the atmospheric transport of volatile precursors (e.g., fluorotelomer alcohol) and their oxidation to PFOA (and other PFAAs) and further deposition onto land or water. The second pathway involves a long-range aqueous

transport of the anionic forms of emitted perfluorinated carboxylates, such as PFOA, from the vicinity of industrial sources via the surface water currents (Butt et al., 2010; Post et al., 2012).

Experimental values of $LogK_{oc}$ vary between 1.2 and 4.5 (Dekleva, 2003; Higgins and Luthy, 2006; Prevedouros et al., 2006; ATSDR, 2009; Environment Canada and Health Canada, 2012; Zareitalabad et al., 2013). Data suggest that the sorption of PFOA can be described reasonably as a partitioning-like process with an average $LogK_{oc}$ of 2.8 (Zareitalabad et al., 2013).

PFOA may bioaccumulate in tissues of aquatic and terrestrial living organisms. Bioaccumulation data for different species of marine and terrestrial ecosystems indicate that PFOA has a low to moderate potential to accumulate in aquatic species (on a whole-body basis), while accumulation may be higher in certain organs/tissues (e.g., liver, blood) (Environment Canada and Health Canada, 2012). Briefly, the PFOA log bioaccumulation factors (BAFs) ranged from 0.02 to 0.63 for trout and from 9.6 to 19.4 for Pacific oysters. Log bioconcentration factors (BCFs) were estimated at 4.0 for the rainbow trout (carcass), 3.1–9.1 for carp, 1.8 for fathead minnows (whole body) and 0.8–3.0 for Pacific oysters. PFOA may also biomagnify in certain food webs (e.g., polar bears) (Environment Canada and Health Canada, 2012).

Under environmental conditions, PFOA does not hydrolyze, photolyze or biodegrade, and is considered extremely persistent in the environment (OECD, 2006; Environment Canada and Health Canada, 2012). PFOA is also resistant to microbial degradation (Liou et al., 2010). Moreover, biodegradation of precursor compounds could lead to increasing concentrations of PFOA in the environment (Ahrens, 2011; Clarke and Smith, 2011). Considering its empirical and physico-chemical properties, it was concluded that PFOA and its salts meet the persistence criteria in water, soil, sediment and air (half-lives of $\geq$ 182 days in soil and water, $\geq$ 365 days in sediment and $\geq$ 2 days in air) (Environment Canada and Health Canada, 2012).

5.0 Exposure

Canadians can be exposed to perfluorinated compounds present in food, consumer products, dust and drinking water. The major sources of perfluorinated compounds are expected to be food and consumer products, including solution-treated carpeting and treated apparel (Tittlemier et al., 2007); however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water.

The estimated total daily intake of PFAAs (estimates not provided for individual PFAAs) in Canadians was reported to be 410 ng/day for the general population of Canada (Tittlemier et al., 2007). Drinking water ingestion contributed only a minor amount to the overall estimated exposure (estimated at 0.3 ng/day). Although some exposure data are available, they are considered insufficient to justify modifying the default allocation factor for drinking water of 20%. This default allocation factor for drinking water is used as a "floor value" when drinking water is not a major source of exposure (Krishnan and Carrier, 2013); therefore, this value is applicable for PFOA, even though water is expected to be only a minor contributor to PFOA exposure for the general population.

5.1 Water

Although PFOA is not regularly monitored at water treatment plants in Canada, the analysis has been performed for a few locations. PFOA was not detected (MDL 0.51 ng/L) in raw or finished water from samples obtained in 2012 from two water treatment plants in Calgary (Alberta Environment and Water, 2013). In Quebec, raw and treated water samples were obtained monthly between April 2007 and March 2008 from seven sites (a total of 84 raw and treated water samples each). PFOA was detected in 75% of treated samples (MDL of 0.3–0.6 ng/L), with a

median value of 2.5 ng/L. The detection rate and median concentrations were higher in treated water than in raw water, for which the detection rate and median were 55% and 2.0 ng/L, respectively (Ministère du Développement durable, de l'Environnement, de la Faune et des Parcs, 2012). The reported PFOA concentration in 5 tap water samples from Niagara-on-the-Lake, Ontario was 2.1 ng/L (Mak et al., 2009). Lower concentrations of PFOA (0.2 ng/L) were reported in tap water from Calgary and Vancouver (Tanaka et al., 2006).

For a national survey of emerging contaminants in drinking water (including PFOA) performed by Health Canada, treated and raw water was monitored in winter and summer at 35 locations in 2009 and 30 locations in 2010. PFOA was detected (MDL of 0.023 ng/L) in 68% of raw water samples and 64% of treated water samples in summer 2009, with averages of 0.067 ng/L and 0.071 ng/L, respectively. PFOA concentrations were slightly lower in winter 2009, with an average of 0.057 ng/L in detected raw samples (59% detection) and 0.056 ng/L in detected treated samples (55% detection). Detection rates for PFOA were lower in the 2010 locations, with detection rates in the summer of 18% in raw water (average of 0.066 ng/L) and 15% in treated water (average of 0.046 ng/L), and in winter of 33% in raw water (average of 0.055 ng/L) and 27% in treated water (average of 0.05 ng/L) (Health Canada, 2013a).

5.2 Food

Food is generally considered to be the main source of PFOA exposure for the majority of the Canadian population, but exposure from food is still well below what is considered unsafe to humans. PFOA was measured in a selection of Canadian food composite samples (samples from the Canadian Total Diet Study [TDS]) conducted in 2004 and additional samples collected within 1992 and 2001) to estimate the dietary intake. PFOA was detected in 3 out of 54 food composites. The detected PFOA concentrations (on a w.w. basis) were 0.74 ng/g (pizza; the sample was above the limit of detection but below the limit of quantitation), 2.6 ng/g (roast beef) and 3.6 ng/g (microwave popcorn). Values were used to estimate the average dietary daily exposure of Canadians; food was estimated to contribute 250 ng/day of perfluorinated compounds, of which approximately 70 ng was attributed to PFOA (Tittlemier et al., 2007).

Store-bought and restaurant foods commonly consumed by Canadians were collected in Whitehorse (Yukon Territory, Canada) in 1998 and analyzed for PFAAs. PFOA was detected in several composite samples (0.36–0.77 ng/g w.w. for cookies, processed cheese, peppers, canned lunchmeats, and pizza), but all measurements were below the limits of quantification (0.65–1.52 ng/g w.w.) (Ostertag et al., 2009a).

The concentrations of PFAAs in the traditional foods of Inuit in Northern Canada was measured to estimate their dietary exposure. PFOA was rarely detected (9% out of 68 samples) in the traditional foods collected from Chesterfield Inlet, Igloolik, Pond Inlet and Qiqiktarjuak in Nunavut, between 1997 and 1999. PFOA was detected in ringed seal (liver: 0.3 ng/g; blood: 0.1 ng/g), eider duck (whole body: 0.4 ng/g), caribou liver (baked: 0.7 ng/g; raw: 0.1 ng/g) and caribou stomach (raw: 0.8 ng/g); the other concentrations were below the detection limit (<0.1 to <0.6 ng/g) (Ostertag et al., 2009b).

PFOA is a processing aid in the manufacture of polytetrafluoroethylene (PTFE), which is used for many purposes, including non-stick cookware. Residual PFOA was detected in PTFE cookware and film (Begley et al., 2005); however, only minor transfer of PFOA from these products was observed in investigations on the migration into watery and fatty simulated foodstuff (Begley et al., 2005; Powley et al., 2005; Washburn et al., 2005; Sinclair et al., 2007). PFOA has also been detected in microwave popcorn bags (Begley et al., 2005; Sinclair et al., 2007; Dolman and Pelzing, 2011), and found in food contact papers treated with polyfluoroalkyl phosphate surfactant (PAPs) or di-perfluoro-alkyloxy-amino-acid (PAA) (Xu et al., 2013). The

migration rates of PFOA from food contact papers treated with these compounds ranged from 7% to 92% for five different food simulants (Xu et al., 2013).

5.3 Air

The inhalation intake of PFOA for Canadians was considered negligible due to its low volatility (Tittlemier et al., 2007).

The levels of PFAAs in outdoor air were determined in a Canadian study conducted in 2007 in Vancouver (Shoeib et al., 2011). PFOA samples were collected using outdoor passive samplers deployed in residential yards for approximately 3 months. PFOA was detected in 4 out of 6 samples (<0.47–9.2 pg/m^3; mean: 1.4 pg/m^3) (Shoeib et al., 2011). Similar concentrations were measured in the Canadian Arctic (Resolute Bay, Cornwallis Island, Nunavut) in 2004, with a mean concentration (gas and particulate phase of atmospheric air) of 1.4 pg/m^3 (Stock et al., 2007).

In indoor air, the levels of PFOA primarily depend on its concentration in air particulates and are thus related to the levels in indoor dust, as well as the number, type and age of the potential sources (e.g., carpeting, furniture and paint) (Fraser et al., 2012). To date, data on indoor air concentrations of PFOA are limited to those reported in the aforementioned residential study (Shoeib et al., 2011). The authors collected PFOA in indoor air using passive samplers deployed for approximately 4 weeks in bedrooms of 59 participants. PFOA was the dominant ionic PFAA, with a geometric mean concentration of 28 pg/m^3 (arithmetic mean: 113 pg/m^3, median: 21 pg/m^3, range: 3.4–2,570 pg/m^3).

5.4 Consumer products

Owing its use patterns, human exposure to PFOA would likely result from contact with, or the use of, certain consumer products (Health Canada, 2006). Estimates of the contribution of solution-treated carpeting and treated apparel to Canadians' daily intakes of total perfluorinated compounds were 120 ng/day and 12 ng/day, respectively (Tittlemier et al., 2007). As no Canadian data were available on exposure to PFOA in consumer products, data from other countries are summarized below.

FOA has been measured in a variety of consumer products, including waterproofing agents, fluorotelomer-treated textiles, apparel and carpeting, aqueous firefighting foams, non-stick ware, industrial floor waxes and wax removers, latex paint, home and office cleaners, PTFE-coated dental floss and dental tape, and PTFE film/sealant tape (Begley et al., 2005; Washburn et al., 2005; Herzke et al., 2012). PFOA has also been measured in ski waxing blocks and glider powders, with occupational exposure to airborne PFAAs measured during professional ski waxing (Freberg et al., 2010).

5.5 Soil and household dusts

The estimated contribution of dust to Canadians' daily intakes of total perfluorinated compounds was 28 ng/day (Tittlemier et al., 2007). The study did not estimate the total daily contribution of soil to perfluorinated compound exposure.

PFOA concentrations in dust from Canadian houses were reported to vary from <2.3 to 1,234 ng/g with a median value of 19.7 ng/g (mean: 106 ng/g). House age and fraction of floor covering were reported to be significantly correlated with the concentration of PFAAs in dust—older houses and those with smaller fractions of the floor covered with carpet were characterized by lower concentrations of PFAAs (Kubwabo et al., 2005).

In another Canadian study conducted in the City of Vancouver, PFOA was detected in all house dust samples analyzed for this compound (n = 132). The PFOA concentrations ranged from 1.9 to 1,390 ng/g (median: 30 ng/g, mean: 97 ng/g) (Shoeib et al., 2011).

No study reporting background PFOA levels in soils was located. Some data are available in soil surrounding perfluorochemical industrial facilities (as reviewed by ATSDR, 2009).

5.6 Human biomonitoring data

Human PFOA blood levels have been shown to be influenced by gender and age. The Canadian Health Measures Survey (CHMS), Cycle 1 (2007–2009) indicates that PFOA plasma levels in adult males (geometric mean [GM]: 2.94 ng/mL; 95% CI: 2.74–3.15, 95th percentile: 5.98 ng/mL, n=1376) are higher than in adult females (GM: 2.17 ng/mL; 95% CI: 1.99–2.36, 95th percentile: 4.99 ng/ml, n=1504) (Health Canada, 2010). This effect persisted in Cycle 2 of the study (2009–2011) (Males—GM: 2.6 ng/mL, 95% CI: 2.4–2.9, 95th percentile: 6.0, n=511; Females—GM: 2.0 ng/mL, 95% CI: 1.8–2.2, 95th percentile: 4.4 ng/mL, n=506) (Health Canada, 2013b).

5.7 Multi-route exposure through drinking water

The multi-route exposure assessment process is not applicable for PFOA, due to the compound's high molecular weight and low volatility (Krishnan and Carrier, 2008); therefore, the relative contributions of exposure to PFOA from both inhalation and dermal routes during showering and bathing were not estimated. Based on the high molecular weight of 414.07 g/mol and the ionic properties of PFOA at pH levels typical in drinking water, volatility and dermal penetration are expected to be low. Moreover, dermal permeability coefficients measured in *in vitro* studies predict that PFOA is impermeable to skin under typical conditions (Fasano et al., 2005; Franko et al., 2012). Consequently, exposure to PFOA via inhalation and dermal routes during showering or bathing is expected to be negligible.

6.0 Analytical methods

To date, the United States Environmental Protection Agency has not approved any analytical methods for the analysis of PFOA in drinking water. There are some methods that can be used to measure PFOA in drinking water at levels well below the proposed MAC. However, they require good quality control procedures to produce accurate results.

6.1 Available methods

U.S. EPA Method 537 ver. 1.1, International Standard Organization (ISO) Method, 25101 (ISO, 2009) and 3M Method ETS-8-154.3 (3M, 2008) can all be used for the analysis of PFOA in drinking water (3M, 2008; ISO, 2009; U.S. EPA, 2009a). All methods use a solid phase extraction (SPE) technique followed by a liquid chromatograph (LC) coupled to electrospray ionization (ESI) tandem mass spectrometry (MS/MS) operated in negative ion mode. For the purpose of trace quantitation of PFOA in drinking water, the chromatographic conditions are selected such that all isomers (linear and branched) are co-eluted together.

In the EPA method, a water sample is fortified with labelled internal standards and passed through a SPE cartridge to extract target analytes in addition to their corresponding internal standards. The compounds are eluted from the SPE cartridge, concentrated and injected into a LC-MS/MS. The mass spectra and retention times of the analytes are identified by comparison to internal standards. The method detection limit (MDL) of PFOA is 1.7 ng/L (0.0017 µg/L) and the Lowest Concentration Minimum Reporting Level (LCMRL) is 5.1 ng/L (0.0051 µg/L) (U.S.

EPA, 2009a). PFOA has been included in the third Unregulated Contaminant Monitoring Rule (UCMR3), which stipulates that using Method 537 ver. 1.1, an MRL of 20 ng/L (0.02 µg/L) for PFOA must be achieved and reported by the utilities during monitoring (U.S. EPA, 2012b).

The results of an inter-laboratory trial (Taniyasu et al., 2013), conducted in 2006, were used to establish whether ISO Method 25101 was reliable for the analysis of PFOA and PFOS in environmental water samples, including drinking water. The intra- and inter laboratory precisions were in the range of 3–7% and 15–22%, respectively for PFOA for all environmental water samples analyzed. The recovery of the internal standards for PFOA ranged from 91 to 98%. These results confirmed that this analytical method was reliable and can be used for the analysis of PFOA in environmental water samples. The method uses SPE, LC-MS/MS and is applicable for the quantification of the linear and branched isomers of PFOA and PFOS. The branched isomers can be separated from the linear isomers by using specific chromatographic column and optimized conditions. ISO Method 25101 was found to be appropriate for determination of PFOA levels in unfiltered samples of drinking water, groundwater and surface water with concentrations in the range of 10 – 10,000 ng/L (0.01 – 10 µg/L) (ISO, 2009).

Method (ETS-8-154.3) was developed and validated by 3M for PFOA analysis in drinking water, groundwater and surface water samples. The analytical steps are similar to EPA Method 537 Ver 1.1 and the method has an LOQ of 25 ng/L (0.025 µg/L) for PFOA (3M, 2008).

6.2 Challenges in the analysis of PFOA/PFOS

In spite of the significant improvements in the analytical methods for the determination of PFASs in environmental water samples, challenges, uncertainties and drawbacks still remain. Major challenges associated with the trace quantitation of PFASs included matrix effects and a background contamination in the analytical blanks. In order to generate accurate data, quality control (QC) procedures (matrix spikes, duplicates, spike-recovery experiments, surrogate recovery checks) are critical. In addition, the use of isotope-labelled internal standards is a standard practice and must be used in the analysis of PFASs.

6.2.1 Matrix effect

Although LC-MS/MS is a highly selective and sensitive technique, it is susceptible to matrix effects which is one of the major uncertainties in the trace quantitation of PFOA in environmental water samples (Martin et al., 2004; Yamashita et al., 2004; Taniyasu et al., 2005; van Leeuwen et al., 2006; Arsenault et al., 2008). Matrix effects result from the co-extracted components from the sample, which affect the signal intensity of the target analyte and either suppress or enhance the spectral signal. The extent of the matrix interference varies, depending on the nature of the samples. Although the matrix interferences are negligible for drinking water and groundwater (ISO, 2009), the PFOA quantification requires efficient extraction and clean-up procedures. The aim of these procedures is to separate the compounds in the sample by their chemical and physical properties, to concentrate the target analyte and to purify the extract prior to the instrumental determination. The most frequently used technique for the extraction of PFASs from drinking water samples includes SPE cartridges with different packing material such as reverse phase (C18) cartridge (Loewen et al., 2005; Wolf and Reagen, 2011; Zainuddin et al., 2012), mixed hydrophobic/polar (Oasis HLB) cartridges (Yamashita et al., 2004; Taniyasu et al., 2005; Villaverde-de-Saa et al., 2015) and a weak anion exchange (WAX) cartridges (Taniyasy et al., 2005; 2013). Several studies conducted a liquid-liquid extraction (LLE) technique to extract and concentrate PFASs in different environmental aqueous matrices prior to LC-MS/MS (Gonzales-Barreiro et al., 2006; Szostek et al., 2006; Backe et al., 2013). A laboratory study (Gonzales-Barreiro et al., 2006) used an LLE to extract PFASs (C6-C12) from tap water. The

recovery of the PFASs with a carbon chain greater than C8 was in the range 80-93%. The authors indicated that the method was less efficient in extracting short-chained PFASs when compared to the SPE technique (Gonzales-Barreiro et al., 2006).

The clean-up procedures involved a washing step after the sample enrichment on the SPE cartridge and a filtration to remove solids from the final extract (Yamashita et al., 2004; Larsen and Kaiser, 2007; van Leeuwen and Boer, 2007). Care should be taken to avoid contamination of the extract or losses of PFASs during the clean-up procedures. Prior to a SPE, a sample pre-treatment (filtration) may be required to facilitate extraction or to remove matrix constituent that will interfere with analyses (van Leeuwen and Boer, 2007; Ding et al., 2012).

The most suitable approach to assist in the quantification of PFASs is to use of isotopically-labelled internal standards (isotope dilution). It is important that the appropriate isotope-labelled internal standards are used for the quantitation of the corresponding native compound. Isotope-labelled internal standards will have the same retention time as the target analytes (excluding isomeric separation) and the monitoring of their signals will determine whether the analytes signal are suppressed or enhanced. The application of surrogates or isotopically-labelled internal standards early in the sampling or the sample preparation steps will compensate for the inefficiency/losses in the extraction and other sample preparation steps (Martin et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007). Wolf and Reagen (2011) reported that an addition of isotope-labelled internal standards prior to sample collection simplified the sample preparation procedures. The method demonstrated an accuracy of 105% and a precision of 12% for PFOA in laboratory Milli-Q water samples (Wolf and Reagen, 2012).

If isotope-labelled internal standards are not available, a standard addition quantitation, which involves spiking known quantities of a standard into the sample, is an alternative to use when matrix effects are unavoidable (Weremiuk et al., 2006; Furdui et al., 2007; van Leeuwen et al., 2009).

The use of MS/MS for analysis of PFOA enables the detection of product (daughter) ions. The transitions from m/z ratio 413 (parent ion $C_7H_{15}COO^-$) to m/z ratio 369 and 169 (daughter ions) are used for PFOA quantification (ISO, 2009; U.S. EPA, 2009a).

6.2.2 Background contamination in the analytical blanks

A known source of background contamination is the presence of fluoropolymers, such as polytetrafluoroethylene (PTFE) and perfluoroalkoxy compounds in various laboratory consumables. Ammonium perfluorooctanoate and ammonium perfluorononanoate are used as fluoropolymer processing aids and are common components in the laboratory products. These fluoropolymers may lead to quantifiable background levels in the analytical blanks especially when quantifying trace levels in water samples. Contacts with such laboratory materials and products during analysis of PFOA should be avoided (Martin et al., 2004; Yamashita et al., 2004; ISO, 2009).

Yamashita et al. (2004) studied the sources of background contamination at various analytical steps, including sample collection, extraction and sample clean up prior to the instrumental analysis. Polypropylene bottles used for sample collection and storage, in addition to different types of SPE cartridges and purified reagent water, were found to be sources of PFASs contamination in the analytical blanks. Taniyasu et al.(2005) and Berger et al. (2011) found that the polypropylene containers are unsuitable for collection and storage of water samples intended for analysis of long-chain PFCAs such as perfluoroundecanoic and perfluorododecanoic acids, because of the adsorption of the compounds on the containers' surface. The authors recommended the use of high density polyethylene or glass containers. However, ISO method 25101 and EPA Method 537 recommended against the use of glassware for sampling due to the potential

adsorption of PFOA on the walls (ISO, 2009; U.S. EPA, 2009a). The storage and sample preservation steps prior to the instrumental analysis should prevent changes in composition of the sample matrix and the concentration of the analyte (van Leeuwen et al., 2007).

SPE cartridges can also be a source of contamination and the U.S. EPA (2009a) recommends that SPE devices be tested prior to using them for analysis to ensure that there is no contamination of the sample. Several studies performed on a direct injection (DI) of the water samples into LC-MS/MS. The method avoids the use of additional materials and sample preparation processes, which may limit possible contamination and target compound losses (Schultz et al., 2006; Furdui et al., 2008; Dickenson and Higgins, 2013).

HPLC tubing, nylon filters, auto-sampler vial caps made of Teflon or Viton fluoropolymers, valve seals and degassers were identified as the potential sources of contamination of the instrumental blanks with PFOA (Yamashita et al., 2004; Taniyasu et al., 2005; Schultz et al., 2006; Larsen and Kaiser, 2007) and to lesser extend with PFOS (Yamashita et al., 2004). The instrumental background contamination can be reduced by replacing or bypassing the fluoropolymers parts such a degasser (Arbuckle et.al, 2013) with offline degassing of mobile phases; replacing fluoropolymer components with stainless steel, polyetheretherketone (PEEK) tubing, installing an upstream guard column, extensively flushing of the LC system or reducing the LC-column equilibration time (Martin et al., 2004; Yamashita et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007; Nakayama et al., 2007; Shoemaker et al., 2009; Arbuckle et.al, 2013).

6.3 Analytical performance

Recent analytical improvements have been realized through the availability and use of high quality standards and stable isotope internal standards to compensate for the matrix effect and for inefficiencies in the extraction procedure and/or other sample preparation steps (Yamashita et al., 2004; Lowen et al., 2005; Taniyasu et al., 2005; Nakayama et al., 2007; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). There are currently, a number of high quality analytical-grade standards that are commercially available and the list of these standards continues to expand (van Leeuwen et al., 2009, Berger et al., 2011).

In the early 2000s, quantification of PFASs was biased by the lack of proper analytical standards, isotopically labelled surrogates and reference material and there was a significant analytical variability between laboratories. Two inter-laboratory studies were conducted to analyze PFASs, including PFOA and PFOS, in environmental water samples and found a varying degree of accuracy. In the first study (van Leeuwen et al., 2006), conducted in 2004/2005, factors resulting in poor agreement between participating laboratories, were determined to be low PFOA/PFOS concentrations (below 20 ng/L) in water samples; the use of low purity standards, high matrix effect, and a high background contamination in the analytical blanks. The relative standard deviation (RSD) reported in the study was 118% for PFOA (van Leeuwen et al., 2006). In the second inter-laboratory study, the performance of the participating laboratories improved due to the minimization of the matrix effects; the use of higher quality (purity and isomeric composition) shared standards (provided by a single source), and the use of mass-labelled internal standards. The reported RSD value in this study was 32% for PFOA.

Methods using SPE and DI procedures followed by LC/ESI/MS/MS have been reported in the literature for the determination of PFAAs, including PFOS in water samples (Yamashita et al., 2004; 2005; Taniyasu et al., 2005; 2013; Furdui et al., 2008; Hansen et al., 2010; Berryman et al., 2012; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). Details regarding the preconditioning procedures of the SPE cartridges, eluent, clean-up procedures, MS quantification parameters and QC procedures specific to each method are available in the cited reference.

A study reported a limit of detection (LOD) [signal-to-noise (S/N) = 3:1] of 0.28 ng/L and a limit of quantitation (LOQ) (S/N= 10:1) of 0.94 ng/L using an SPE followed by LC-MS/MS for analyzing PFOA in surface water. A water sample of 500 mL was loaded on the Oasis WAX cartridge, a target fraction was eluted, dried under nitrogen gas and before the analysis the samples were filtered. The recovery value of 115±6% for PFOA was calculated by isotopically-labelled internal standards calibration (Sun et al., 2011; Li et al., 2011).

Villaverde-de-Saa et al. (2015), using an SPE followed by LC–MS/MS, developed a method for the determination of seven PFCAs (C6–C12) and PFOS in environmental waters samples. A water sample of 1.0 liter, fortified with internal standards, was loaded on the Oasis HLB cartridge. The method reported a LOD of 0.03 ng/L and a LOQ of 0.11 ng/L for PFOA, (LOD and LOQ were calculated as 3 and 10 times the standard deviation, respectively). The recovery value of 89±4% for PFOA was calculated by isotopically-labelled internal standards calibration.

Furdui et al. (2008) investigated the concentration of PFASs in water samples from the Great Lakes. The analysis of nine target contaminants including PFOA, were performed by directly injecting the samples into LC-MS/MS. Quantification was performed using internal standard correction and standard addition. An isotope dilution provides the most accurate and precise results. The method had a LOQ (signal-to-noise [S/N] =10:1) of 0.5 ng/L for PFOA (Furdui et al., 2008).

The province of Québec reported results of the monitoring PFASs at 16 sites, including seven drinking water treatment plants. A total of 226 water samples (84 raw, 84 treated and 58 surface water samples) were analyzed. Both raw and treated water were sampled monthly for a period of one year. Sampling of the surface water was limited through the year. The samples were analyzed using C18 cartridges and LC-MS/MS in positive ionization mode. Reported DLs ranged from 0.5 to1.0 ng/L and 0.3 to 0.6 ng/L for untreated (250 mL analysed sample) and finished water (500 mL sample), respectively. In order to compensate and correct the instrumental variations and the matrix effect, isotopically-labelled internal standards were added prior to the LC (Berryman et al., 2012). Although the photoionization technique is less sensitive than the electrospray ionization, it is less prone to matrix effect (Martin et al., 2004).

Berger et al. (2004) compared different mass spectrometric techniques (time-of-flight [TOF] high resolution MS, triple-quadrupole tandem MS, and IT-MS) coupled with a high performance liquid chromatography (HPLC) for analysis of PFASs including PFOA. The instrument parameters such as vaporizer temperature, collision energy, and cone voltage fragmentation were optimized for each mass spectrometry technique. Negative electrospray ionization was selected as the ionization mode for all instruments. The study indicated that both TOF high resolution MS and triple-quadrupole tandem MS methods had higher sensitivities than IT-MS for all tested PFASs. Although IT-MS had a higher DL and smaller linear range, it provided the best results for tentative structure elucidation and qualitative analysis of branched PFASs isomers (Berger et al., 2004; Jahnke and Berger, 2009).

The analysis of PFASs in environmental water samples has been dominated by the use of LC coupled to MS or MS/MS, although other techniques such as ^{19}F nuclear magnetic resonance (NMR) and and gas chromatography (GC)–MS have also been explored. ^{19}F NMR analysis is a less sensitive and non-specific method due to the determination of the presence of CF_2 and CF_3 moiety in the sample. Gas chromatography (GC) can be used to determine neutral and volatile PFASs and fluorotelomer alcohols. PFAAs are derivatized in order to be amenable for GC analysis. However, the use of the derivatization techniques is limited for PFOS analysis due to the instability of the PFOS's derivatives (Moody et al., 2001; Villagrassa et al., 2006).

7.0 Treatment technology

The available data and calculated pKa (2.8) values indicate that PFOA is a strong acid which predominantly dissociates to a negatively charged form (anion) at environmentally relevant pH values (U.S. EPA, 2005; Lange et al., 2006; Prevedouros et al., 2006). Based on the physical-chemical properties of the ionized form (a negligible vapor pressure, a high solubility in water and moderate sorption to solids), Prevedouros et al. (2006) suggested that PFOA would accumulate in surface water. Given the hydrophobic and oleophobic nature of the fluorinated alkyl chain and the hydrophilic nature of the carboxylate group, hydrophobic and electrostatic effects likely influence PFOA adsorption (Higgins and Luthy, 2006; Xiao et al., 2011). The nature of the chemical structure of PFOA (i.e., strong carbon - fluorine (C-F) bonds) makes it resistant to hydrolysis and biodegradation as well as to several chemical treatment processes (Lange et al., 2006; ATSDR, 2009).

7.1 Municipal scale

Dickenson and Higgins (2013) evaluated the ability of wide range of full-scale treatment techniques to remove PFASs, including PFOA and PFOS, from raw water or potable water reuse plants. The treatment trains varied, but generally consisted of coagulation followed by physical separation, aeration, chemical oxidation, UV irradiation, and disinfection. Regardless of the treatment train applied, there was little or no decrease in PFOA and PFOS concentrations and the authors concluded that these treatment methods are not effective in removing PFASs.

GAC adsorption and membrane filtration techniques appear promising for removal of PFOA in drinking water, achieving treated water concentrations below 0.2 µg/L (Tang et al., 2006; Lampert et al., 2007; Wilhem et al., 2008; Deng et al., 2010; Takagi et al., 2011; Appleman et al., 2014). In order to achieve a PFOA concentration below 0.2 µg/L, the GAC system must be specifically designed and appropriately operated for PFOA removal in drinking water. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance by directly competing for adsorption sites and preloading (fouling) the GAC beds. Therefore, the effectiveness of GAC to remove PFOA in drinking water appears to be dependent on the regeneration frequency and/or replacement of the carbon (Kolstad 2010; Takagi et al., 2011; Appleman et al., 2014). Membrane filtration such as reverse osmosis (RO) and bench-scale nanofiltration (NF) studies demonstrated effective removal of all tested short-and long-chain PFASs including PFOA in drinking water. Although the RO process is effective, it is likely to be an expensive treatment method (Steinle-Darling et al., 2008); Quinones and Snyder, 2009; Appleman et al., 2013; Flores et al., 2013). Anion exchange resins may also be effective in removal of PFOA. However full-scale evaluation of this technology has not been conducted specifically for PFOA removal in drinking water.

The selection and effectiveness of each treatment strategy is driven by several factors, including source water chemistry, concentration of PFOA and/or other PFASs and pre-existing treatment processes. If long-chain PFASs are detected in the drinking water sources, the utility may consider the implementation of treatments such as GAC. However, utilities that have shorter chain PFASs in their raw water source may choose to implement RO or NF. The treatment technologies need to be designed specifically for PFASs removal and operated appropriately in order to achieve contaminants removal objectives in drinking water (Dickenson and Higgins, 2013).

The ability of various drinking water treatment processes and treatment trains to remove PFOS have been summarized by Dickenson and Higgins (2013) and Rahman et al. (2014). Appendix A summarizes the percentage removal of PFOA in full-scale plants where both raw and finished water concentrations were reported (Rahman et al., 2014). Data show that the treatment

technologies employed by these plants (with the exception of GAC, RO and NF) did not appreciably remove PFOA. They also show that in some cases concentrations in the finished water were higher than in the raw water, likely due to the breakdown of precursor compounds to form PFOA during the treatment (Takagi et al., 2008; Shivakoti et al., 2010). Takagi et al. (2011) also postulated that these higher finished water levels may result from desorption from GAC filters used for long periods of time without reactivation and the leaching of these compounds from Teflon-coated treatment equipment.

7.1.1 Conventional treatment

Conventional drinking water treatment processes generally incorporate coagulation, flocculation, sedimentation, and filtration, followed by primary and secondary disinfection. Common coagulants used in drinking water include aluminum sulfate (alum), ferric hydroxide, ferric chloride, polyaluminum chloride and coagulant aid polymers. Filtration media can consist of sand (single media); sand and anthracite (dual media); or sand, anthracite, and garnet (multi or mixed garnet media). GAC may also be used as the filter media.

Conventional full-scale drinking water treatment techniques have been found ineffective in removing PFOA from source waters. Samples collected from several full scale conventional treatment plants indicated essentially no difference in the PFOA concentrations between plant influent and concentrations in water following the coagulation, sedimentation, and sand filtration steps (Loos et al., 2007; Shivakoti et al., 2009; Takagi et al., 2011; Thompson et al., 2011). Similarly, Eschauzier et al. (2012) reported that slow- and rapid- sand filtrations were ineffective for PFOS and PFOA removal. The inability of conventional water treatment to remove PFOA and PFOS may be due to their extremely low concentrations in water and their hydrophilicity which renders them unamenable to removal by conventional treatment processes (Rahman et al., 2014). These findings are in agreement with recently conducted bench-scale studies of the removal of PFOA from water (Deng et al., 2011; Xiao et al., 2013).

Jar tests (Xiao et al., 2013) achieved an approximately 3% removal of an influent concentration of 0.083 µg/L (83 ng/L) of PFOA, with an alum dose of 30 mg/L and pH of 7.9. A removal efficiency below 10% was reported under a range of alum doses ranging from 10 to 60 mg/L and pH levels ranging from 6.5 to 8.0. Removal rates of approximately 25% were observed using enhanced coagulation with alum doses greater than 60 mg/L and pH 4.5 – 6.5. In general, the removal efficiencies were below 35% under the examined coagulation conditions (alum doses 3-110 mg/L and pH 4.5-8.0). Ferric chloride coagulation exhibited similar results. The authors indicated that removal rates were lower for PFOA than PFOS in both conventional and enhanced coagulation conditions, possibly due to PFOA having a lower molecular size and a potential for being less hydrophobic.

However, Deng et al. (2011) demonstrated that the addition of powdered activated carbon (PAC) before the coagulation process was capable of enhancing the removal efficiency of PFOA in water after the coagulation. In the experiments, an initial PFOA concentration of 21.2 µg/L was decreased to 5.8 µg/L with a polyaluminium chloride (PACl) dose of 10 mg/L. A concentration below 1.0 µg/L was measured in the finished water after the addition of 10 mg/L of PACl and PAC doses up to 16 mg/L, to the initial PFOA concentrations in the range of 0.5-3.0 mg/L. The study found that the concentration of PFOA in the finished water decreased with increasing initial turbidity and PACl dose, and increased with increasing pH or temperature

7.1.2 Adsorption

Adsorbents typically used in drinking water treatment include activated carbon, activated alumina, zeolites, clays, metal oxides, hydroxides, and carbonates (AWWA, 2011; U.S. EPA,

2012). GAC is used in a fixed bed, while PAC is generally added directly to the raw water as a powder or mixed with water to form a slurry.

Several laboratory studies of PFOA and PFOS adsorption kinetics indicate that PAC reached sorption equilibrium in 4 hours while GAC reached equilibrium in 168 hours, (Yu et al., 2009) and that PFASs removal percentages were generally higher for PAC than for GAC (60–90% versus 20–40%, respectively) for 10 minutes adsorption time (Hansen et al., 2010). These results may be due to PAC's smaller particle size, and higher specific surface area per volume of carbon when compared to GAC (Yu et al., 2009; Hansen et al., 2010). If PFASs are present in the raw water year round, Rahman et al. (2014) suggested that GAC adsorption may be the preferred method for PFASs removal, while PAC may be more appropriate for short-term spill response remediation.

7.1.2.1 GAC

Full-scale evaluations of the effectiveness of GAC adsorption for the removal of PFOA in drinking water sources have been mixed. Several full-scale studies, specifically designed and operated for PFASs removal in drinking water, observed successful removal of PFOA by GAC with a long empty bed contact time (EBCT) and an appropriate regeneration regime (MDH, 2008a; Wilhem et al., 2008; Rumsby et al., 2009; Little Hocking Water Association, 2010; Appleman et al., 2014). Other water treatment plants found similar levels of PFOA in both source and finished water, suggesting that GAC treatment only partially removes this contaminant, if at all. These treatment plants were not specifically designed for PFASs removal in drinking water. As the GAC had been in place for a variable period of time, it was likely that the preloading by NOM had deteriorated the GAC performance leading to similar PFOA levels in the influent and treated water (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012, Flores et al., 2013).

A full-scale GAC treatment system with a flow rate of 1.5 m^3/minute was specifically designed for PFASs removal in groundwater. The system used two GAC contactors in a lead/lag configuration with an EBCT of 13 minutes each. The lead vessel operated for approximately 10 months and treated 30,1293 BVs before the concentration of PFOA exceeded 0.05 µg/L. The GAC unit was capable of reducing an influent PFOA concentration in the range of 0.45–0.83 µg/L to below 0.05 µg/L, in the treated water from the lag vessel, for 72,775 BVs (approximately 22 months). At that point, the lead vessel water reached 0.25 µg/L PFOA, its carbon was replaced with virgin media and the vessel was put in the lag position (Appleman et al., 2014). Another full-scale 400 gpm (1.5 m^3/minute) GAC treatment system proved effective for the removal of PFOA in surface water, with an influent concentration decreasing from 0.9 µg/L to below the DL of 0.01 µg/L in the treated water. An increase in PFOA concentration in the treated water was observed after approximately 3 months with levels exceeding the treated water goal of 0.1 µg/L after 5 months of operation (Wilhelm et al., 2008; Rumsby et al., 2009).

The behaviour and fate of PFASs, including PFOA and PFOS, was assessed by analyzing influent and treated water from several drinking water treatment plants that included GAC in the treatment train. These plants were not specifically designed for PFASs removal in drinking water. The hydraulic retention time of individual treatment steps was considered when the efficiency of each these steps was assessed (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013). The studies found that only the GAC step was capable of removing PFASs in drinking water. Removal of approximately 50% of PFOA was reported when a GAC process was included in the treatment train (Eschauzier et al., 2012; Flores et al., 2013). The paragraphs below provide more details on some of these studies.

A full-scale 5 million gallons per day (MG/D) treatment plant, designed to remove trace levels (ng/L) of organic contaminants in surface water, consisted of river bank filtration, softening, UV/H_2O_2, biologically-active GAC filtration and six GAC contactors. The GAC system operated in parallel mode with an EBCT of 10.5 minutes. Water samples analyzed before and after the GAC system demonstrated reduction of an influent PFOA concentration of 9.7 ng/L to below 5 ng/L (Appleman et al., 2014).

Eschauzier et al. (2012) monitored the concentrations of PFOA and PFOS in a drinking water treatment train consisting of coagulation, rapid sand filtration, dune passage, softening, ozonation and GAC treatment. Only the GAC step was effective for PFASs removal. The system used two-stage GAC contactors in a lead/lag configuration. Of the 40 filters, 20 were used in parallel mode as a first stage and the other 20 were used as a second stage filter. Each GAC filter operated at a flow rate of 348 m^3/hour and an EBCT of 20 minutes, resulting in a total EBCT of 40 minutes. Each virgin GAC filter was installed as a second stage filter and was switched to the first stage after 15 months of operation. After another 15 months, the carbon was reactivated and put back in service as a second stage filter. The GAC system achieved approximately 50% reduction on the average influent PFOA concentration of 8.8 ng/L in the feed water to the first GAC stage (Eschauzier et al. 2012). Flores et al. (2013) reported similar results for the removal of PFOA (45%) in a water treatment plant, which had 24 GAC contactors installed and that were regenerated approximately once a year.

Takagi et al. (2008, 2011) investigated the behaviour, fate and removal efficiency of PFOA and PFOS in drinking water treatment processes from several drinking water treatment plants that included GAC in the treatment train. The removal efficiency of PFOA and PFOS were less than 50% in many of the water treatment plants. A negative removal rate in certain plants suggested that desorption from GAC filters, used for long periods of time without reactivation, may be responsible for these observations. The negative removal rates could also result from the formation of PFOA and PFOS from the degradation of the precursor compounds found in the raw water (Takagi et al., 2011). However, greater than 90% removal of PFOA was observed for 4 months in a 1.5 MLD water treatment plant after the replacement of its activated carbon in the GAC unit. The treatment train consisted of coagulation/sedimentation, rapid sand filtration and two GAC contactors (coal and coconut-shell carbon) in parallel mode. Both GAC contactors were capable of reducing the PFOA concentrations in the range of 25–44 ng/L to below the LOQ of 0.7 ng/L for 4 months. The concentration of the GAC filtered water gradually increased to13 ng/L at the end of the 8 month study period (Takagi et al., 2011).

Rapid small-scale column tests (RSSCTs) are a common bench scale test used to evaluate GAC. Using RSSCTs, Appleman et al. (2013) compared the effectiveness of three different types of GAC for removal of several PFASs including PFOA and PFOS. The column experiments were conducted with an EBCT of 0.38 minutes using deionized water and surface water [dissolved organic carbon (DOC) of 1.7 mg/L], both spiked with 1.0 µg/L of each PFASs. The tests were run for a total of 125,000 BVs (approximately 33 days). Carbon performance varied based on the type of carbon and water chemistry, with GAC being more effective at removing PFASs in deionized water. Of the three carbons, F300 achieved the best results. In the experiments conducted with deionized water, a concentration greater than 0.02 µg/L PFOA (2% of influent concentration C0) was observed at approximately 30,000 BVs (8 days) and a filtered water concentration of 0.05 µg/L (5% of C0) was measured after 56,000 BVs. However, the filtered water concentration reached 0.2 µg/L (20% of C0) after 11,000 BVs (3 days) and full (100%) breakthrough was observed at a run length of 26,000 BVs in spiked surface water. Although RSSCTs are not suitable for evaluating the effect of preloading/fouling of GAC columns by DOC, the observed rapid breakthrough in the spiked natural water demonstrated that the presence of DOC affects the

GAC performance in the removal of PFASs by directly competing for adsorption (Appleman et al., 2013).

The efficiency of PFOA removal by GAC adsorption is impacted by NOM in source water which compete for the carbon adsorption site and will adsorb irreversible, causing the carbon's capacity for the target compound to be reduced. When the adsorption capacity of the GAC is exhausted, it must be removed from the contactor and replaced with fresh or reactivated carbon. GAC is used in a fixed bed reactor, as a substitute for existing filtration media (i.e., sand) in a conventional filter, as a layer in a multi-media rapid filter, or in a separate contactor. The reactor can be located at the beginning of the treatment train in a dual-media or sand-replacement mode, or later in the treatment train as a second-stage contactor. The rate of GAC exhaustion will vary substantially for the same water source depending in which configuration GAC will be employed. A dual media (GAC and sand) is used when turbidity removal and the adsorption/removal of the contaminants are combined in a single unit process. The dual media filter (typically located after sedimentation) is likely to be exposed to higher DOC concentrations, and this filter will be exhausted faster. A GAC contactor located at the end of a treatment train will likely experience slower preloading/fouling, since the treatment steps prior to a GAC contactor will reduce the DOC influent concentrations. GAC contactors in lead/lag configuration have also been shown to achieve a PFOA concentration below 0.2 µg/L in treated water (Appleman et al., 2014; Little Hocking Water Association, 2010). This treatment strategy will assist in completely utilizing the entire GAC capacity and reducing operating cost (i.e., carbon replacement cost) (Crittenden et al., 2012).

Close monitoring of PFOA breakthrough (treatment objective) is necessary for efficient operation of GAC unit. Studies indicated that PFOA was successfully removed from drinking water when a frequent regeneration or replacement (3 to 6 months) of the GAC was performed (e.g., Wilhelm et al., 2008; Rumsby et al., 2009; Takagi et al., 2011). Takagi et al. (2011) observed that GAC regenerated over periods greater than one year were not effective in removing PFOA and PFOS and suggested regenerating the carbon 2 to 3 times per year. A GAC replacement at approximately every 3 months was needed to achieve PFOA removal to below 0.004 µg/L in a system where the influent PFOA concentrations ranged from 1.9 to 15 µg/L (Little Hocking Water Association, 2010). A full-scale 2,500 gpm GAC treatment plant, using two GAC contactors in series observed breakthrough of PFOA and PFOS after 286 days and 550 days, respectively. With the replacement of the GAC at the earliest time of PFOA breakthrough, the system was able to treat 1.9 million gallons of water for 23 months (MDH, 2008a; Kolstad, 2010).

Eschauzier et al. (2012) observed that the removal efficiencies of PFASs by GAC increased with increasing carbon chain length and that sulfonate compounds were removed for a longer period of time than the carboxylate compounds. Shorter-chained PFASs (especially PFBA and perfluorobutane sulfonate [PFBS]) were not removed by GAC. These findings were in agreement with previous batch experiments showing that the sorption of PFASs on activated carbon decreased with decreasing the carbon chain-length and perfluorosulfonates adsorbed stronger than perfluorocarboxylates with the same carbon chain length (Ochoa-Herrera and Sierra-Alvarez, 2008; Hansen et al., 2010; Dudley et al., 2012; Appleman et al., 2014). Branched isomers of PFOS and PFOA were found to be less sorbable to GAC than linear isomers. Desorption of shorter chain PFASs due to competition for sorption sites with longer chain PFASs or NOM (i.e., DOC) may result in higher levels of shorter chain PFASs in the treated water (Eschauzier et al. (2012).

7.1.2.2 PAC

No full-scale data were reported on the efficacy of PFOA removal by PAC. Most published studies on the efficacy of PAC were conducted at the bench-scale. PFOA concentrations in some of these bench-scale studies were order of magnitude higher than the concentration observed in natural waters. However, trends observed for PAC in terms of preferential adsorption (chain-length dependence) and competition with NOM were similar to that documented for GAC (Hansen et al., 2010; Dudley et al., 2012).

Dudley et al. (2012) evaluated the adsorbability of ten PFASs with different carbon chain lengths (from C4 - C10) on commercially available PACs (coconut shell, lignite, wood, and bituminous coal) and superfine PACs (S-PACs) obtained by wet-milling the commercially obtained PACs. Sulfonate substances were found to be more adsorbable than carboxylate substances and sorption kinetics were faster with S-PACs when compared to PACs. The removal efficiencies of PFAAs increased with increasing carbon chain length (i.e., negligible removal of C4 compounds but greater than 90% removal for C7-C10 compounds). The presence of NOM was found to decrease the effectiveness of PFAS removal by PAC in batch studies. The authors also concluded that significant removal of smaller chain PFASs may not be achievable at practical PAC dosages (Dudley et al., 2012).

Yu et al. (2009) investigated the sorption kinetics and isotherms of PFOA and PFOS on PAC, GAC and an anion-exchange resin. The anion exchange resin had the highest sorption capacity for PFOA while PAC was found to be the adsorbent of choice for PFOS. Another laboratory experiment found 88% and 25% removal of PFOA by PAC and GAC, respectively, based on an initial concentration of 1.4 µg/L in groundwater. The study also observed that PFOS sorption on PAC was faster than on GAC, suggesting that the sorption kinetics were influenced by the size of the activated carbon (Hansen et al., 2010). Qu et al. (2009) inferred that PAC could be used as an effective adsorbent for the removal of PFOA from water because the removal efficiency increased from 51.1% to 99.9% when the PAC doses were increased from 0.1 g/L to 10 g/L (initial PFOA concentration of 20 mg/L).

7.1.3 Membrane filtration

There are four main types of membrane filtration processes in drinking water treatment applications: microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO). Low pressure membranes such as MF and UF are not capable of rejecting PFASs since their pores sizes are larger than the effective diameter of the PFASs molecules (~1 nm) (Tsai et al., 2010; Rahman et al., 2014). Bench-scale studies indicated that the membrane molecular weight cut-off (MWCO) of NF/RO is probably the most important factor for removal of PFASs for these technologies. In general, NF membranes have a lower rejection (95%) than RO (greater than 99%), which is consistent with the fact that NF membranes have larger pores (Tang et al., 2006, 2007; Steinle-Darling and Reinhard, 2008; Lipp et al., 2010; Appleman et al., 2013; Rahman et al., 2014).

The available scientific information on the removal of PFOA and PFOS from drinking water supplies by membrane filtration is limited to one full-scale RO drinking water utility (Flores et al., 2013) and several indirect potable water reuse plants (Quinones and Snyder, 2009; Appleman et al., 2014). Due to the physical location of these indirect potable water reuse plants, they were considered to be major potential contributors to the drinking water facilities' source water in the conducted studies (Quinones and Snyder, 2009).

Although a full-scale conventional treatment was reported as being ineffective for PFOA removal in surface water; 92% removal of PFOA was achieved when RO followed the conventional treatment train (Flores et al., 2013). The RO system's feed water was filtered by the

conventional treatment process and blended with untreated groundwater. Feed water PFOA concentration ranged from 15 to 26 ng/L (average 21 ng/L) and the RO system was capable of reducing these PFOA concentrations to an average of 2.1 ng/L (Flores et al., 2013).

Two indirect potable water reuse plants with RO units in their treatment trains were capable of reducing a PFOA concentration to below 55 ng/L in the RO treated water. Both RO systems had a flux rate of 12 gallons per square foot per day (gfd) (20 $L/m^2/h$) and water recovery in the range 80-85%. The feed PFOA concentrations to the RO units ranged from 9.5 to 200 ng/L (Dickenson and Higgins, 2013; Appleman et al., 2014). A survey of several drinking water utilities and indirect potable water reuse plants showed that the PFOA concentrations in the treated water were comparable to the levels found in the raw water samples in almost every case. However, removal was only observed in one planned potable reuse facility when an integrated membrane treatment consisting of MF and RO was employed. The membrane system was capable of rejecting a feed PFOS concentration of 15 ng/L to below 5 ng/L (Quinones and Snyder, 2009).

Bench-scale experiments evaluated the rejection behaviour of unfouled and fouled NF membranes on the removal of PFASs, including PFOA (Appleman et al., 2013). The study found that a polyamide thin film composite flat-sheet NF membrane was capable of rejecting all of tested compounds in the range of 93 to 99%. Greater than 97% rejection of an average influent PFOA concentration of 664 ng/L (LOQ of 20 ng/L) was observed in all experiments using virgin membranes and spiked de-ionized water; virgin membranes and spiked groundwater; and fouled membranes and spiked groundwater. The fouling layer on the NF membrane showed no negative effect on PFOA rejection (Appleman et al., 2013). Another bench-scale study was conducted on one RO (MWCO of 100 Da) and three NF (MWCO range of 200 – 360 Da) membranes for the removal of PFOA. The RO membrane achieved a 99.9% rejection of PFOA from the feed water concentration of 3500 ng/L with a permeate PFOA concentration in the range of 3–6 ng/L. The RO system was operated with a flux rate of 30–40 $L/m^2/h$ and a feed pressure of 8 bars (116 psi). All tested NF membranes achieved a rejection in the range of 95.5–99.8% of an average feed PFOA concentration of 3000 ng/L, with a flux rate of up to 70 $L/m^2/h$ and an operating pressure in the range of 4–7 bars (58-101 psi) (Lipp et al., 2010).

Although there is limited information on full-scale RO and only bench-scale NF treatment information, both technologies are considered effective for PFOA removal from drinking water (Appleman et al., 2014). The results of the NF studies are promising since NF is a less energy intensive process than RO. Testing of the selected NF membrane for PFOA removal at both pilot- and full-scale is an important step for utilities when considering this treatment process. Since the size exclusion is an important mechanism for PFASs rejection by NF membranes, consideration should be taken to select membranes with MWCO smaller than the size of PFOA.

Considerations when using RO treatment include disposal of the reject water and the potential for increased corrosivity of the treated water. RO rejects a significant portion of the influent water as contaminant-rich brine, and the concentrate discharge must be disposed of appropriately. The removal of contaminants can cause mineral imbalances that could increase the corrosive nature of the treated water. In most cases, post-treatment corrosion control measures need to be taken.

7.1.4 Ion exchange

PFOA is in an anionic form at ambient water pH values and therefore is expected to be amenable to removal by anion exchange resins (Senevirathna, et al., 2010). Two primary mechanisms, hydrophobic and electrostatic interactions, were proposed for the removal of PFOA by ion exchange resins (Carter et al., 2010; Deng et al., 2010; Xiao et al., 2012).

Appleman et al. (2014) reported results for the only one known full scale application of ion exchange for the removal of PFASs. However, this system was not specifically designed for PFASs removal in drinking water. A 350 gpm full-scale ion exchange plant reduced the concentrations of PFOA in the range of 68–120 ng/L to an average concentration 24 ng/L in groundwater. A strong base anion resin impregnated with iron oxide used for arsenic removal was assessed for PFOA removal after the resin had been in use for 5 and 9 months. The highly porous strong base anion exchange resin, achieved greater than 75% removal of PFOA, partial removal of perfluoroheptanoic acid (PFHpA) (46%), and high removal of both PFOS (>92%) and perfluorohexanesulfonate (PFHxS) (97%). Shorter carbon chain compounds such as PFBA, and perfluorohexanoic acid (PFHxA) exhibited little to no removal. Results also indicated that perfluorosulfonic acids were preferably removed by anion exchange resin over the perfluorocarboxylic acids.

Exchange resins exhibit a degree of selectivity for various ions, depending on the concentration of ions in solution and the type of resin selected. Laboratory-scale evaluations of different types of resins (i.e., ion exchange resins, non-ion exchange resins) for removal of PFASs in water have been reported in the literature (Lampert et al., 2007; Carter et al., 2010; Deng et al., 2010; Senevirathna et al., 2011; Xiao et al., 2012; Chularueangaksorn et al., 2013). Batch kinetic tests conducted with a high initial PFOA concentration (mg/L) demonstrated a greater than 99% removal of PFOA in 25 hours of contact time using a commercial anion exchange resin, while another anion resin achieved only 37% removal. The study also observed that PFOS anions were preferably removed over PFOA anions in the ion exchange process (Lampert et al., 2007). In laboratory experiments, anion exchange resins demonstrated greater capacity for PFASs removal than non-ion exchange resins (Chularueangaksorn et al., 2013, 2014). Laboratory-scale fix-bed columns compared the performance of anion exchange and non-ion exchange resins. The tests were conducted with an influent concentration of 5 µg/L PFOA for 120 days of operation. The breakthrough goal of 0.5 µg/L was observed with run lengths of 119,880 BVs (111 days) and 68,040 BVs (60 days) by the anion exchange and non-ion exchange resins, respectively (Chularueangaksorn et al., 2013).

While findings showed that anionic resins had a higher capacity for PFOA than non-ion exchange resins (Deng et al., 2010; Chularueangaksorn et al., 2013, 2014), it was also observed that moderately polar non-ionic resins performed better than non-polar non-ionic resins for removal of PFOA from water (Xiao et al., 2012).

Studies indicate that the ion-exchange process is a promising technology (Dickenson and Higgins, 2013) for the removal of PFAAs, including PFOA, from drinking water. However, additional studies on the, selectivity of the resins, kinetic limitations, the impact of DOC, regeneration rates, and the presence of competing ions such as sulfate and nitrate on removal efficiency are needed (Dickenson and Higgins, 2013; Rahman et al., 2013).

7.1.5 Oxidation, UV irradiation and advanced oxidation processes

Advanced oxidation processes (AOPs) have been developed for removal of contaminants that are resistant to more typical chemical oxidation treatment processes. They include the use of appropriate combinations of ultraviolet (UV) light, chemical oxidants and catalysts (e.g., ozone, hydrogen peroxide, titanium dioxide,) to generate highly reactive radicals, such as hydroxyl radicals, which are strong oxidants and react rapidly and non-selectively with organic contaminants.

Rahman et al. (2014) summarized studies that have demonstrated that PFAAs like PFOA will likely be resistant to oxidation, even by molecular ozone and hydroxyl radicals. Due to the low reactivity of PFOA with ozone and AOPs, chlorine–based oxidation processes will likely not

oxidize PFOA under typical drinking water conditions. The resistance of PFOA to oxidation is due to the shielding effect of the fluorine atoms and the strength of the carbon-fluorine bonds (3M, 1999; ATSDR, 2009).These conclusions have been confirmed in surveys of full-scale treatment plants (Quinones and Snyder, 2009; Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013) described below.

In a survey of several drinking water utilities, Quinones and Snyder (2009) observed that PFOA was resistant to chlorination, chloramination and ozonation even in a combination with other treatment processes such as coagulation/flocculation, deep bed filtration and UV irradiation. Results from drinking water treatment plants in Japan reported similar concentrations of PFOA in samples of water treated with an ozonation process and in the raw water samples (Shivakoti et al., 2010; Takagi et al., 2011). Ozone doses in the range 0.37–0.85 mg/L and contact time as high as 120 minutes showed that the ozonation process was ineffective to degrade PFOA at four utilities (Takagi et al., 2011). Thompson et al. (2011) observed that an ozone dose of 5 mg/L with a contact time of 15 minutes in reclaimed water was not effective at reducing PFOA concentrations in the range of 7.1–12.4 ng/L.

A full scale treatment plant employing two UV reactors, each capable of treating 3 MG/D groundwater with a UV dose of 80 mJ/cm^2 and UV transmittance of 95% %, were not capable of reducing an influent PFOA concentration in the range of 11–15 ng/L. Another full scale 5 MG/D treatment plant reported that a UV dose of 500 MJ/cm^2 in combination with a dose of 4 mg/L H_2O_2 was also ineffective at degrading 19 ng/L PFOA in surface water (Appleman et al., 2014). Oxidation/AOPs and UV irradiation appear ineffective for PFOA removal in drinking water. However, ozone or AOPs may be able to oxidize polyfluorinated precursor chemicals that may be present in raw water, resulting in the potential for increasing the concentration of PFOA and PFOS in the finished water (Rahman et al., 2014).

7.1.6 Aeration/air stripping

The removal of compounds using air stripping is based on the equilibrium partitioning of chemicals between air and water, which is affected by the contact surface area between the air and the water, as well as temperature, vapour pressure and the pH of the water.

Dickenson and Higgins (2013) evaluated 23 PFASs (including PFOA and PFOS) in raw and finished drinking water and at various steps along the treatment train. They found that aeration was ineffective at removing PFOA and PFOS (10% removal).

7.1.7 River bank filtration (soil aquifer treatment)

River bank filtration (RBF) is a drinking water treatment method where surface water flows through the subsurface sand and gravel layers of the bank or bed of a river to extraction wells and contaminants are removed through the processes of filtration, sorption, dilution and biodegradation.

A drinking water utility utilizing RBF with a hydraulic residence time of approximately 10 days observed approximately 30% removal for PFOA, variable removal of some PFASs, and increases in concentration for other PFASs (Appleman et al., 2014). The authors concluded that this variation was possibly due to the variability in the influent concentrations from wastewater effluents impacted the drinking water sources and/or due to breakdown of precursor compounds through the river bank. Dickenson and Higgins (2013) concluded that RBF was not likely to result in significant removal of PFASs.

7.1.8 Emerging technologies

Other potential treatment technologies for removal of PFOA and PFOS have promise, but are still being researched actively. They have not yet all been evaluated on drinking waters by laboratory, pilot, or full-scale studies, but have been mentioned in reviews of bench scale studies of some PFASs removal from drinking water and wastewater (Vecitis et al., 2009; Eschauzier et al., 2012).

7.1.8.1 Nanomaterials and nanotechnologies

Nanomaterials are being developed for drinking water treatment applications, including ion exchange, sorption and oxidation processes, and abiotic reduction (e.g., nanozerovalent iron) (Boyd et al., 2013). Different nanomaterials/nanotechnologies show promise for removal of PFOS including carbon nanotubes (CNTs), chitosan-based molecularly imprinted polymers (MIPs), electrospun nanofibrous membranes (ENFMs), and titanium dioxide (TiO_2) assisted photocatalysis (Yu et al., 2008; Deng et al., 2012; Dai et al., 2013). CNTs are carbon molecules composed of carbon lattices that can take the form of tubes. Chitosan is a natural polysaccharide based on the shells of crustaceans. It may be prepared as a nanoparticle or electrospun in nanofibers (Sonia and Sharma, 2011; Zhao et al., 2011a; Boyd et al., 2013). Molecular imprinting is a technique where specific sites for target compounds are constructed on a polymer so that specific adsorbates are recognized in the sorption process. ENFMs are prepared by electrospinning nanofibers of polymer or polymer composite materials to create membranes of non-woven fibers with diameters ranging from several hundreds to tens of nanometers (Greiner and Wendorff, 2007; Dai et al., 2013; Boyd et al., 2013).

Deng et al. (2012) have demonstrated the effectiveness of CNTs for removal of perfluorinated contaminants, including PFOA and PFOS, from aquatic environments when the hydrophobic interactions were involved in the sorption of perfluorinated contaminants onto the CNTs. The sorption of the perfluorinated contaminants was increased with increasing carbon-fluorine chain length with the same functional group.

7.1.8.2 Photolysis and photochemical degradation

Although a full-scale UV treatment process was reported ineffective in removal of PFOA in drinking water, several laboratory-scale evaluations of synthetic waters, wastewaters and industrial waters have reported that UV-visible light, UV in the presence of persulfate, UV in the presence of TiO_2 and perchlorate, UV in the presence of iodide and UV irradiation using carbonate radical ions may degrade PFOA concentrations (Hori et al., 2004a, 2005; Chen and Zhang, 2006; Chen et al., 2007; Fujii et al., 2007; Giri et al., 2011, 2012, 2013; Dillert et al., 2007; Panchangam et al., 2009; Qu et al., 2010).

A laboratory-study reported 87% degradation and defluorination of an initial PFOA concentration of 25 mg/L under 185 nm UV light irradiation in the presence of persulfate. When compared to direct photolysis the photochemical reaction enhanced PFOA degradation. The study observed a formation of short-chain PFCAs (Chen and Zhang, 2006). Another laboratory-study reported on the effectiveness of sulfate radical anion ($SO_4^{\cdot -}$) to decomposed PFOA in a photochemical reaction. The authors reported that PFOA concentration of 1.35mmol was completely decomposed by the photochemical system using $SO_4^{\cdot -}$ and 4 hours of UV visible light irradiation. The study also reported on the formation of shorter-chain PFCAs in a stepwise manner (Hori et al., 2005). After UV-visible light irradiation was applied under 0.48 MPa of oxygen, 89.5% of an initial PFOA concentration of 1.35 mmol was decomposed and the formation of CO_2, F^- and short-chain PFCAs was observed. The authors also reported that heteropolyacids due to their high stability are attractive photocatalysts in the degradation

reactions of PFCAs. In the presence of heteropolyacid, 7.44 µmol PFOA in aqueous solution were completely degraded after 24 hours of UV irradiation. The photocatalyst enhanced the PFOA degradation and suppressed the formation of the short-chain PFCAs (Hori et al., 2004a). Tang et al. (2012) studied the effectiveness of the UV–Fenton technique for PFOA removal in water and found almost complete degradation and defluorination of PFOA within several hours, while PFOA was hardly degraded by a conventional Fenton system alone.

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to municipally treated water. In cases where an individual household obtains its drinking water from a private well, a private residential drinking water treatment device may be an option for reducing PFOA concentrations in drinking water.

Although there are no certified residential treatment devices for the reduction of PFOA from drinking water, available data suggests that residential activated carbon and reverse osmosis can achieve treated PFOA concentrations of 0.2 µg/L and below 0.05 µg/L, respectively. In addition, treatment devices using anion exchange may be effective for the reduction of PFOA.

The Minnesota Department of Health (MDH, 2008b) completed a study of the effectiveness of point-of-use (POU) water treatment devices for PFOA, PFOS and PFBA removal and demonstrated that RO and activated carbon filters were capable of reducing PFOA concentrations typically found in drinking water. Laboratory screening tests and field evaluation of devices installed in municipal water systems were undertaken. In the laboratory tests, the challenge waters had a PFOA concentration of 3.0 µg/L and the target goals for performance was 0.2 µg/L. The field testing involved monitoring and sampling of four activated carbon and seven RO point-of-use devices installed at two municipal wells. One of the wells had concentrations of 0.6 µg/L PFOA, 0.9 µg/L PFOS, and 1.4 µg/L PFBA, while only PFBA was present (1.5 µg/L) at the second well. All RO devices were equipped with an activated carbon pre-filter (before the RO membrane) and a post-treatment (after the RO membrane) activated carbon polishing filter. Results indicated that all activated carbon and RO devices were effective in removing PFOA to below the quantification limit of 0.2 µg/L and below the detection limit of 0.05 µg/L, respectively. Based on these results, activated carbon and RO are expected to be effective at reducing the level of PFOA in drinking water to levels below the proposed MAC of 0.2 µg/L.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2015):

- CSA Group (www.csagroup.org);
- NSF International (www.nsf.org);
- Water Quality Association (www.wqa.org);
- UL LLC (www.ul.com);
- Bureau de normalisation du Québec (www.bnq.qc.ca); and
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

Activated carbon filtration systems may be installed at the faucet (POU) or at the location where water enters the home [point-of-entry (POE)]. RO systems are intended for POU installation, as larger quantities of influent (incoming) water are needed to obtain the required volume of treated water, which is generally not practical for residential-scale point-of-entry systems. RO systems should only be installed at POU as the water they have treated may be corrosive to internal plumbing components. A consumer may need to pre-treat the influent water to reduce fouling and extend the service life of the membrane.

Ion exchange treatment technology using anion exchange resins may also be a feasible for PFOA removal in residential scale applications. Ion exchange treatment devices is typically designed and constructed for residential use by drinking water treatment system providers or dealer. Health Canada strongly recommends that homeowners ensure that these systems are constructed using materials certified to NSF/ANSI Standard 61 (NSF/ANSI, 2014). If an ion exchange system is used, the water may need to be filtered through a GAC filter to remove any chlorine or chloramine (if connected to a treated water supply) from the water before it reaches the resin.

Before a treatment device is installed, the water should be tested to determine general water chemistry and verify the presence and concentration of PFOA. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Devices can lose removal capacity through use and time and need to be maintained and/or replaced.

8.0 Kinetics and metabolism

PFOA is considered chemically unreactive, and it is not metabolized. The oral absorption of PFOA is rapid and complete (Kemper, 2003; Hundley et al., 2006; Lau et al., 2007). Once absorbed, PFOA is primarily restricted to plasma and extracellular fluid (Butenhoff et al., 2004a; Han et al., 2012) and excreted in urine.

8.1 Absorption

PFOA is rapidly and nearly completely absorbed in the GI tract. In rats, studies consistently estimated the oral absorption rates of PFOA at >93% after a single dose (0.1 to 25 mg/kg bw) by gavage (Johnson and Ober, 1979, 1999; Kemper, 2003; Cui et al., 2010). Hundley et al. (2006) derived similar absorption rates for mice, rats, hamsters and rabbits after a single oral bolus of PFOA at 10 mg/kg bw. The estimated absorbed fractions were generally higher in males (rats: 89%, mice: 82%, hamsters: 92%) than in females (rats: 76%, mice: 61%, hamsters: 75%) except for rabbits (88% in both sexes). Fasted rats exhibited PFOA plasma concentrations approximately 2–3 times higher after a single oral bolus at 10 mg/kg bw (Hinderliter et al., 2006).

No controlled study data regarding the oral absorption of PFOA in humans are available; however, studies of residents living in areas with contaminated drinking water (Emmett et al., 2006a; Wilhelm et al., 2008) provide evidence of elevated serum PFOA concentrations. Emmett et al. (2006a) correlated the number of glasses of tap water ingested per day with blood concentrations, indicating this was the primary exposure route for populations with elevated PFOA concentrations in drinking water.

Limited inhalation or dermal studies have reported PFOA kinetics; however, the physicochemical properties of the compound suggest that these routes of exposure are not important when PFOA is found in drinking water (see Section 5.7).

8.2 Distribution

PFOA is mainly present in serum/plasma (Johnson and Ober, 1999b; Kudo et al., 2007). The volume of distribution, which is similar across species (approximately 170 mL/kg bw), suggests extracellular distribution (Butenhoff et al., 2004a; Han et al. 2012). PFOA is tightly bound to serum protein, which plays an important role in distribution in blood and to tissues (Han et al., 2005). Binding in blood is primarily to serum albumin, with >90% of PFOA in serum expected to be bound to albumin in rats and humans (Han et al., 2003). To a lesser extent, PFOA can also bind to plasma γ-globulin, α-globulin, α-2-macroglobulin, transferrin and β-lipoproteins (Kerstner-Wood et al., 2003; Butenhoff et al., 2012a). Protein binding also occurs in organs and tissues. Luebker and coworkers (2002) reported *in vitro* binding of PFOA to rat liver fatty acid binding protein (L-FABP). PFOA has also been shown to bind to rat kidney and urine α2μ-globulin; however, dissociation constants were low compared to other ligands known to induce hyaline droplet nephropathy (Han et al., 2004).

PFOA kinetics are non-linear at high doses, which is hypothesized to be due to the saturation of organic ion transporters (OATs) responsible for renal reabsorption at high doses, resulting in a higher excretion rate at high doses than at low doses (Andersen et al., 2006). Serum levels did not increase proportionally with increasing dose, except at lower doses in some studies and steady-state was reached more rapidly than expected at high doses with classical kinetics (4–5 half-lives). However, at lower doses closer to those relevant to human environmental exposures, kinetics are consistent with first order processes, and serum levels are proportional to administered dose (Loveless et al., 2006; Lou et al., 2009). This non-linearity can affect PFOA distribution; for example, after a single intravenous dose in male rats, a lower proportion of the dose was distributed to the liver (27%) at 17 mg/kg bw compared to 52% at 0.4 mg/kg bw (Kudo et al., 2007).

Few data have been gathered on the human tissues to which PFOA is typically distributed. PFOA was detected in approximately one half of the analyzed liver samples (in 6 males and 6 females from Catalonia, Spain; aged 27–79 years), and was significantly higher in males than in females (Kärrman et al., 2010), but was below the limits of quantification in livers in cadavers with environmental exposure (Olsen et al., 2003a). Neither cerebrospinal fluid (Harada et al., 2007) nor thyroid (Pirali et al., 2009) have been observed to be relevant partitioning sites for PFOA.

In rats, PFOA concentrations were consistently higher in males than in females after single or repeated exposures (Ylinen et al., 1990; Kemper, 2003). The differences have been attributed to more rapid elimination of PFOA in females than males. In mice and non-human primates, there do not appear to be sex differences in PFOA concentrations (Griffith and Long, 1980; Butenhoff et al., 2004a; Lou et al., 2009). Lou et al. (2009) reported similar serum, liver and kidney PFOA concentration time-courses in male and female CD-1 mice after a single oral gavage of 1 or 10 mg/kg bw. Sex differences in PFOA concentrations have also been noted in human biomonitoring studies (see Section 5.6). As previously described in Section 5.6, serum PFOA levels in humans appeared to be influenced by age and gender in CHMS. The effect was also observed in U.S. studies, such as NHANES 1999–2008 (Kato et al., 2011) and other reference populations (Harada et al., 2004; Hölzer et al., 2008; Ingelido et al. 2010). As age increases, PFOA concentration has been shown to decrease in males and increase in females (Kato et al. 2011). Plausible explanations are menstrual bleeding, especially in nulliparous women (Ingelido et al., 2010), pregnancy and lactation. Supporting this hypothesis is the observation of higher serum PFOA levels in primiparous women than multiparous women (Kim et al., 2011), as

well as the significant decrease in serum PFOA levels with duration of lactation (2–7 weeks vs. 3–4 months after delivery) (von Ehrenstein, 2009; Monroy et al., 2008).

PFOA exposure can occur transplacentally and lactationally. Fetal transfer via the placenta has been demonstrated in rats (Hinderliter et al., 2005) and mice (Fenton et al., 2009). In humans, concentrations of PFOA in cord blood of newborns are similar to maternal blood concentrations (Tittlemier et al., 2004; Midasch et al., 2007; Monroy et al., 2008; Beesoon et al., 2011; Needham et al., 2011; Gützkow et al., 2012). Moreover, serum concentrations in young children have been noted to be higher than serum concentrations in their mothers in a reference (i.e., not PFOA-contaminated) area (Hölzer et al., 2008) and in an area with elevated environmental PFOA levels (Mondal et al., 2012); however, serum concentrations were similar between children and mothers in an area with elevated PFOA levels in drinking water (Hölzer et al., 2008). Lactational transfer of PFOA has been measured in various mammal species, including humans, rats, mice, and sheep (Hinderliter et al., 2005; Fenton et al., 2009; Kim et al., 2011; Needham et al., 2011). Concentrations of PFOA in milk are consistently lower than in maternal plasma (Hinderliter et al., 2005; Fenton et al., 2009); in humans, a review of milk and maternal serum concentrations found the maternal milk:serum ratios across several studies to be approximately 0.11–0.12 (Liu et al., 2011). PFOA levels in human milk decrease significantly throughout the lactation period (Thomsen et al., 2010), and with increasing number of infants breastfed (Tao et al., 2008; Kadar et al., 2011).

8.3 Metabolism

The available data indicate that PFOA is not metabolized. Studies conducted in rodents and non-human primates did not reveal quantitatively significant metabolism of PFOA, and PFOA was not metabolized when incubated with microsomal fractions of human or rat intestine, kidney or liver homogenates (Kemper and Nabb, 2005; EFSA, 2008; ATSDR, 2009).

8.4 Excretion

Remarkable species-dependent differences in elimination half-life have been observed, with PFOA remaining in human bodies for a much longer duration than other species, including non-human primates, rats and mice (Post et al., 2012). Elimination half-lives from serum in humans is significantly longer than in non-human primates and rats. Species- and sex-related differences are primarily attributed to elimination kinetics where, at higher doses, the kinetics of PFOA in rodents and primates do not follow one-compartment or simple first-order models (Andersen et al., 2006). Half-life values for serum elimination of PFOA in humans were derived from data obtained in retired workers (arithmetic mean = 3.8 years; range = 1.5–9.1 years; 95% CI = 3.1–4.4 years; Olsen et al. 2007). In populations exposed environmentally through the consumption of PFOA-contaminated drinking water, half-life values could be estimated using measured declines in serum or plasma PFOA levels after exposures ceased due to filtration of drinking water. The geometric average half-life in Germany was reported as 3.26 years (range = 1.03–14.67; no 95% CI reported; Brede et al., 2011), and the average value for Mid-Ohio Valley was 2.3 years (95% CI = 2.1–2.4 years; no range provided; Bartell et al., 2010). An additional cross-sectional study in the Mid-Ohio Valley (with estimated, rather than measured, initial serum concentrations) identified average half-life values of 2.9–10.1 years (with values varying depending on the average serum concentrations in the community and duration since cessation of exposure) (Seals et al., 2011). The half-life of PFOA in animals varies depending on experimental protocols, but is on the order of days to weeks in rodents and monkeys (see Table 1).

Table 1: Serum half-life estimates in humans and experimental animals

Species	Dosing regime	Mean half-life (days)	Reference
Rat	Single oral dose of 0.1 mg/kg bw; followed for 22 days (M) or 5 days (F)	8.41 ± 1.56[a] (M) 0.13 ± 0.04[a] (F)	Kemper, 2003
	Single oral dose of 0.1 mg/kg bw; followed until PFOA < quantitation limits	11.55 ± 2.36[a] (M) 0.14 ± 0.05[a] (F)	
	Single oral dose of 1 mg/kg bw; followed for 22 days (M) or 5 days (F)	5.76 ± 1.33[a] (M) 0.14 ± 0.05[a] (F)	
	Single oral dose of 5 mg/kg bw; followed for 22 days (M) or 5 days (F)	7.26 ± 1.21[a] (M) 0.19 ± 0.03[a] (F)	
	Single oral dose of 25 mg/kg bw; followed for 22 days (M) or 5 days (F)	6.56 ± 1.60[a] (M) 0.68 ± 0.41[a] (F)	
	Single i.v. dose of 1 mg/kg bw; followed for 22 days (M) or 5 days (F)	7.73 ± 0.815[a] (M) 0.12 ± 0.02[a] (F)	
Mouse	Single oral dose of 1 or 10 mg/kg bw; followed for up to 80 days	21.7 (19.5–24.1)[b] (M) 15.6 (14.7–16.5)[b] (F)	Lou et al., 2009
Monkey	Single i.v. dose of 10 mg/kg bw; followed for 123 days	20.9 ± 12.5 (M) 32.6 ± 8 (F)	Butenhoff et al., 2004b
	Daily oral dose of 10 mg/kg bw for 6 months; followed for up to 147 days post-dosing	19.5[c] (M)	
	Daily oral dose of 20 mg/kg bw for 6 months; followed for up to 147 days post-dosing	20.8[c] (M)	
Human	26 former workers with an average of 31 years of work and 2.6 years retired; external exposure data not provided	1387 (1132–1606)[b]	Olsen et al., 2007
	138 adults and children, 2 years after reduction of PFOA concentrations in drinking water; doses not provided (Arnsberg, Germany)	1190[c]	Brede et al., 2011
	200 adults, ~1–2 years after reduction of PFOA concentrations in drinking water; doses not provided (Mid-Ohio Valley)	840 (767–876)[b]	Bartell et al., 2010

[a] ± Standard deviation
[b] 95% confidence interval
[c] No standard deviation or confidence interval was provided by authors

Urinary excretion is the major route of elimination in rats (particularly females, which have much greater urinary elimination rates than males) (Vanden Heuvel et al., 1991; Kudo et al., 2001) and monkeys (Butenhoff et al., 2002, 2004a). The urinary excretion process involves glomerular filtration, secretion into the tubular fluid, and reabsorption from tubular fluid. Glomerular filtration of PFOA is limited by extensive binding of PFOA to plasma proteins. Renal reabsorption of PFOA is thought to be driven by OAT proteins residing on membranes of proximal tubular cells (Yang et al., 2010; Han et al., 2012), and contribute to rat sex-related differences in renal clearance (Yang et al., 2009a). Unlike the rat, no gender differences in PFOA

urinary elimination are apparent in the mouse (ATSDR 2009) or monkey (Butenhoff et al., 2004a). A dose-dependent (non-linear) upward trend for urinary excretion of PFOA was observed in male rats (Butenhoff et al., 2004b). Consistent with observations in animals given low doses, the relationship between external dose and internal dose (serum level) is linear in humans with environmental exposures to PFOA (Clewell, 2009); however, non-linear kinetics—as seen in animals at higher doses—might occur at higher human exposures. The relevance of urinary clearance in humans has been questioned, as renal clearance of PFOA was substantially lower than in animals (Harada et al., 2005).

Biliary and fecal excretion also contribute to the elimination of PFOA, which may be subject to extensive enterohepatic recirculation (Vanden Heuvel et al., 1991; Kudo et al., 2001; Harada et al., 2007; Kudo et al., 2007). The relative importance of fecal excretion of PFOA depends on the urinary clearance. Fecal excretion is less important than urinary excretion in rats (Harada et al., 2007) and monkeys (Butenhoff et al., 2004a); however, data in rats indicate that the proportion of excretion occurring from this route becomes greater as doses and exposure durations increase (Cui et al., 2010). The relevance of this excretion route in humans is unclear. Harada et al. (2007) reported that the biliary excretion rate in four humans was significantly higher than serum clearance via urine and concluded that biliary excretion may represent a major excretion route in human; however, these data are not consistent with a case history that reported detection of PFOA in urine but not feces in a man with elevated serum PFOA levels (Genius et al., 2010).

In females, lactation can be a significant route of excretion, as shown in mice (Abbott et al. 2007) and in women (von Ehrenstein, 2009; Kim et al., 2011). Menstrual bleeding may be a significant route of excretion for women (Harada and Koizumi, 2009) and could potentially contribute to differences in serum levels measured between genders in humans.

8.5 Physiologically-based pharmacokinetic (PBPK) models

Several models with varying complexities have been developed to describe the kinetics of PFOA in both experimental animals and humans (Andersen et al., 2006; Tan et al., 2008; Loccisano et al., 2011, 2012a, 2012b, 2013). Due to the non-linear nature of PFOA pharmacokinetics, where faster clearance is seen with high bolus dosing, physiological models can provide an improved means of assessing cross-route and cross-species dosimetry for risk assessment.

The first model developed for PFOA was a biologically-motivated compartmental pharmacokinetic (PK) model for monkeys, which included saturable renal resorption of filtered PFOA (Andersen et al., 2006). Subsequent work to refine the model included the addition of a liver compartment and of time-dependent functions for protein binding and volume of distribution to fit high-dose monkey and rat oral and intravenous plasma, urine and feces kinetic data (Tan et al. 2008). PFOA PBPK models for adult rats (Loccisano et al., 2012a), monkeys (Loccisano et al., 2011) and humans (Loccisano et al., 2011) built upon the compartmental models. Further models for lactation and pregnancy were developed for rats (Loccisano et al., 2012b) and humans (Loccisano et al., 2013). No models have been developed for mice, and no pregnancy and lactation models have been developed for monkeys. The basic structure of the PBPK model was the same for all three species, with only time-dependent changes in physiology included to describe pregnancy and lactation along with the time-dependency for plasma and tissue binding. The models included tissue compartments for gut (for oral/dietary dosing), skin (human and monkey model only; for dermal dosing), liver, fat, and kidney, with remaining body tissues grouped together (and not divided into richly and poorly perfused compartments). Biliary excretion and fecal elimination of the unabsorbed bolus oral dose or dietary exposure was added

to the rat model; moreover, the rat version did not include a fat compartment (which became lumped with the rest of the body) or physiological gut, which was described as a one compartment non-physiological compartment. The PBPK model assumes only the free plasma fraction of PFOA is available for uptake into tissue, excretion or resorption. Elimination from plasma is described as glomerular filtration of the free fraction into a filtrate compartment. The filtered PFOA can either be eliminated in urine or resorbed into the kidney where it can return to systemic circulation. The models were relatively good at reproducing controlled dosing data for rats (dietary, oral gavage, and IV routes of exposure; Loccisano et al., 2012a), and monkeys (IV and oral gavage routes of exposure; Loccisano et al., 2011). Although no controlled dosing data were available for humans, biomonitoring data (for typically only a single timepoint) were within similar ranges as model simulations (using measured water concentrations for the biomonitored populations, along with assumptions on ingestion patterns; Loccisano et al., 2011).

The Loccisano models for humans (2011), monkeys (2011) and rats (2012a) were considered for use in the current assessment (see Section 10); moreover, a mouse model (that was scaled from the rat model, but that could not be validated) was used. Further specifics of the models used for this assessment, including the values used for each of the physiological and chemical-specific parameters, are described in Campbell and Clewell (2013). Exposure was described as a constant intake of PFOA in humans (ingesting 1.5 L of water per day) and the model was allowed to reach steady state conditions prior to determining the predicted drinking water concentration consistent with the internal dose metric. To be conservative, the longest regularly reported half-life (3.8 years) was used, as this would result in the lowest predicted water concentration. The human was simulated as a 70 kg adult.

The Andersen et al. (2006) pharmacokinetic model was modified by Wambaugh and colleagues (2013) by adding a gut compartment for oral absorption and specifying an upper limit on tissue distribution. The authors used the model to translate dose regimes and available LOEL, NOEL, and benchmark dose (BMD) values from 9 *in vivo* studies of PFOA into internal dose metrics (area under the curve, average, and maximum serum concentrations). The data were modelled for cynomolgus monkeys, male and female Sprague-Dawley rats, and CD-1 and C57Bl/6 mice. A Bayesian approach was employed to model ranges of various physiological parameters. Wambaugh et al. (2013) identified relatively good concordance between predicted and measured (at study termination) serum concentrations, with few outliers, and identified that mean and maximum serum concentrations were most consistent among the various adverse endpoints. Dose metrics for points-of-departure (PODs) tended to be similar, indicating consistency between species and adverse outcomes.

Dermal and inhalation routes from contact with drinking water were not included in as potential routes of exposure in this effort, as their contribution to exposure is considered to be negligible (see Section 5.7).

8.6 Animal-to-human extrapolation

Although animal-to-human extrapolations are typically discussed after the selection of potential PODs, consideration has been given to this extrapolation earlier in the PFOA assessment, as the large variability between species can affect POD selection. The large differences in PFOA clearance between humans and other species must be accounted for when using animal studies as a basis for human risk assessments. The application of default approaches for animal-to-human extrapolation—such as the use of an interspecies uncertainty factor of 10 or allometric scaling—might not be sufficiently protective of humans, who receive longer internal exposures to target tissues. For this reason, chemical-specific approaches that can account for pharmacokinetic differences between species and nonlinear behavior of PFOA were considered

for the risk assessment. These approaches include the application of chemical-specific adjustment factors (CSAFs) and PBPK modelling. A discussion and application of each of these approaches is outlined below, and further details can be found in a report prepared for Health Canada by Summit Toxicology (2015).

8.6.1 Derivation of CSAFs

A major advantage of the application of CSAFs over default uncertainty or allometric scaling factors is that the approach incorporates both species- and chemical-specific data. Despite this strength, the approach relies on single values representative of pharmacokinetics in each species, and does not necessarily account for non-linear pharmacokinetics.

IPCS guidelines on calculating CSAFs (IPCS, 2005) were applied to derive the toxicokinetic portion of the interspecies uncertainty factor (AK_{UF}). IPCS recommends that the default interspecies uncertainty factor of 10 be divided into values of 4.0 ($10^{0.6}$) for the toxicokinetic portion (AK_{UF}) and 2.5 ($10^{0.4}$) for the toxicodynamic component (AD_{UF}). The default AK_{UF} of 4.0 becomes replaced with any AK_{UF} values calculated based on chemical-specific data (IPCS, 2005). As data were not available to quantitatively evaluate toxicodynamic differences between species, no AD_{UF} was calculated.

To calculate the AK_{UF} (i.e., reflecting interspecies toxicokinetic differences), the following equation was used:

$$AK_{UF} = \frac{CL_{animal}}{CL_{human}}$$

where:

- AK_{UF} is the toxicokinetic component of the interspecies uncertainty factor; and
- CL is clearance in animals and humans (e.g., mL/kg bw per day)

In rats, a single oral dose of 0.1 mg/kg bw per day was provided to Sprague-Dawley rats (4/sex), who were followed for 22 days (males) or 5 days (females) (Kemper et al., 2003). Increased clearance and decreased half-life in female vs. male rats has been repeatedly demonstrated (see Section 5); females appear to have increased urinary excretion of PFOA over males, but the reason for this phenomenon is not clear. For this reason, AK_{UF} values are presented separately for each sex. Clearance rates for male and female rats were 23.1, and 777, respectively.

Clearance was not reported directly for monkeys, mice, or humans, and must be calculated based on species-specific half-life values using the following equation:

$$CL = \frac{\ln 2 \times V_d}{T_{½}}$$

where:

- CL is clearance in animals and humans (L/kg bw per day);
- ln 2 is the natural log of 2;
- V_d is the volume of distribution, which is the theoretical volume of blood in which the amount of a chemical would need to be uniformly distributed to produce the observed blood concentration; and
- $T_{½}$ is the half-life of a compound.

A half-life of 20.15 days was obtained from cynomolgus monkeys, which was averaged from monkeys provided a daily oral dose of 10 and 20 mg/kg bw for 6 months and followed for up to 147 days post-dosing (Butenhoff et al., 2004a). No volume of distribution was presented for monkeys in the chronic exposure study, but an average value of 190 mL/kg was obtained from the single dose study that was presented in the same publication (Butenhoff et al., 2004a). Half-life values in mice were obtained from a study that provided a single oral dose of 1 or 10 mg/kg bw per day to CD-1 mice (3/sex/dose) that were followed for up to 80 days (Lou et al., 2009); the average value was 18.7 days. In humans, a half-life of 1387 days (3.8 years) was calculated from decreases in serum concentrations of 26 workers previously occupationally exposed to PFOA, with an average of 31 years of work and 2.6 years retired (Olsen et al., 2007). Despite the availability of half-life values for general populations, the occupationally-derived half-life was selected to be conservative, as it is the longest of half-life values estimated from longitudinal data (see Section 8.4). Volume of distribution values for PFOA are typically relatively consistent among species (Thompson et al., 2010); as no volumes of distribution were provided in the human and mouse studies, a value of 200 mL/kg was used to represent a chemical that is mostly distributed extracellularly. Using the above equation, the resulting clearance values were 6.5 mL/d-kg in monkeys, 7.4 mL/d-kg in mice, and 0.1 mL/d-kg in humans. Using the human:animal ratios of clearance values described above, the calculated AK_{UF} values for PFOA for monkeys, mice, and average, male, and female rats were 65, 74, 231, and 7774, respectively.

Clearance was selected as the dose metric for the derivation of AK_{UF} values because data for this metric were readily available in most species, and could be calculated from half-life data in humans. Moreover, the use of clearance as a dose metric is a reasonable assumption for chemicals with long half-lives. Preliminary analyses have suggested that peak concentrations might be more predictive of PFOA toxicity for certain adverse endpoints (Haber et al., 2013); PFOA was not investigated in these analyses. Although this hypothesis was not further explored for the present analysis, using clearance is considered to be a more conservative alternative to using peak concentrations as the dose metric for AK_{UF} derivation. Finally, ratios of clearance levels are considered an appropriate basis for AK_{UF} derivation typically only if first-order kinetics are assumed to apply; however, as urinary clearance of PFOA is complex, this assumption might not be appropriate.

8.6.2 PBPK modelling

A typical approach for PBPK modelling is to use the model to calculate human-relevant PODs, which are derived by applying a human PBPK model to internal dose metrics (e.g., concentrations of PFOA in plasma) that were either calculated or measured in animals. With sufficiently validated models, this approach is considered to be the most robust approach for performing animal-to-human extrapolations. However, there is only medium confidence in human, monkey, and rat models, because different model codes were used for different species, and model fits to some datasets were not optimal. Moreover, the limited understanding of reasons for the observed sex differences in clearance in rats means there are weaknesses in how this could be addressed in the model. Finally, a major drawback in using the standard PBPK modelling approach is that human models have not been fully verified. Human data available for verification are limited to biomonitoring studies that allow for only rough estimates of exposure scenarios, and for which serum concentration measurements were typically only performed once (with a few populations with measurements at two timepoints). Loccisano and colleagues did not develop PBPK models for mice, but Health Canada modelling approaches using mouse studies scaled the rat models using mouse data. As insufficient toxicokinetic data exist to verify whether the mouse

model is appropriate, confidence in the mouse model is low. Therefore, there is insufficient confidence to use precise PBPK model results as points-of-departure for the risk assessments.

As an alternative approach to using the PBPK model for POD calculations, ratios of PBPK model-predicted dose metrics were used to calculate AK_{UF} values for relevant doses. This approach is thought to provide more robust estimates of the AK_{UF} than the traditional calculations described in Section 8.6.1, as it can address the non-linear kinetics of PFOA, identifying different values at steady state for different oral dose levels. In contrast, the AK_{UF} values calculated above are dependent on the specific doses and dose regimes used in the pharmacokinetic studies; uncertainties arise in the values obtained from these studies, as the animals were provided only single doses, and the human data were not obtained from controlled dosing studies. Furthermore, clearance-based AK_{UF} values are ratios of low doses in humans to high doses in animals, and therefore exposures between the species are not of the same magnitude; using the PBPK model to derive the AK_{UF} allows for a more appropriate comparison of doses of the same magnitude.

The selected dose metric for the PBPK-derived AK_{UF} values was steady-state concentrations of PFOA. Steady-state concentration was selected as it is typically relevant for chemicals with long half-lives, and is a conservative assumption. Although alternative dose metrics—including peak concentrations (Haber et al., 2013)—might be more predictive of PFOA toxicity for certain adverse endpoints, additional work was not performed to further investigate the most appropriate dose metric. Plasma was selected as the relevant tissue for steady-state concentrations, as it is a metric that can act as a relevant proxy for a wide variety of organs, because blood flows to these different organs. Liver steady state concentrations were also incorporated into the assessment for comparison with plasma-based AK_{UF} values, as liver has been identified as a primary organ for PFOA distribution in pharmacokinetic studies, and is also a potential target organ for toxicity. However, there is lower confidence in liver-based values than plasma values, as very little pharmacokinetic data exists to be able to perform verification of the PBPK model for liver concentrations. Liver concentrations could not be verified for humans, mice, and monkeys; for rats, minimal verification could be performed, but as data were available for only one to two timepoints in each study, the comparisons are not robust. Moreover, the use of plasma concentrations as a proxy for a variety of organs simplifies the application of AK_{UF} values in the assessment, which is already complex due to the use of AK_{UF} values that are species- and dose-specific.

Using the Loccisano PBPK models described in Section 8.5, steady-state plasma and liver concentrations were obtained at various doses in each of the species. The same doses were used for each of the species. For each dose run in the PBPK model, ratios of steady-state PFOA concentrations in humans vs. other species were calculated to obtain dose- and species-specific AK_{UF} values (Summit Toxicology, 2015). Steady-state concentrations and AK_{UF} values for plasma and liver at potentially relevant doses are listed in Table 2.

Table 2: PBPK dose metrics and PBPK-derived AK_{UF} values at relevant doses

Metric	Species	Oral dose (mg/kg bw per day)			
		0.001	0.01	0.1	1
Steady-state plasma PFOA predictions (µg/mL)	Human	8.74	86.1	706	1493
	Monkey	0.17	1.61	11.5	38.9
	Mouse	0.05[a]	0.47	4.74	47.4
	Rat	0.09	0.9	8.96	89.5
Steady-state liver PFOA predictions (µg/mL)	Human	19.2	189	1555	3289
	Monkey	0.37	3.58	25.5	88.3
	Mouse	NC	NC	NC	NC
	Rat	0.32	3.16	31.6	316
AK_{UF} derived based on plasma predictions	Monkey	52	53	62	38
	Mouse[b]	184	182	149	31
	Rat	97	96	79	17
AK_{UF} derived based on liver predictions	Monkey	52	53	61	37
	Mouse[b]	NC	NC	NC	NC
	Rat	61	60	49	10

[a]NC = could not be calculated due to limitations in the PBPK model
[b]AK_{UF} values for rats will be applied due to low confidence in the PBPK model

To select the appropriate AK_{UF} for each POD, the POD is rounded down to the nearest value in the oral dose column (i.e., values within the same order of magnitude are used). As discussed above, low confidence is placed on the mouse PBPK model. Until a PBPK model has been developed based on mouse data, the use of rat AK_{UF} values for mice is recommended (Summit Toxicology, 2015).

8.6.3 Recommended interspecies extrapolation approach

The recommended approach for interspecies extrapolation is the use of a PBPK model for the calculation of the AK_{UF} component of the CSAF, using steady-state plasma concentrations as the dose metric. The use of plasma concentrations ensures the relevance of the dose metric to adverse effects that occur in a variety of organs. Organ-specific dose metrics are typically preferred over blood-based values, whenever available; however, using the plasma metrics for this assessment provides consistency in the application of the AK_{UF} over a wide variety of adverse endpoints. AK_{UF} values were calculated for liver metrics for comparison with plasma values; the behaviour of PFOA in the liver was similar to that in the plasma, and AK_{UF} estimates were on the same order in both compartments. These results indicate that plasma values are appropriate proxies to be used for adverse hepatic effects. The liver-based values in rats were slightly lower than plasma-based values; however, greater confidence is placed in the plasma values because more data were available to verify this compartment of the PBPK model. The dose- and species-specific AK_{UF} values (for steady-state plasma concentrations) in Table 3 are applied in Sections 10.1 and 10.2.

Although PBPK-derived AK_{UF} values were selected as the recommended approach for this assessment, several weaknesses have been identified. As described above, the AK_{UF} was plasma based rather than being organ specific. Steady state concentrations were also selected as the dose metric, as a conservative assumption relevant to the nature of the compound; detailed work was not performed to identify whether other dose metrics (e.g., peak concentrations) would be more appropriate for the various adverse endpoints. Steady state was also not reached in the human

model at doses below 0.1 mg/kg bw per day. Furthermore, PBPK models have not been developed specifically for the mouse, and have been scaled instead from the rat, without further pharmacokinetic data for mice to be used for verification; the application of AK_{UF} values for rats is therefore recommended for use in mice in the absence of robust data in the species. AK_{UF} values for rats are also derived based on male rats only, despite faster clearance—and therefore greater interspecies differences—observed in females.

Despite these weaknesses, using the PBPK model to derive the AK_{UF} was thought to be equally or more robust when compared with other potential interspecies extrapolation approaches. The selected approach quantitatively incorporates pharmacokinetic differences among species; however, non-linear kinetics of PFOA are addressed, which cannot be done using the default AK_{UF}-derivation approach. Moreover, the PBPK-derived AK_{UF} values do not rely on individual pharmacokinetic studies that are often single-dose studies and not easily comparable among species. An ideal approach to address species differences would be to use blood concentrations of PFOA—either by using pharmacokinetic models to estimate the concentrations, as employed by Wambaugh et al. (2013), or using the values specifically measured in individual studies—as PODs for the assessment. However, the human PBPK models that would be used to extrapolate from this serum concentration cannot be fully verified based on existing human pharmacokinetic data, which decreases the level of comfort of using this approach to estimate precise PODs. The recommended approach was selected as a means of quantifying interspecies differences while addressing the non-linear kinetics of PFOA, without relying on precise PBPK-derived estimates of PODs.

9.0 Health effects

The summary of literature on health effects for PFOA is based on a comprehensive review conducted by a consultant (Sanexen Environmental Services Inc., 2013), and includes only the studies of direct relevance to the derivation of the health-based value.

9.1 Effects in humans

9.1.1 Acute toxicity

No information related to acute or short-term epidemiological studies could be located.

9.1.2 Subchronic and chronic toxicity

Many quality epidemiological studies have been conducted. Large cohorts of workers and environmentally-exposed populations have been followed, with observations of significant relationships between exposure to PFOA and various health endpoints, such as haematological and clinical biomarkers (cholesterol, uric acid), cancer (testicular, kidney), preeclampsia, immunological, endocrine (thyroid), renal functions, and fecundity (semen quality, birth weight) outcomes. Although all of these studies present limitations to some extent, including in terms of study design, bias and confounders, the human weight of evidence provides a strong argument in favor of detrimental health effects of the compound. This information should support the choice of a health endpoint; however, deriving a safe human exposure dose based on studies in humans remains a challenge because of the difficulties in characterizing a dose-response pattern with current studies. Their use in the present assessment is important to verify the relevance of animal to human extrapolation, and the monitoring of future studies will help in determining the accuracy of the observed associations.

Most environmental studies among PFAA-exposed populations were conducted in the Mid-Ohio Valley within the C8 Science Project. The C8 Science Panel was convened as a result of a class action settlement against DuPont, and is composed of independent epidemiologists jointly selected by lawyers for the community and DuPont. The C8 Health Project is the largest study of a population exposed to PFAAs in drinking water, containing residents of Ohio and West Virginia communities surrounding the DuPont Washington Works plant. The health survey was conducted in 2005–2006 on approximately 69,000 individuals, including children and adults. The median PFOA serum concentrations in this population were 28.2 ng/mL, compared to 4.2 ng/mL in the general American population during the same period (Frisbee et al., 2009). Some longitudinal/prospective studies were also conducted among this population after a follow-up period. Some recent data in the project have not yet been published in peer reviewed literature; summaries of these studies—as well as panel conclusions and further information on the members of the panel—are available on the C8 Science Panel website (www.c8sciencepanel.org/panel.html).

9.1.2.1 Liver effects

Some level of association between PFOA exposure and alteration in liver enzymes has been observed, but no clear trend has been defined. A negative association for bilirubin and a positive association for aspartate transaminase (AST) and gamma glutamyl transpeptidase (GGT) have been reported in workers (Sakr et al., 2007a; Sakr et al., 2007b). Abnormal increases of liver enzymes (ALT and GGT) were reported in a cross-sectional study of adults aged 18 years or older in the general U.S. population, particularly in obese or in subjects with insulin resistance and/or metabolic syndromes (Lin et al., 2010). The clinical significance of results in the occupationally-exposed population is unclear, because the magnitudes of the changes were small and inconsistent (Steenland et al., 2010a). Moreover, the high number of endpoints analyzed also increases the likelihood of chance findings. Causal interpretation of general population results is limited by the study design, and multiple covariates were not included in the analysis.

9.1.2.2 Lipidemia

Increased exposure to PFOA has been associated with increases in serum cholesterol levels in several studies. A recent study including large cohorts of workers and environmentally-exposed residents found an increased risk of hypercholesterolemia with higher PFOA exposure compared to lower exposure (Winquist and Steenland, 2014). A small longitudinal study conducted in workers in Italy showed a positive association between PFOA and total cholesterol (Costa et al., 2009). A cross-sectional study and a longitudinal study were conducted among DuPont production workers. In the cross-sectional study, positive associations between PFOA and total cholesterol, LDL and VDLD were observed (Sakr et al., 2007a). In the longitudinal study, a negative association with bilirubin was observed, whereas positive associations between serum PFOA and total cholesterol were found after adjustment for cofounders (Sakr et al., 2007b).

Inconsistent results were found concerning the association between PFOA and cholesterol and lipoproteins in studies of fluorochemical production workers from U.S. and European 3M plants (Olsen and Zobel, 2007). An increase in HDL level, a decreased total cholesterol/HDL ratio and no changes in total cholesterol and non-HDL cholesterol were observed in an occupational study (Olsen et al., 2012). Under the C8 Health Project, associations between serum PFOA and different blood components, such as an increase in cholesterol levels, were found in children and adults (Steenland et al., 2009, Frisbee et al., 2010, Kerger et al., 2011). Associations also occurred for lipoproteins (LDL, HDL), but were inconsistent between studies. A positive association with cholesterol was also found in the general U.S. population (Nelson et al., 2010),

while another cross-sectional study conducted in the Mid-Ohio valley found no association (Emmett et al., 2006b). A longitudinal study conducted in 560 adults (2005–2006 with follow-up in 2010) indicated that the level of LDL decreased with the decreased serum PFOA level. A similar (but not statistically significant) pattern was found for total cholesterol; however, there were no changes for HDL or triglycerides (Fitz-Simon et al., 2013).

Overall, cross-sectional and longitudinal study data indicate some level of association between serum PFOA and total cholesterol and/or LDL observed in different populations, although results were inconsistent in terms of exposure and effects observed. The strength of association was generally higher in the general population than in workers. Considering the weight of evidence, the C8 Science Panel (2012a) concluded that there is a probable link between elevated cholesterolemia and PFOA. The clinical significance is uncertain, given the results inconsistencies, the unknown mechanism of action, the limits inherent to the study design, and the low magnitude of the changes. In particular, the conclusions and associations found from the cohort studies are limited by the risk of selection and misclassification bias, and uncontrolled variables, as some associations were lost when the participants were stratified by location (Costa et al., 2009; Winquist and Steenland, 2014).

9.1.2.3 Thyroid disruption

Inconsistent effects on thyroid hormone levels were observed in PFOA-exposed populations. An occupational study conducted among 552 employees in three plants found a negative association between PFOA and free thyroxine and a positive association between PFOA and triiodothyronine, after adjusting for confounders (Olsen and Zobel, 2007). However, no adjustment for PFOS was performed, and the authors indicated there were no associations between PFOA and thyroid hormones because the results were inconsistent and within normal values. Moreover, no significant association of PFOA with T3, T4, or TSH was observed in two other occupational studies (Olsen et al., 1998, 2003b). Multiple cross-sectional studies (C8 Health Project and NHANES) have evaluated the relationship between environmental exposure to PFOA and thyroid functions. These studies have reported alterations in the levels of thyroxin, T3 uptake, serum albumin, hypothyroidism in children, thyroid disease in women (Chan et al., 2011; Knox et al., 2011b; Lopez-Espinosa et al., 2012). However, temporality cannot be established with the study design, and it is not possible to know the PFOA serum levels before the development of thyroid disease. A positive correlation between maternal serum PFOA levels and fetal TSH levels (but not T3 or T4 levels) was found after adjustment for covariates in a South Korean study (Kim et al., 2011).

9.1.2.4 Hypertension and cardiovascular outcomes

Cardiovascular outcomes were not consistently found to be associated with PFOA in cohort and cross-sectional studies (Sakr et al., 2007a; Costa et al., 2009; Steenland et al., 2010b). Elevated PFOA exposures were associated with higher cerebrovascular risk in an occupational cohort study (Lundin et al., 2009), and with cardiovascular, peripheral arterial disease, systolic blood pressure, and a marker of inflammation in cross-sectional studies of the general U.S. population (Shankar et al., 2012; Min et al., 2013). These results are equivocal and were not confirmed in other occupational cohort studies (Leonard et al., 2008; Sakr et al., 2009; Steenland and Woskie, 2012), nor in another cross-sectional study in the general population (Melzer et al., 2010). The C8 Science Panel concluded there is not a probable link between exposure to PFOA and diagnosed high blood pressure and coronary artery disease (including myocardial infarction, angina and coronary bypass surgery) (C8 Science Panel, 2012a).

9.1.2.5 Kidney effects

An association between adverse kidney effects and PFOA was observed; however, several factors limit the generalizability of the results to the general population. An increased risk of renal disease was found in a cohort mortality study conducted in 5,791 workers at a DuPont Chemical Plant (Steenland and Woskie, 2012). This level of evidence does not support a causal relationship between reduced kidney function and exposure to PFOA, particularly because altered kidney function could cause an increase in serum PFOA levels. Likewise, if PFOA induces adverse effects on the kidney, elevated PFOA levels may induce alterations of the kidney function. Moreover, only a small number of cases were observed in the occupational study (as attested by the large margin of error), and many workers were lost to follow-up, increasing the risk of selection bias, and was not supported by the results of an unpublished cohort study conducted in the same region.

9.1.2.6 Diabetes

The possible association between PFOA and diabetes was studied in mortality studies conducted among workers occupationally exposed to PFOA (Leonard et al., 2008, Lundin et al., 2009, Steenland and Woskie, 2012), and in two environmental studies regarding the prevalence of diabetes conducted within the C8 Health Project (MacNeil et al., 2009, C8 Science Panel, 2012b). The results from the occupational studies of employees of a 3M Company plant in Cottage Grove, MN, and of the DuPont polyfluorimer plant were inconsistent. Considering that diabetes is usually not fatal (and is not necessarily indicated on death certificates) and that mortality may thus not be the best way to study diabetes (C8 Science Panel, 2012b), the findings based on diabetes prevalence within exposed residential populations may be more reliable. The data available from cross-sectional environmental studies conducted within the C8 Health Project (MacNeil et al., 2009, C8 Science Panel, 2012b) suggest that there is no link between PFOA and Type II diabetes.

9.1.2.7 Immune suppression

Studies in environmentally-exposed populations have identified associations between PFOA levels and decreased antibodies against various illnesses, but the influence of PFOA exposure on clinical immunosuppression (i.e., incidence of illnesses) appears to be more tenuous. A study in children found an inverse relationship in immune response with PFAA exposure (Grandjean et al., 2012; Grandjean and Budtz-Jørgensen, 2013), with prenatal PFOA exposure negatively correlated with antidiphtheria antibody concentrations. A two-fold increase in the PFOA concentration in children in this population was associated with increased odds of not reaching antibody protective levels for tetanus and diphtheria after vaccination at 7 years old (Grandjean et al., 2012). The prospective nature, sample size, low risk of selection bias and defined objectives make the results relevant to the studied population; however, relevance to other populations is questionable, as increased exposure to the other potential immunosuppressants occurring in this region (Faroe Islands) was not accounted for in the study. Increased PFOA exposure was also associated with decreased antibodies against rubella (in children from a prospective birth cohort of pregnant women from Norway, 2007–2008) (Granum et al., 2013) and influenza (for A/H3N2 only; in adults living in communities with PFOA-contaminated drinking water) (Looker et al., 2014). A higher risk of not attaining the recognized influenza A/H3N2 threshold was also observed (Looker et al., 2014). Cord blood IgE decreased with maternal PFOA in female infants in a prospective cohort study of pregnant women from 2002 to 2005 in Japan (Okada et al., 2012).

Hospitalizations for infections were not associated with prenatal exposure to PFOA in a Danish Cohort (1996–2002) (Fei et al., 2010); however, positive associations between maternal PFOA and the incidence of colds and gastroenteritis were observed in the Norwegian birth cohort (Granum et al., 2013).

There is some level of consistency across studies since they generally observed an association between environmental PFAA exposure and immunomodulatory effects in children of different ethnicities. The diversity of the study settings and the prospective nature of the observational study designs lower the risks of spurious associations and enhance generalizability of the results. However, the dataset remains relatively small with only 5 studies, which were all observational, and the risk of residual confounding, bias and chance cannot be discounted. Although all studies investigated the effects on the immune system, the outcomes were not specific (measured different effects), no clear dose-response was observed, and most associations were weak. Conflicting results were common in the dataset, with variations observed between genders, specific microbial immunoglobulins, PFAAs, infections, mother vs. child exposure, and child years, amongst other characteristics. These flaws impede concluding on a causative mechanism, and the nature of the association remains unclear.

9.1.2.8 Autoimmune disease

The C8 Science Panel (unpublished study) found an increased risk of inflammatory bowel disease with increased cumulative exposure to PFOA, which was driven by associations for ulcerative colitis. The C8 Science Panel concluded that there is a probable link between PFOA and ulcerative colitis (C8 Science Panel, 2012c). However, there is a risk of selection bias because the panel was able to include only a portion of the sample population—participants were only included if their medical charts could be accessed and if exposure estimates could be derived. These results are concerning and should be corroborated in future studies.

9.1.3 Carcinogenicity

Several occupational and environmental cohort studies have been developed for PFOA. The U.S. studies are considered to be the highest quality studies, because they were based on registries covering all residents in the study area, were conducted in districts with large and measured contrasts in PFOA concentrations in water, were linked to cancer registry data, had a large study population and were adjusted for major confounders.

A case-only study that investigated the relationship between cancer and exposure to PFOA through drinking water among Mid-Ohio residents living near the DuPont Teflon-manufacturing plant found that higher PFOA concentrations were associated with testicular and kidney cancers in some of the areas (Vieira et al., 2013). Amongst all cancer endpoints, the odds of testicular cancer were elevated only in one of the two areas with the highest concentration of PFOA in drinking water. There was no statistically significant increase in the odds of testicular cancer in the total exposed, in the other districts, or in any dose level categories (except for the highest dose category). Kidney cancer was increased significantly in one district and in the two highest levels of individual exposure. Associations were not significant for cancers of the breast, prostate, ovarian and non-Hodgkin lymphoma. Although this study shows some cancer associations with PFOA exposure, the meaning of the cancer results remain uncertain because no dose-response was observed, the variability of the risk estimates was high, the number of cases was low, there were multiple endpoints calculated with two modelling approaches (geographical and individual), and risk of exposure misclassification bias (the lack of residential history information to account for duration of exposure, latency, migration, and other issues regarding timing of exposure

relative to cancer). The geographical analysis (testicular cancer findings in the Mid-Ohio study) shares the bias and risk of confounding inherent to ecological studies.

Cumulative exposure to PFOA (retrospective estimates of log serum concentration) was associated with an increased risk of self-reported testicular, kidney, and thyroid cancers in a large cohort (n = 32,254) of C8 Health Project participants and DuPont Teflon-manufacturing plant workers above 20 years old (mean of 53 years old), after adjusting for smoking, alcohol consumption, sex, and education, and stratifying by age (Barry et al., 2013). Some cases were included in both the Barry et al. (2013) and in the Vieira et al. (2013) studies. The associations less likely to have occurred by chance alone (lowest p-values) were the ones between PFOA cumulative log serum concentration and testicular cancer (using the geographical and the water district individual approaches) and kidney cancer (using the residential analysis, individual approach) risks; while the associations with thyroid cancer and melanoma were considered to have occurred by chance based on poor statistical support. However, the associations were inconsistent between exposure quartiles and scenarios (e.g., residential, geographical), after follow-up (with very few, or no reported cases since 2005 regarding testicular cancer while background rates indicated that 5 cases were expected), and lost for testicular, kidney, and thyroid cancer risks, when compared with rates in the general U.S. population. Moreover, the 95% CI of the hazard ratios were large, the trends for testicular, kidney, and thyroid cancer risks were likely to have occurred by chance in at least one exposure scenario, Barry et al. (2013) mentioned the likelihood of exposure and outcome misclassifications, and the trends reported for testicular cancers were based on 6 cases only in the high exposure group (C8 Science Panel, 2012b; Barry et al., 2013).

In another occupational study conducted on workers in Minnesota, increased risk of prostate cancer mortality was observed; however, uncertainty persists because of the low number of cases, leading to poor precision in the risk estimates (Lundin et al., 2009). No statistically significant excess death from kidney, liver, pancreas, testicular, thyroid or breast cancer was found in another occupational study in West Virginia (Leonard et al., 2008) nor in the six-year follow-up of this cohort, except for excess of mortality by kidney cancer (Steenland and Woskie, 2012). Caution in the interpretation of these results is required, because the results were based on a small number of cases, and there was a considerable risk of selection bias.

No increase in the incidence of prostate, bladder, pancreas or liver cancer was found in a prospective cohort study conducted in the general population of Denmark, although the PFOA plasma concentrations [plasma concentration in men with cancer: 6.8 ng/mL (5–95% percentiles: 3.1–14.0); women with cancer: 6.0 ng/mL (5–95% percentiles: 2.6–11.0)] tended to be lower than in the U.S. cohorts [mean of 76.5 ng/mL (SD = 208) in male serum concentration and 42.3 ng/mL (SD = 118) in women, in a community exposed population reported by Frisbee et al. (2009); and, as high as a mean of 2,210 ng/mL (SD = 6.4) in the serum of PFOA manufacture employees, as reported in Olsen and Zobel (2007)] (Eriksen et al., 2009). Also, no evidence of a relationship for PFOA and breast cancer was found in a small-case control study in Greenlandic Inuit (Bonefeld-Jorgensen et al., 2011).

The C8 Science Panel (2012b) provides an assessment of the probable link between PFOA exposure and cancer. The "probable link" defined by the Science Panel means that "given the available scientific evidence, it is more likely than not that among class members a connection exists between PFOA exposure and a particular human disease." Testicular and kidney cancers were the particular types of cancer on which the association was based. However, a causal relationship cannot be determined because there were inconsistencies in the dataset, and the cancer risks were found to be equivocal across studies (lack of coherence). Moreover, the interpretation of the observed increased risk in testicular and kidney cancers is limited by the risk

of residual confounding (because not all covariates and exposures to other contaminants were included in the model), the small case numbers, the uncertainties in exposure characterization (roughly estimated based on residency within a certain area), and the high number of outcomes included in the models, increasing the likelihood of chance findings. Based on these considerations, it would be premature to base a guideline on a cancer risk in epidemiology studies, without a stronger understanding of the potential causality between PFOA and the observed cancers. It is suggested to continue monitoring the epidemiological evidence to understand better the relationship between PFOA and cancer risk.

9.1.4 Developmental and reproductive toxicity

9.1.4.1 Developmental toxicity

Based on data available for gestational age, birth weight and length, head and abdomen or chest circumference, developmental milestones, miscarriage, and birth defects, previous reviews of developmental epidemiology studies concluded that developmental effects are not expected in humans (Olsen et al., 2009). Although increases in the risk of some of these outcomes occurred in individual studies, there was a lack of consistency across studies. Newer environmental studies have shown a positive association between prenatal exposure to PFOA and obesity in female offspring at age of 20 years (Halldorsson et al., 2012), and a negative association between maternal serum PFOA and birth weight and related anthropometric parameters at birth (Apelberg et al., 2007; Fei et al., 2007; 2008b; Andersen et al., 2010; Maisonet et al., 2012; Whitworth et al., 2012a).

The obesogenic properties of PFOA and other PFAAs were investigated in a prospective cohort study with long-term follow-up (20 years) among pregnant women recruited within the Danish National Birth Cohort (1988–1989) and their offspring (Halldorsson et al., 2012). At 20 years of age, the female offspring from mothers with elevated serum concentration of PFOA were more likely to be overweight and to have a high waist circumference, after adjusting for mother's education, BMI, smoking, age, and infant birth weight. This large longitudinal study also showed alteration in serum biomarkers with an increase in maternal PFOA (increase in serum insulin and leptin and decrease in serum adiponectin in female offspring), suggesting biological plausibility. However, important confounders, such as physical activity and diet, were not included in the analysis, which is likely to result in spurious associations. The authors also indicated that loss to follow-up was the main limitation of the study. More studies with better adjustments and follow-up in different populations would be needed to confirm the observed associations.

The data currently available regarding an association between PFOA and reduced birth weight are not consistent. Positive associations were reported among the general population in some studies, whereas no association was reported in other studies in the general population and in communities highly exposed to PFOA through drinking water. Longitudinal studies conducted in Danish and British general populations have found inverse associations between plasma PFOA levels and birth weight (Fei et al., 2007; Andersen et al., 2010; Maisonet et al., 2012). A small unpublished study based on birth certificates for C8 Health Project Community Cohort follow-up participants found some level of association between serum PFOA and term low birth weight; however, results were inconsistent and significance was not provided for all results. These studies represent concerning findings; however, the validity of the results still need to be confirmed, because these studies presented risk of selection bias, recall bias, chance findings, uncontrolled covariates, and absence of dose–response pattern. Moreover, no significant association between serum PFOA levels or PFOA water concentrations and low birth weight was found in cross-sectional studies or highly exposed communities (Nolan et al., 2009; Stein et al., 2009; Savitz et al., 2012a; 2012b). The C8 Science panel concluded that there is no probable link between PFOA

and low birth weight (C8 Science Panel, 2011). However, considering that PFOA was found to be obesogen in mice (Hines et al., 2009) and humans (Halldorsson et al., 2012), and that *in utero* exposure to low doses of obesogens are known to reduce weight at birth (and induce obesity later in life; Holtcamp, 2012), a link between PFOA and low birth weight cannot be ruled out and close monitoring of new studies is recommended.

Investigation of different fetal growth indicators in association with PFOA exposure gave equivocal results. PFOA levels in maternal blood from the Danish National Birth Cohort (1996–2002) demonstrated negative associations with abdominal circumference (with a dose–response relationship) and birth length, after adjustment for multiple relevant cofounders (Fei et al., 2008b). These associations were obtained from large databases, and errors in exposure and outcome measurements and coding is possible. There is also a risk of residual confounding, as stated by the authors. Small negative associations were observed with head circumference, ponderal index and birth weight in a cross-sectional study of the general population (n = 293 singleton births) in Maryland (Apelberg et al., 2007). These must be considered with caution due to the limits inherent to the study design. Also, no associations between maternal serum PFOA levels and birth weight were observed in other general population studies in Canada (Hamm et al., 2010) or Japan (Washino et al., 2009).

There was no conclusive evidence of attention deficit/hyperactivity disorder (ADHD), learning disorder, motor developmental milestones, or behavioral or motor coordination problems based on results of cross-sectional studies conducted within the C8 Health Project and in the general population with exposure to PFOA (Fei et al., 2008a; Hoffman et al., 2010; Fei and Olsen, 2011; Stein and Savitz, 2011).

9.1.4.2 Puberty and sex hormone disruption

Serum PFOA levels were associated with delayed puberty in girls (reduced odds for the 2nd, 3rd, and 4th quartiles vs. the lowest quartile: delay of 142, 163 and 130 days for menarche and delay of 155, 158 or 183 days for combined high estradiol or menarche) in a cross-sectional study within the C8 Health Project (Lopez-Espinosa et al., 2011). Further investigations are needed to establish the nature of the relationship, and identify the mechanisms behind these associations. No association was found between PFOA and serum estradiol levels in perimenopausal or menopausal age groups of women (n = 25,957) from the C8 Health Project (Knox et al., 2011a).

9.1.4.3 Reproductive toxicity

No clear pattern of pregnancy-induced hypertension was observed in cohort studies on residents of the Mid-Ohio Valley within the C8 Health project and a cross-sectional study based on Washington County (Savitz et al., 2012b; Nolan et al., 2010; C8 Science Panel, 2011). Conversely, an unpublished prospective study presented by the C8 Science Panel (2011) addressed pregnancies among participants enrolled in the C8 Health Project. The four highest quintiles had higher odds of pregnancy-induced hypertension; however, there was no clear dose–response pattern. Based on this dataset, it would be premature to conclude a link exists between PFOA and pregnancy-induced hypertension.

Overall, no definitive association between PFOA and preeclampsia has been established. No increased occurrence of preeclampsia was observed in a study conducted among Mid-Ohio Valley residents (pregnant in 2000–2006) exposed to PFOA-contaminated drinking water (Stein et al., 2009). In a second study, risk of preeclampsia was examined among C8 Health Project participants from 1990–2005 (Savitz et al., 2012a). Self-reported preeclampsia was weakly associated with estimated serum PFOA at the time of pregnancy, and there was no dose–response pattern. The association was strengthened when restricted to pregnancies occurring after 1999.

An association between PFOA exposure and a reduction in fecundity has been observed; however, the studies were not robust and the results are inconclusive. A reduction of fecundity (increased time to pregnancy and irregular menstrual periods) was found to be associated with the plasma PFOA levels in 1,240 parous/nulliparous women; however, the information for multiple confounders was omitted from the analysis (e.g., sperm quality, occurrences of intercourses; Fei et al., 2009). Relative increases in the odds of subfecundity (time to pregnancy greater than 12 months) were reported in a case–control study on parous women enrolled in the Norwegian Mother and Child Cohort Study (with no increased odds of subfecundity in nulliparous women) (Whitworth et al., 2012b). Time to pregnancy and fecundity were not associated with serum PFOA levels in nulliparous women in a longitudinal cohort study in Denmark (Vestergaard et al., 2012). The lack of adjustment for confounders and of consistency in the results generates doubt on the link between lower fecundity and PFOA.

A prospective cohort study recruited 1,400 pregnant women (randomly out of 43,045) within the Danish National Birth Cohort (DNBC, 1988–1989) and measured PFOA concentration in their plasma (Fei et al., 2010b). Duration of breastfeeding was reported 6 and 18 months after birth by phone interviews. The risk of breastfeeding for a shorter period was higher with increasing plasma PFOA. For example, the risk (adjusted hazard ratio) of shorter breastfeeding duration (weeks) for women with plasma PFOA > 7.0 ng/mL was 1.4 (95% CI 1.2–1.7) times higher than for those with plasma PFOA < 3.9 ng/mL, after adjusting for maternal age at delivery, pre-pregnancy BMI, maternal socioeconomic status, alcohol consumption and smoking (the trend for an increase in risk with increasing four-quartile comparison was also significant). Also, the odds (adjusted odds ratio) of weaning before 6 months of age was 1.23 (95% CI: 1.1–1.3) times higher for each 1 ng/mL increase in plasma PFOA when restricting the model to multiparous women (not significant in primiparous women), after statistical adjustments. A similar association was observed with weaning before 3 months of age. However, more studies would be needed to support these results, since PFOA plasma concentration was measured only one time, only 18% of eligible women participated in the DNBC study, there is a risk of outcome recall bias (mothers might not report accurately the date of weaning), and the authors did not rule out the possibility that reverse causation could explain the association (especially since not observed in primiparous women, and considering that women that have breastfed longer can be more likely to breastfed longer their next infants, and that PFOA is excreted in breast-milk, lowering the plasma concentration).

The studies on the associations between PFOA exposure and sperm quality or hormone levels are sparse, inconsistent, and need to be corroborated in larger studies to better inform the possibility of a relationship. In a cross-sectional study conducted in 256 men from Durham, NC, a positive correlation was found between plasmatic PFOA and serum luteinizing hormone levels. No association between PFOA and semen quality measurements was found (Raymer et al., 2012). A positive association between PFOA and semen motility was identified in a group of men from one country, but not in the two other countries studied (Greenland, Poland and Ukraine). The author indicated the positive result might be attributable to chance findings (Toft et al., 2012). A prospective study has suggested that *in utero* exposure to PFAAs may affect adult human male semen quality and reproductive hormone levels; however, there are concerns about the selection of participants (Vested et al., 2013).

Considering the weight of evidence, it is not possible to rule out possible adverse effects of PFOA on development and reproduction. Large cohort studies of offspring of mothers with high serum PFOA have reported an increased risk of lower abdominal circumference, length and weight at birth, as well as being overweight and having a high waist circumference 20 years after birth. These results are supported by effects on serum biomarkers (insulin, leptin, and

adiponectin). Moreover, some evidence of reproductive toxicity has been observed, although to a lower extent. Higher level of exposure to PFOA has been associated with an increased risk of pregnancy-induced hypertension, preeclampsia, shorter duration of breastfeeding, altered sperm quality and reduced fecundity in longitudinal studies. However, the dataset for each individual outcome remains relatively small and definitive conclusions on the relationship between reproduction and developmental outcomes and exposure to PFOA are mainly limited by a lack of consistencies in the results and the possibility of confounding. These limitations do not allow determining the nature of the association for the moment.

9.2 Effects on experimental animals

The vast majority of animal studies stated that exposure to PFOA was through its ammonium salt (APFO). Studies that did not state the specific salt used in their study were assumed to have used the ammonium salt, as this was the only compound used in studies that stated the PFOA salt. No studies stated whether the administered dose referred to the APFO compound, or specifically to the PFOA ion, separate from the ammonium salt. The summaries described herein use the concentrations and doses stated by authors. This approach is also used for quantitative assessments; however, as the PFOA ion contributes to 96% of the molar weight of APFO and is released from the compound upon exposure, only minor quantitative differences would result from using APFO and PFOA doses interchangeably.

9.2.1 Acute toxicity

The acute toxicity studies for PFOA or APFO indicate oral LD_{50} values of >500 and 680 mg/kg bw for male Sprague-Dawley and CD rats, respectively (Glaza, 1997), 250–500 mg/kg bw and 430 mg/kg bw for female Sprague-Dawley and CD rats, respectively (Dean and Jessup, 1978; Glaza, 1997), and <1,000 mg/kg for Sherman-Wistar rats of both sexes (Gabriel, 1976).

No mortality was reported in Sprague-Dawley rats of both sexes following inhalation exposure to PFOA at 18,600 mg/m^3 for 1 hour (Rusch, 1979).

The dermal LD_{50} in rabbits was determined to be >2,000 mg/kg bw or 4,300 mg/kg bw (Glaza, 1995; Kennedy, 1985). Higher values were obtained in rats, with a LD50 at 7,000 mg/kg bw in males and at 7,500 mg/kg bw in females (Kennedy, 1985).

Acute developmental neurobehaviour studies are discussed in Section 9.2.5.5.

9.2.2 Short-term exposure

Studies documenting the toxicity of PFOA after short-term oral exposure identified three main targets, namely reproductive and developmental effects (summarized in Section 9.2.5), hepatic effects, and serum lipid effects. Delayed mammary gland development appears to be the most sensitive target, with a LOAEL of 0.001 mg/kg bw per day (serum PFOA: 74.8 ng/mL; no NOAEL) in mice (see Section 9.2.5.1). The lowest LOAELs for hepatic effects were 0.15 mg/kg bw per day in adult mice (Kennedy, 1987; NOAEL of 0.05 mg/kg bw per day). Serum lipid effects were observed at ≥0.3 mg/kg bw per day in rats (Loveless et al., 2006, 2008). This section will focus primarily on these key effects observed at the lowest levels, and will only briefly discuss other types of changes observed in animals.

9.2.2.1 Hepatic effects

The hepatic effects observed at the lowest levels in short-term studies were hepatocellular hypertrophy in male rats and mice (Perkins et al., 2004; Loveless et al., 2008) and increased liver weight in rats (Kennedy, 1987) and mice (Loveless et al., 2006). These studies will be described in greater detail, and other hepatic effects observed at higher levels will be discussed only briefly.

The lowest LOAEL for liver weight was in pups exposed *in utero* to 0.1 mg/kg bw per day on GD 1–17; further details on this study are provided in Section 9.2.5.4. In adults, the studies that observed liver weight increases at the lowest levels were Loveless et al. (2006; LOAEL of 0.3 mg/kg bw per day) and Kennedy (1987; LOAEL of 0.15 mg/kg bw per day and NOAEL of 0.05 mg/kg bw per day). These studies are described below.

A LOAEL of 0.3 mg/kg bw per day (no NOAEL) was identified in male CD-1 mice (n=10/dose) after oral exposure to PFOA (0, 0.3, 1, 3, 10 or 30 mg/kg bw per day) for 14 days (Loveless et al, 2006). Different preparations of PFOA were used (branched, linear, or combined branched/linear APFO). The LOAEL refers to increased relative liver weight in mice treated with linear and with branched APFO (most studies expose animals to a mixture that is predominantly linear APFO). Liver weights were also increased in rats, but only at ≥1 mg/kg bw per day. Absolute liver weights were significantly increased in at least one APFO form at ≥1 mg/kg bw per day in both species. In both rats and mice, the overall liver weight responses to linear and branched forms of PFOA were similar. The same researchers performed a 29-day study with linear APFO, and found no increases in liver weight at 0.3 mg/kg bw per day—absolute liver weight was increased in both species at ≥1 mg/kg bw per day, and relative liver weight was increased at ≥1 mg/kg bw per day in mice and ≥10 mg/kg bw per day in rats (Loveless et al., 2008). The latter study contained a high-dose (i.e., 30 mg/kg bw per day) recovery group (with exposure cessation at test days 23 in rats and 24 in mice), with liver weight increases still present at termination of the study in both species.

In the study with the lowest LOAEL for the endpoint (Kennedy, 1987), male and female CD rats were exposed to APFO at 0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 30 ppm in food (using Health Canada default assumptions of 1 ppm in food = 0.05 mg/kg bw per day in rats [Health Canada, 1994], the approximate doses were 0.0005, 0.0015, 0.005, 0.015, 0.05, 0.15, 0.5, and 1.5 mg/kg bw per day) for 21 days. Increased absolute and relative liver weight was observed at ≥0.15 mg/kg bw per day in both males and females, with a NOAEL of 0.05 mg/kg bw per day. The same study also exposed rats for 14 weeks, and observed increases at the lowest in the study (30 ppm in food, equivalent to 1.5 mg/kg bw per day).

A wide variety of short-term studies observed increases in liver weight in adult animals at higher doses. These effects were observed in rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Staples et al., 1984; Kennedy et al., 1986; Biegel et al, 2001; Perkins et al., 2004; Cui et al., 2009) and in mice (Marias, 1977; Liu et al., 1996; Yang et al., 2001, 2002; Lau et al., 2006; Abbott et al., 2007; Wolf et al., 2007; DeWitt et al., 2008; Son et al., 2008; Christopher and White et al., 2009; Qazi et al., 2010; Yahia et al., 2010). Increases in liver weight appear to be generally reversible, as they were no longer observed after the exposure period in most studies with a recovery period (Palazzolo, 1993; Thomford, 2001a; Butenhoff et al., 2002; Perkins et al., 2004). In contrast, in a study of mice exposed for 10 days, the effect was still observed 10 days after ceasing exposure (Yang et al., 2001). Increases in liver weight were also observed in mice exposed *in utero* or peripubertally to PFOA; descriptions of these results can be found in Section 9.2.5.4.

The study that observed hepatocellular hypertrophy at the lowest levels exposed male Sprague-Dawley rats (n=10 per group) and male CD-1 mice (n=19–20 per group) to 0, 0.3, 1, 10, or 30 mg/kg bw per day of PFOA by for 29 days (Loveless et al., 2008). Incidence and severity of hypertrophy increased with dose, with effects of greater severity in mice. In the high-dose recovery group, hypertrophy persisted at the end of the study, despite cessation of exposure on study days 23 (rat) or 24 (mouse).

The most robust study with an observed NOAEL for increased liver weight and hepatocellular hypertrophy exposed male Crl:CD rats (n=55 per dose) to 0, 0.06, 0.64, 1.94, and

6.5 mg/kg bw per day in food (Perkins et al., 2004). Two control groups were included in the study—one set of controls pair-fed with the high dose group, and one *ad libitum* feeding group. The rats were divided into sacrifice groups exposed for a duration of 4, 7, or 13 weeks (n=15 per dose per duration), and each dose (and the *ad libitum* controls) had a recovery group that was observed for 8 additional weeks after cessation of exposure at week 13 (n=10 per dose). Dose-related increases in incidence and severity of hypertrophy were observed (Table 3). Most rats exposed to ≥0.64 mg/kg bw per day had minimal-to-slight hypertrophy, which was most severe in the high-dose group exposed for 13 weeks; effects did not persist in recovery groups. Hypertrophy was not accompanied by degenerative lesions in the liver. Relative liver weight was increased at ≥0.64 mg/kg bw per day in the 4-week group and at ≥1.94 mg/kg bw per day at the longer durations; the effect did not persist in the recovery groups.

Table 3: Incidence and severity of hepatocellular hypertrophy in Perkins et al. (2004)

Dose (mg/kg bw per day)	Duration of exposure (wk)	Grade of hypertrophy			
		None	Minimal	Slight	Moderate
Ad libitum control	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	10	0	0	0
Pair-fed control	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	N/A	N/A	N/A	N/A
0.06	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	10	0	0	0
0.64	4	3	12	0	0
	7	3	12	0	0
	13	2	13	0	0
	13 (recovery)	10	0	0	0
1.94	4	0	7	8	0
	7	0	14	1	0
	13	1	12	2	0
	13 (recovery)	10	0	0	0
6.5	4	0	5	9	0
	7	0	6	9	0
	13	0	3	12	0
	13 (recovery)	10	0	0	0

Higher dose studies also identified hepatocellular hypertrophy in mice (Yahia et al., 2010) and rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Cui et al., 2009).

Other histological effects observed in the liver at higher doses in short-term studies include single cell and focal necrosis in mice (Loveless et al., 2008; Yahia et al., 2010) and rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Loveless et al., 2008; Cui et al., 2009); increased mitosis in mice (Yahia et al., 2010); mild calcification in mice (Yahia et al., 2010);

cytoplasmic enlargement of hepatocytes in rats (Metrick and Marias, 1977); and cytoplasmic vacuolation in rats (Cui et al., 2009). Histological effects were also observed in livers of rats exposed to PFOA for 2 years; these effects are described in Section 9.2.3.

Changes in serum levels of markers of liver damage were observed in mice at higher levels than the LOAELs for increased liver weight and hepatocellular hypertrophy. These effects included increased ALT (Son et al., 2008; Yahia et al., 2010), increased AST (Son et al., 2008; Yahia et al., 2010), increased GGT (Yahia et al., 2010), and increased ALP (Yahia et al., 2010; Qazi et al., 2010a). Increased ALP was also observed in rats (Kennedy et al., 1986).

9.2.2.2 Serum lipid effects

Alterations in serum lipid parameters were some of the effects observed at the lowest PFOA exposure levels in adult animals in short-term studies. The effects include changes in HDL, total cholesterol and triglycerides. Total cholesterol and HDL were decreased in most studies of mice (Loveless et al., 2006, 2008; Qazi et al., 2010) and rats (Loveless et al., 2006, 2008), but total cholesterol (along with phospholipid and free fatty acid) was increased in one high-dose study in mice (Yahia et al., 2010). Triglycerides were observed in mice to be increased in certain studies (Loveless et al., 2006; Yahia et al., 2010) and decreased in another (Loveless et al., 2008). They were decreased in both rat studies (Loveless et al., 2006, 2008).

The studies in which serum lipid changes were observed at the lowest levels were both performed by Loveless et al. (2006, 2008), which are described in greater detail in Section 9.2.2.1. The lowest LOAELs were in rats, with values of 0.3 mg/kg bw per day for decreases in cholesterol and triglycerides (Loveless et al., 2006, 2008) and 0.3 mg/kg bw per day for decreases in HDL (Loveless et al., 2008; in 2006 the LOAEL was only 3 mg/kg bw per day). Most of the effects were only observed at higher levels in mice—in Loveless et al. (2008), the LOAELs were 1 mg/kg bw per day for decreased HDL and 10 mg/kg bw per day for decreased total cholesterol and triglycerides, and most of the LOAELs in Loveless et al. (2006) were 3 mg/kg bw per day. An exception was for triglyceride increases specifically in the linear/branched APFO-exposed mice, as effects were observed at ≥0.3 mg/kg bw per day.

The effects on cholesterol and HDL did not appear to be persistent upon cessation of exposure, because total cholesterol and HDL levels returned similar to control levels when exposure was ceased at days 23 (rat) or 24 (mouse) in the 29-day study (Loveless et al., 2008). Triglyceride levels in both species continued to be lower than controls after the recovery period, but in mice the levels had increased enough to be significantly higher than the 29-day high dose group.

Loveless et al. (2006) investigated different forms of PFOA (branched, linear, or combined branched/linear). The linear form (the form most commonly appearing in PFOA mixtures used in studies) appeared to have the lowest LOAELs in rats for all lipid endpoints. In mice, the PFOA form did not appear to have any effect on HDL or cholesterol, but the linear/branched mixture appeared to be the only form that had any effect on triglycerides.

Additional studies saw increases in triglyceride, total cholesterol, and free fatty acid at 10 mg/kg bw per day in ICR mouse dams (Yahia et al., 2010) and reduction in total serum cholesterol in male C57BL/6 mice (Qazi et al., 2010).

9.2.2.3 Other effects

Other effects besides hepatic and serum liver effects in short-term studies of adult animals occurred at PFOA exposure levels of ≥1 mg/kg bw per day. The studies are described briefly below.

At ≥1 mg/kg bw per day, increased kidney weight was observed in several studies of mice (Yahia et al., 2010) and rats (Goldenthal et al., 1978; Butenhoff et al., 2004b; Cui et al., 2009). In many of the studies, the increases were only in relative, but not absolute, kidney weight. The effects were also often accompanied by histological effects (Butenhoff et al., 2004b; Cui et al., 2009; Yahia et al., 2010).

Changes in weight of neurologically-relevant organs occurred at ≥3 mg/kg bw per day in monkeys. These observations were an increased group mean weight of the pituitary gland and decreased absolute brain weight (Goldenthal et al., 1978). The only other neurological effect noted in adult animals exposed for a short-term duration was reduced activity and lethargy in rats (Cui et al 2009).

Indications of immunosuppression occurred at ≥3.75 mg/kg bw per day in mice. These included decreased immunoglobulin levels, changes in cellularity and subtypes of immune cells, and changes in cytokine expression (Yang et al., 2001, 2002; DeWitt et al., 2008; Loveless et al., 2008; Son et al., 2008; Qazi et al., 2009, 2010). Splenic and thymic atrophy were also observed in mice (Yang et al., 2001, 2002; Loveless et al., 2008; Qazi et al., 2009), and histological changes were observed in these organs in rats (Cui et al., 2009; Qazi et al., 2009). Studies in mice also indicated a possibility for hypersensitivity due to exposures to PFOA, with a dose-related increase of serum histamine levels at ≥1 mg/kg bw per day (Singh et al., 2012) and increased IgE after challenge with OVA in mice exposed dermally to ≥18.75 mg/kg bw per day (Fairley et al., 2007).

Effects on other organs were observed at ≥10 mg/kg bw per day. These effects included hypertrophy and vacuolation of the zona glomerusa of the adrenal gland in rats (Butenhoff et al., 2004b); pulmonary congestion, thickening of epithelial walls, cell infiltration and vasodilation in rats (Cui et al., 2009); pulmonary edema in rats (Kennedy et al., 1986); and decreased heart weight in monkeys (Goldenthal et al., 1978).

The only study indicating changes in thyroid hormone levels reported decreased free and total T3 and T4 in monkeys exposed for 6 months (Butenhoff et al., 2002). Decreases in total and free T4 were observed at most timepoints, including termination, for monkeys exposed to 10 or 20–30 mg/kg bw per day; at termination (and not earlier timepoints), a significant decrease was also observed for total (but not free) T4 at the 3 mg/kg bw per day dose. Decreased total and free T3 was observed at most timepoints (including termination) in monkeys exposed to 20–30 mg/kg bw per day; decrease in total (not free) T3 was also observed at two mid-study timepoints, but not at termination, in low-dose monkeys. The effects were accompanied by significant increases in TSH at study termination in monkeys exposed to 3 or 10 mg/kg bw per day (no effect at high dose). The 4-week range-finding study for the Butenhoff monkey study (Thomford, 2001b) did not note any effects on TSH, or in total or free T3 or T4.

Decreased bodyweight or bodyweight gain was observed in many different studies. The effects were observed at LOAELs of 3 mg/kg bw per day in rats (Metrick and Marias, 1977; Goldenthal et al., 1978; Staples et al 1984; Kennedy et al., 1986; Butenhoff et al., 2004b; Cui et al., 2010), 3 mg/kg bw per day in mice (Christopher and Marias, 1977; Lau et al., 2006; Wolf et al., 2007; Asakawa et al., 2008; Son et al., 2008; White et al., 2009; Yahia et al., 2010; Suh et al., 2011), and 30 mg/kg bw per day in monkeys (Goldenthal et al., 1978). This effect was accompanied by a decrease in food consumption at ≥5 mg/kg bw per day in rats (Metrick and Marias, 1977; Butenhoff et al., 2004b;Cui et al., 2009) and at 20.7 mg/kg bw per day in mice (Asakawa et al., 2008).

Clinical signs observed in studies included soft stools, diarrhea, and frothy emesis in monkeys (Goldenthal et al., 1978) and roughed fur, muscle weakness, and cyanosis in mice (Christopher and Marias, 1977).

Few studies reported increased mortality in animals. The endpoint was observed at high levels in studies of rats (Metrick and Marias, 1977; Staples et al., 1984; Butenhoff et al., 2004b), mice (Christopher and Marias, 1977), and monkeys (Goldenthal et al., 1978b; Thomford, 2001a; Butenhoff et al., 2002).

9.2.3 Long-term exposure and carcinogenicity

Two chronic toxicity studies in laboratory animals were identified for the oral route. No inhalation or dermal study was located. As was observed in long-term carcinogenicity studies, the liver was the most sensitive target organ in the chronic studies (LOAEL = 1.3 mg/kg bw per day in male rats for increased serum liver parameters) (3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b). Other effects observed in rats after chronic exposure to PFOA include an increased incidence of hyperplasia and tumors in various tissues (mammary gland in females, Leydig cells, pancreas and liver in males) and alteration of serum hormone levels (3M, 1983; Sibinski, 1987; Biegel et al., 2001).

The only study including more than one dose identified a LOAEL of 1.3 mg/kg bw per day (no NOAEL) in male rats for liver toxicity (3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b). Sprague-Dawley rats (50/sex/group) were given APFO at 0, 30 or 300 ppm in the diet for 2 years (0, 1.3 or 14.2 mg/kg bw per day for males; 0, 1.6 or 16.1 mg/kg bw per day for females). The LOAEL of 30 ppm was based on significant increases in serum liver parameters in males (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and albumin at many timepoints, which were still elevated—although not significantly at the low dose—at termination) and a dose-related increase of chronic sialadentitis in the salivary gland of males. Hepatocellular hypertrophy was also elevated in both male treatment groups, with significance only being reached at the high dose (incidence was 0% in controls, 12% at the low dose, and 80% at the high dose). Other effects in males include a dose-dependent increased incidence of Leydig cell adenomas, statistically significant at 300 ppm (14.2 mg/kg bw per day). In female rats, the first data analysis indicated a dose-dependent increase in mammary fibroadenomas, statistically significant at ≥30 ppm; however, a more recent analysis was conducted by a pathology working group using current diagnostic criteria, which concluded that PFOA treatment did not result in proliferative lesions in the mammary tissues (Hardisty et al., 2010; Butenhoff et al., 2012b). Non-neoplastic changes in the liver (hepatocellular hypertrophy, portal mononuclear cell infiltrate or cystoid degeneration at the high dose) and the lungs (alveolar macrophages and hemorrhage at the high dose) were observed, and proliferative acinar cell lesions were observed in the pancreas of rats at the high dose. PFOA did not increase the incidence of neoplastic or non-neoplastic lesions in the other organs (thyroid, pituitary, adrenal gland, kidney, uterus).

A follow-up study was performed in male CD rats given APFO in the diet (0 or 300 ppm) for 2 years (average daily dose of 13.6 mg/kg bw per day) (Biegel et al., 2001). Two controls groups were used; the first was an *ad libitum* fed (AL) group, and the second was a pair-fed (PF) group in which the food intake was controlled to match the food intake of the PFOA exposed group. Rats were evaluated at 1 and 3 months and at every 3 months for hormone status, cell proliferation in liver, testis and pancreas and hepatic peroxisome proliferation. Treatment with PFOA increased the relative liver weight at all time points (except at 24 months) compared to both controls. Hepatic β-oxidation activity was significantly elevated at all times, but cell proliferation was not increased in the liver. Pancreatic acinar cell proliferation was increased at 15, 18, and 21 months. Serum estradiol was increased during the first year of the study, serum LH at 6 and 18 months, and serum FSH at 6 months; changes in serum testosterone did not show any consistent pattern. There was a significant increase in tumours in treated animals when compared with one or both of the control groups for Leydig cell adenomas, hepatic adenomas, acinar cell

adenomas and combined pancreatic adenomas and carcinomas. An increased incidence of hyperplasia was also observed in Leydig cells and acinar cells (Biegel et al., 2001).

Although the LOAEL for liver endpoints was higher in chronic studies than in shorter-term studies, the comparisons are difficult to make, as the lowest dose used in the chronic study (1.3 mg/kg bw per day) is higher than the lowest LOAELs for liver effects in the shorter-term studies (i.e., 0.1–0.3 mg/kg bw per day). However, some endpoints observed at these low doses in shorter duration studies, most notably hepatocellular hypertrophy in male rats (Loveless et al., 2008) were not observed at the lowest doses used in the chronic studies (i.e., the chronic NOAEL for this endpoint is 1.3 mg/kg bw per day).

9.2.4 Genotoxicity

The genotoxicity database indicates that PFOA compounds are not mutagenic, and generally not genotoxic (U.S. EPA, 2005; UK HPA, 2009; Environment Canada and Health Canada, 2012).

9.2.4.1 In vitro *findings*

Testing of PFOA (or its ammonium or sodium salts) produced no evidence of genotoxic activity in several Ames bacterial mutation assays and in three *in vitro* chromosomal aberration tests (two in hamster cells and one in human cells) (Environment Canada and Health Canada, 2012). More recently, PFOA (tested up to 1,000 µM) had no mutagenic activity in the *umu* test (Oda et al., 2007) and in the Ames test, with or without S9 metabolic activation (Fernandez Freire et al., 2008). PFOA did not increase oxidative DNA damage (as measured in a comet assay) in rat testicular cells exposed to 100 and 300 µM for 24 hours (Lindeman et al., 2012). In human hepatoma HepG2 cells, PFOA (up to 400 µM for 24 h) did not induce ROS generation, DNA single strand breaks or micronucleus (Florentin et al., 2011). In another study using human HepG2 cells, PFOA induced slight ROS generation (0.4-2,000 µM) without generating detectable DNA damage (200 µM) (Eriksen et al., 2010).

In contrast, positive results were obtained in one chromosome damage test in hamster cells and one micronucleus assay in human cells *in vitro*, and PFOA caused oxidative DNA damage in human hepatoma cells in culture (Environment Canada and Health Canada, 2012). PFOA (200 µM) led to mutagenicity induction in human-hamster hybrid (A_L) cells and mitochondria-dependent ROS was shown to play an important role in this process (Zhao et al., 2011b).

9.2.4.2 In vivo *findings*

Testing of PFOA (or its ammonium or sodium salts) for genotoxic potential produced no evidence of activity in three *in vivo* bone marrow micronucleus tests in mice (up to 5,000 mg/kg bw per day). PFOA caused oxidative DNA damage in the liver of rats treated through the oral route (200 ppm in diet for 2 weeks) or the intraperitoneal route (100 mg/kg bw, once) (Environment Canada and Health Canada, 2012).

9.2.5 Reproductive and developmental toxicity

The reproductive and developmental database for PFOA is robust. Two 2-generational studies have been developed in rats (Butenhoff et al., 2004b/York et al., 2010; White et al., 2011), and reproductive and developmental parameters have been investigated in many one-generation studies in rats, mice, and monkeys. Furthermore, early life or peripubertal exposures were performed in mice (Johansson et al., 2008, 2009; Yang et al., 2009b; Zhao et al., 2010; Dixon et al., 2012).

The most sensitive effects identified are delayed mammary gland development in the offspring of mice (Macon et al., 2011; White et al., 2011), obesity in the female offspring of mice at adulthood (Hines et al., 2009), uterine effects in immature female mice (Dixon et al., 2012), liver weight changes in pups (Abbott et al., 2007; Macon et al., 2011; Onishchenko et al., 2011) and altered neurobehaviour (Johansson et al., 2008, 2009; Onishchenko et al., 2011). These effects were all observed at exposure levels of ≤0.3 mg/kg bw per day, and will be discussed in greater detail. Other reproductive and development effects occurred at higher doses, and will only be described briefly in this section.

9.2.5.1 Mammary gland effects

Changes in mammary gland development (MGD) have only been studied in mice. Delayed MGD was consistent in 1-generation (White et al., 2007, 2009; Wolf et al., 2007; Macon et al., 2011), 2-generation (White et al., 2011), and peripubertal (Yang et al., 2009; Zhao et al., 2010) studies, and has been observed to be significantly different than controls at every dose level studied (≥0.001 mg/kg bw per day) in maternal and F1 generations (both as offspring and dams). The studies primarily identified delayed MGD development (noted to be as long as 10 days in a study that exposed mice to 5 mg/kg bw per day [White et al., 2007]) and lower MGD scores[1] at many different time points. The specific mammary gland structures that were affected included ducts (reduced and delayed ductal elongation and branching), terminal ducts (decrease in number of stimulated TDs), terminal end buds (delayed time of appearance, excess of and decrease in number of TEBs), and longitudinal epithelium (reduced and delayed growth). One study also noted higher densities of darkly staining foci, along with other histological changes, at 18 months (White et al., 2009).

Three studies investigated MGD at ≤1 mg/kg bw per day (Macon et al., 2011; White et al., 2011; Tucker et al., 2015) and will be more thoroughly described below because the LOAELs from these studies are the lowest of any endpoint, including those observed in subchronic and chronic studies. The other studies observing these effects will be summarized more concisely.

A two-generation study (White et al., 2011) found that exposure of mice to low levels of PFOA in drinking water (5 µg/L) delayed mammary gland development in both P0 and F1 dams and F1 and F2 offspring, which persisted until adulthood (at least PND 63). Parental (P0) female CD-1 mice (n = 7–12 per group) were placed into different treatment groups, receiving:

- daily doses of PFOA by gavage (0, 1 or 5 mg/kg bw per day: control, G1 and G5 groups, respectively) on GD 1–17,
- PFOA in drinking water only (5 µg/L, DW group) on GD7–17, or
- PFOA by both gavage (1 mg/kg bw per day on GD1–17) and drinking water (5 µg/L on GD7–17) (G1+DW group).

On PND 1, F1 litters were pooled randomly and redistributed to dams of their respective groups (n=12–13 neonates per litter). F1 female offspring from G1 and G5 groups were not exposed after birth while F1 female offspring from DW and G1+DW groups were exposed via drinking water throughout the rest of the study (n=2–10 F1 dams per group). F1 female offspring were mated with unexposed males to produce the F2 generation. F2 female offspring from DW and G1+DW groups were exposed through drinking water up to the end of the study. Necropsies

[1] MGD is scored on a 1–4 subjective, age-appropriate developmental scale based on the number of primary ducts and large secondary ducts, lateral side branching, appearance of budding from the ductal tree, and longitudinal outgrowth of the epithelia. For female offspring, a score of 4 refers to excellent development/structure and a score of 1 to poor development/structure. For dams, a value of 4 represents well-differentiated, functionally lactating tissue characterized by extensive epithelium, reduced adiposity, and presence of secretory alveoli, consistent with the peak of lactation (PND10). A value of 1 represents little or diminishing presence of lobuloalveoli and extensive involution and regression of the tissue, with the presence of apoptotic bodies, increasing adiposity, and regressing alveoli, as anticipated at weaning (PND22).

were performed on F1 and F2 females at PND 42 and PND 63, and on F1 dams and F2 female offspring at PND 10 and PND 22 (White et al., 2011).

In the P0 (i.e., directly-exposed dams), a significant increase of MGD score was observed in all the treated groups on PND 22, even at the lowest dose (5 µg/L in drinking water on GD 7–17). These elevated scores reflect a delay in the normal weaning-induced mammary involution (on PND 22, the structure of the mammary gland in the treated P0 was similar to the structure normally observed at the lactation peak at PND 10). The authors only provided information on the amount of daily ingestion of PFOA in P0 dams consuming 5 µg/L drinking water (approximately 0.05 µg per day during gestation and 0.1 µg per day during lactation [PND 1–22]). Average daily doses are estimated to be approximately 0.001 mg/kg bw per day during gestation and 0.004 mg/kg bw per day during lactation (based on mean approximate weights of 62 g during gestation and 25 g during lactation; the average maternal weight gain during gestation was 25 g, and the initial body weight of dams was not reported by the authors but is assumed to be approximately 25 g for this strain of mice). The maternal LOAEL was therefore considered to be 0.001 mg/kg bw per day.

F1 pups from all treatment groups exhibited reduced MGD scores (reduced ductal elongation and branching, delays in timing of TEB appearance) until at least 9 weeks of age (PND 63, i.e., the last time point). In F1 dams (i.e., adult F1 pups), all the PFOA-treated groups exhibited reduced MGD scores on PND 10; low score value persisted on PND 22 in the G1+DW, whereas in the G5 group, the score became higher than the control on PND 22 (i.e., normal involution was delayed). In the F2 females, MGD scores at PND 10 and PND 22 did not differ significantly from control; however, this result may be biased due to unusually low scores in the control group. At later times, significantly reduced scores were obtained in all treated groups (PND 42 for DW, G1+DW and G5, PND 63 for G1) and were characterized by an excess of terminal end buds (TEBs) (White et al., 2011).

In summary, White et al. (2011) demonstrated that ingested PFOA alters the development of mammary glands in both dams and offspring of CD-1 mice after exposure to low, human-relevant doses of PFOA (as low as 5 µg/L in drinking water) leading to human-relevant PFOA serum concentrations in pups and dams (range of approximately 20–90 ng/mL). The corresponding dose (LOAEL) was estimated at a maternal exposure of approximately 0.001 and 0.004 mg/kg bw per day during gestation and lactation, respectively. Effects in this study occurred independently of body weight changes, and the only adverse maternal effects observed at these levels were the mammary gland changes.

Macon et al. (2011) performed two separate studies of MGD in CD-1 mice—a late-gestation study and whole-gestation study. In the late-gestation study, dams (n=13 per group) were exposed to PFOA (0, 0.01, 0.1, and 1.0 mg/kg bw per day) by oral gavage on GD 10–17. The whole-gestation study exposed dams (n=13 per group) by gavage to PFOA at 0, 0.3, 1.0 or 3.0 mg/kg bw per day on GD 1–17.

Results of the late gestation study indicate significantly reduced MGD scores (in all treated groups, with a dose-dependent relationship) at PND 21. Other effects observed in the mammary gland at PND 14 (at 0.1 and 1.0 mg/kg bw per day, respectively) included reduced longitudinal epithelial growth by 14.4% and 37.3% compared to control (reduction by 27.4% and 56.5% compared to PND 1) and a statistically significant reduction of TEBs. In the whole-gestation study, the effects observed at all doses were dose-dependent and included reduced MGD scores in female offspring, which persisted until adulthood (PND 84). The LOAELs for the late and whole gestation studies were 0.01 and 0.3 mg/kg bw per day, respectively. No decreases in pup body weight were observed in these studies; therefore, MGD delays did not arise from decreased body weight.

Tucker et al. (2015) studied MGD in both CD-1 and C57Bl/6 female mouse pups that were exposed *in utero* to PFOA. Dams were exposed to PFOA via gavage at concentrations of 0, 0.01, 0.1, 0.3, and 1 mg/kg bw per day on GD 1–17. Significant dose-related trends in decreases in MGD scores were observed in pups of both strains. In CD-1 mice, the decreases were significant at ≥0.1 mg/kg bw per day when measured at PND21, which then decreased to ≥0.01 mg/kg bw per day at PND35 and PND56. The LOAEL for C57Bl/6 was slightly higher, with significant decreases at ≥0.3 mg/kg bw per day at PND21 and PND61. The authors also noted that average serum PFOA levels were lower in C57Bl/6 mice than in CD-1 mice.

Although the LOAEL for MGD scores was lower in CD-1 than C57Bl/6 mice, the results from this study are not sufficient to conclude that strain sensitivity occurs for the endpoint. Fewer pups were born in all C57Bl/6 groups, which resulted in a smaller sample size for the strain. This was particularly notable in the 0.01 and 0.1 mg/kg bw per day groups, which contained 8–22 CD-1 mice, but only 2–5 C57Bl/6 mice. As average MGD scores were similar between the strains at all doses, the lower sample size might have prevented statistical significance from being reached at these lower doses for C57Bl/6 mice. Moreover, the timing of MGD scoring was different for the strains at later timepoints (CD-1 mice were studied at PND 21, 35, and 56, whereas C57Bl/6 mice were only studied at PND 21 and 61), which might also affect results; MGD scores in control C57Bl/6 mice at PND 61 were lower than in control CD-1 mice at PND 35 and 56.

Tucker et al. (2015) also investigated other sexual maturity effects. No treatment-related effects on estradiol or progesterone levels, nor on timing of vaginal opening or first estrus, were observed in either strain.

Several other higher-dose studies have noted delays in MGD at many different time points in female CD-1 mice (dams and offspring) exposed to gavage doses of ≥3 mg/kg bw per day (White et al., 2007, 2009; Wolf et al., 2007). These delays in MGD development are supported by data indicating reduced placental mRNA expression for genes in prolactin family (at ≥2 mg/kg bw per day; Suh et al., 2011), and a delay in lactotransferrin expression at 5 mg/kg bw per day (White et al., 2007).

A peripubertal study in mice (dosing beginning at 21 days of age) noted strain differences, with significant MGD delays at ≥5 mg/kg bw per day in Balb/c, but only at 10 mg/kg bw per day in C57Bl/6 (no inhibition occurred in either strain at 1 mg/kg bw per day; rather, stimulation was observed at this dose in C57Bl/6 mice) (Yang et al., 2009b). An additional peripubertal study (Zhao et al., 2010) noted effects at the only dose in the study, 5 mg/kg bw per day.

Although mammary gland delays can sometimes be associated with decreased body weight, two studies specifically stated that the effects were observed in absence of bodyweight disparities (White et al., 2007, 2009). One study also noted that the effect was not entirely due to underdeveloped offspring and insufficient stimulation by suckling, as the alteration of the functional mammary gland differentiation occurred prior to parturition and lactation (i.e., prior to stimulation of the gland by offspring) (White et al., 2007; 5 mg/kg bw per day).

Other effects related to sexual maturity were accelerated puberty (≥1 mg/ kg bw per day in M mice & 20 mg/kg bw per day in F mice; Lau et al., 2006), delayed sexual maturation (preputial separation & vaginal patency in rats; only at 30 mg/kg bw per day; Butenhoff et al., 2004b), and increased age of vaginal opening (at ≥5 mg/kg bw per day in C57BL/6 mice, but not Balb/c mice; Yang et al., 2009b).

9.2.5.2 Uterine effects

Histological changes in the uterus have been observed in CD-1 mice exposed to low doses of PFOA (Dixon et al., 2012). In immature mice exposed PND 18–20 to 0.01 mg/kg bw per day of PFOA by gavage, endometrial edema, hyperplasia of endometrial mucosa and glands, edema,

and hypertrophy and hyperplasia of myometrium were induced. No histological effects were observed at the two higher doses in the study (0.1 and 1 mg/kg bw per day). The study also saw a dose-related increase of mucification (significant at the high dose only) in the cervix and vagina.

Differential effects were observed in uterine weight in mice. Increases in uterine weight in the Dixon et al. (2012) study were only observed in the lowest (0.01 mg/kg bw per day) group. The only other study reporting changes in uterine weight was a 4-week gavage study that exposed peripubertal Balb/c and C57BL/6 mice to 0, 1, 5, or 10 mg/kg bw per day (Yang et al., 2009b). In Balb/c mice, uterine weight was decreased at all doses (≥1 mg/kg bw per day), whereas in C57BL/6 mice, uterine weight was increased at 1 mg/kg bw per day, with a dose-dependent decrease at higher doses, which became significant only at 10 mg/kg bw per day.

9.2.5.3 Obesity in adulthood

Obesity in adulthood was noted to occur in a non-monotonic dose-response fashion in mice, in the only study that investigated this effect (Hines et al., 2009). Dose-dependent effects on body weight, appetite control (increased leptin and insulin blood concentration) and fat distribution were observed at adulthood in female CD-1 mice exposed *in utero* to PFOA. Pregnant mice (n=7–22 per dose group) were exposed daily by gavage on GD 1–17 (PFOA doses of 0, 0.01, 0.1, 0.3, 1, 3 and/or 5 mg/kg bw per day); offspring were weaned at 3 weeks and then female offspring were selected and received a standard diet for the rest of study.

At low doses (0.01, 0.1 and 0.3 mg/kg bw per day), data indicate an excessive weight gain in mice aged 20–29 weeks that coincided with increased blood levels of leptin and insulin (by approximately 2.5-fold) at 21–33 weeks of age (Hines et al. 2009). At higher doses, tissue weights at 18 months of age revealed a decreased relative weight of abdominal white fat at 1 and 5 mg/kg bw per day (no data at 3 mg/kg bw per day), and an increased relative weight of interscapular brown fat at 1 and 3 mg/kg bw per day (no effect at 5 mg/kg bw per day); overall bodyweight was decreased at the higher tested dose (5 mg/kg bw per day). No effects on bodyweight were observed at 1 or 3 mg/kg bw per day.

Similar experiments conducted in ovariectomized siblings of the exposed offspring (ovariectomy performed at PND 21/22) indicated no effect on body weight and abdominal fat weight, but an increased relative weight of interscapular brown fat at 1 mg/kg bw per day (no effect at 5 mg/kg bw per day). Although the latter data were difficult to interpret, the authors concluded that the ovaries appeared to play an important role in the overweight effect in mid-life and proposed that potential dysregulation of PPAR and its signaling through ovarian hormones may be responsible for the low-dose effects observed (Hines et al., 2009). It should be noted that exposure of 8 week-old mice to the same doses for the same period (17 days) did not lead to any effect on the same endpoints (see Section 9.2.2.1), suggesting the timing of dosing was critical for latent effects (Hines et al., 2009).

9.2.5.4 Developmental hepatic effects

As described in Section 9.2.2.1, hepatic effects are the most sensitive non-developmental effect resulting from short-term exposure to PFOA. Likewise, increases in liver weight were also observed after *in utero* or peripubertal exposure to PFOA.

The lowest maternal exposure dose at which increases in liver weight were observed in pups exposed prenatally to PFOA was 0.1 mg/kg bw per day (Abbott et al., 2007). In this study, 129S1/SvImJ mice (n=5–22 dams/dose) were exposed by gavage to 0, 0.1, 0.3, 0.6, 1, 3, 5, 10, and 20 mg/kg bw per day on GD 1–17. Increased relative liver weight in pups was observed in all doses, and was worsened at higher doses.

One other study observed slight but significant effects at <1 mg/kg bw per day; the study had only 1 dose group, 0.3 mg/kg bw per day (Onishchenko et al., 2011). The effect was observed at ≥1 mg/kg bw per day in other studies in mice exposed *in utero* (Wolf et al., 2007; White et al., 2009, 2011;Macon et al., 2011) or peripubertally (Yang et al., 2009b).

9.2.5.5 Neurodevelopmental effects

Neurobehavioural effects were observed in mice exposed *in utero* or shortly after birth, at the lowest doses applied in two studies—0.3 mg/kg bw per day (Onishchenko et al., 2011) and 0.58 mg/kg bw per day (Johansson et al., 2008). The effects manifested as changes in activity levels in mice.

Dietary exposure of C57BL/6/Bkl mice (n=6 dams/group) to 0 or 0.3 mg/kg (the only treatment group) of PFOA from GD 1 throughout pregnancy was found to induce gender-specific changes in offspring exploratory behaviour (first hour spent in a new environment), with an increased exploring activity in males and a decreased activity in females (Onishchenko et al., 2011). Prenatal exposure to PFOA also decreased the total number of inactive periods during the light phase in both males and females as well as in the dark phase of the circadian cycle in males. Motor coordination was slightly altered in females only. No effects were noted on locomotor activity, anxiety behaviour (elevated plus maze test), immobility in the forced swimming test or muscle strength.

A LOAEL of 0.58 mg/kg for neurodevelopmental effects was identified in NMRI male mice administered a single gavage dose of PFOA (0.58 or 8.70 mg/kg) at the age of 10 days (Johansson et al., 2008). Mice were tested for spontaneous behavior and habituation at the age of 2 and 4 months, and the susceptibility of their cholinergic system was explored in a nicotine-induced spontaneous behaviour test at the age of 4 month (Johansson et al., 2008). Data indicate time-dependent and dose-related effects on the behaviour (deranged spontaneous behaviour, lack of habituation and increased susceptibility of the cholinergic system) reflecting the advance of a brain dysfunction process induced at the time of brain growth spurt in the neonatal mouse. At both doses, the exposed mice exhibited an altered spontaneous behaviour and a hypoactive response to nicotine. Any of the three variables of the behavioural test (locomotion, rearing and total activity) were altered, indicating hypoactivity during the first 20 minutes and hyperactivity in the last 20 min period (40–60 min after start of the test), and the effects worsened with age. These effects were supported by significantly increased levels of proteins that are important for normal brain development (CaMKII, GAP-43, and synaptophysin in the hippocampus, synaptophysin and tau in the cerebral cortex, and tau in the hippocampus) in mice under the same neonatal exposure conditions (Johansson et al., 2009).

9.2.5.5 Other effects

Reproductive and developmental effects other than those described earlier in this section were observed at higher doses; 0.6 mg/kg bw per day was the lowest LOAEL for delayed eye opening (Abbott et al., 2007), and all other effects were observed at ≥1 mg/kg bw per day.

The additional reproductive effects in mouse included a reduced number of implants (White et al., 2011), increased resorption, dead fetuses, post-implantation loss, or prenatal loss (White et al., 2007; Suh et al., 2011; White et al., 2011;) including increases in full-litter resorption or loss (Lau et al., 2006; Wolf et al., 2007; White et al., 2009), decreased placental weight (Suh et al., 2011), increased time to parturition (Lau et al., 2006), reduced number of live fetuses (White et al., 2011), increase in number of stillborn pups (Yahia et al., 2010), decreased survival of pups (Lau et al., 2006; Wolf et al., 2007; White et al., 2009; 2011; Yahia et al., 2010) and histopathological changes in mouse placenta (Suh et al., 2011).

The additional developmental effects in mouse offspring included delayed eye opening at in 1-generation studies (Lau et al., 2006; Abbott et al., 2007; Wolf et al., 2007; White et al., 2009), skeletal effects in one-generational studies [one study observed altered ossification (enlarged fontanel, reduced ossification of sternebrae and calvaria; Lau et al., 2006), another found delayed ossification of phalanges, increased cleft sternum, and delayed eruption of incisor occurred; Yahia et al., 2010], decreased relative spleen weight, without a clear dose–response relationship (Hines et al., 2009), reduced fetal or pup weight (Staples et al., 1984; Lau et al., 2006; Abbott et al., 2007; White et al., 2007; 2009; Wolf et al., 2007; Yahia et al., 2010; Suh et al., 2011), and increased fetal weight (Yahia et al., 2010).

The only effects noted in a 2-generation study of rats included delayed growth (at ≥10 mg/kg bw per day in M and 30 mg/kg bw per day in F) and increased post-weaning mortality (in F only, at 30 mg/kg bw per day), with no effects on the F2 generation (Butenhoff et al., 2004b; York, 2002).

9.3 Mode of action

Mode of action analysis was considered for effects occurring at the lowest PFOA levels (i.e., Leydig cell tumours, hepatocellular hypertrophy, and changes in serum lipids in rats, and liver weight increases, hepatocellular hypertrophy, obesity, developmental delays, and delayed mammary gland development in mice). Only a preliminary evaluation of data could be performed for most of the MOAs; a MOA analysis using recent guidance (Meek et al., 2014) could only be performed for peroxisome proliferation effects on liver endpoints. Based on the MOA analysis, no endpoints were considered to be irrelevant to humans, and the results suggest that the TDI approach is the most appropriate method for cancer risk assessment. Results of the MOA evaluations are summarized in this section.

9.3.1 Direct-acting mutagenicity

Direct-acting mutagenicity and DNA reactivity was considered as a potential MOA for the development of Leydig cell tumours in rats. As discussed in Section 9.2.4, evidence predominantly indicates that PFOA is not mutagenic, with or without metabolic activation. PFOA was negative for genotoxicity in a wide variety of *in vitro* and *in vivo* assays. Positive results were obtained only in one chromosome damage test in hamster cells, one micronucleus assay in human cells, and mutagenicity was observed in human-hamster hybrid (A_L) cells, but mitochondria-dependent ROS was shown to play an important role in this process. The pattern of PFOA-induced tumours also did not follow that of typical mutagens. For example, mutagens are typically expected to cause tumours in many different organs, but PFOA only affected testicular Leydig cells, liver, and pancreas (i.e., organs associated with the PPARα tumour triad) in one study (Biegel et al., 2011), and only Leydig cells in another study at similar doses (Butenhoff et al., 2012b). Furthermore, mutagens often produce a high incidence of tumours, which occur at early timepoints and at low doses. In PFOA-exposed animals, the tumours were only observed after lifetime duration to high doses in PFOA studies, and at low incidences (10–14%).

Further support for non-mutagenic activity of PFOA is provided by a study that suggests that PFOA acts as a tumour promoter. Liver tumours—primarily hepatocarcinomas—were observed in rats that underwent initiation protocols (i.e., were exposed to the mutagen diethylnitrosamine) and were exposed to feed containing 0.015% PFOA (equivalent to 7.5 mg/kg bw per day using the Health Canada [1994] assumption that 1 ppm in food is equivalent to 0.05 mg/kg bw per day in rats) on weeks 5–28 of the study (Abdellatif et al., 1990). Hepatic tumours were observed in 33% of animals (vs. 0% in controls that were initiated but not exposed to tumour promoters); therefore, effects were observed earlier (after 6 months of PFOA exposure

and 7 months after initiation) and at a higher incidence than higher dose studies of rats exposed only to PFOA.

The weight of evidence for non-mutagenic MOAs of tumours (as discussed later in this section) is stronger than for direct-acting mutagenicity, which suggests that low-dose linear extrapolation is not appropriate for PFOA-induced tumours. No further MOA analysis is required for direct-acting mutagenicity, unless contradictory data are published.

9.3.2 Peroxisome proliferation

Peroxisome proliferation was considered as a potential MOA for hepatocellular hypertrophy in rats and mice, serum lipid changes and hepatocellular tumours in rats, and liver weight increase and obesity in mice. Some data exist for hepatic PPAR activity in rats and mice; therefore, this is the primary focus of the analysis. Because few studies directly measured PPAR impact on other outcomes, these could not be fully assessed; however, studies in PPAR-null mice indicate a decreased sensitivity to reproductive and developmental endpoints (including litter loss, delayed eye opening, and decreased body weight in pups [Abbott et al., 2007]) but not mammary gland development delays (Zhao et al., 2010). The evolved Bradford-Hill criteria were applied to evaluate the weight of evidence for the MOA of peroxisome proliferation for liver endpoints, which is summarized below.

Three main key events in the peroxisome proliferation MOA are considered to lead to liver histological effects and hepatocellular tumours. These key events are 1) the activation of hepatic PPARα receptors, which leads to 2) altered cell growth pathways that inhibit apoptosis and/or promote cell replication, eventually leading to 3) hepatocyte proliferation (Corton et al., 2014).

9.3.2.1 Key event 1 – PPARα activation

An absence of hepatic palmitoyl CoA oxidation was observed in rats exposed to 0.3 mg/kg bw per day of PFOA for 14 days (Loveless et al., 2006). The lowest dose at which the hepatic oxidation was observed in rats was 0.64 mg/kg bw per day after 4 weeks of exposure (Perkins et al., 2004), with the effect regularly occurring at higher doses (at ≥1 mg/kg bw per day for 14 days [Loveless et al., 2006], ≥1.94 mg/kg bw per day for ≥4 weeks [Perkins et al., 2004], ≥2 mg/kg bw per day for 14 days [Liu et al., 1996], 7.5 mg/kg bw per day for 23 weeks [Abdellatif et al., 1990], 13.6 mg/kg bw per day for ≥1 month [Biegel et al., 2011], and approximately 20 mg/kg bw per day for ≤28 days [Elcombe et al., 2010]). In mice, hepatic palmitoyl CoA oxidation was observed at lower PFOA doses than rats, with the effect measured at ≥0.3 mg/kg bw per day after 14 days of exposure (Loveless et al., 2006) and higher doses in other studies (Yang et al., 2002; Minata et al., 2010; Nakagawa et al., 2012); moreover, increased expression of PPAR-related genes was observed in wild-type mice, but not humanized PPAR or PPAR-null mice, exposed for 2 weeks to ≥0.1 mg/kg bw per day (Nakamura et al., 2009). In rats exposed to 13.6 mg/kg bw per day of PFOA for 2 years, no increase in palmitoyl CoA oxidation was observed in Leydig cells (Biegel et al., 2011); however, the same study did not measure an increase in the effect in a model peroxisome proliferator (Wyeth-14,643 [WY]).

9.3.2.2 Key event 2 – altered cell growth

No studies of markers of altered cell growth pathways could be found.

9.3.2.3 Key event 3 – cell proliferation

An absence of hepatocyte proliferation was noted in rats exposed to 13.6 mg/kg bw per day for 1–24 months, when it was observed in positive controls (i.e., WY-exposed mice) at the

same time periods (Biegel et al., 2001), but the effect was observed in rats exposed to approximately 20 mg/kg bw per day for 2–29 days (Elcombe et al., 2010). A dose-related increase in labelling index was observed in both wild-type and PPAR-null mice exposed for 7 days, with significance reached at 10 mg/kg bw per day (but not 1 or 3 mg/kg bw per day) in both strains (Wolf et al., 2008).

Cell proliferation was measured in pancreatic acinar cells, but not Leydig cells, in rats exposed to 13.6 mg/kg bw per day for 2 years (Biegel et al., 2011).

9.3.2.4 Assessment of Bradford-Hill considerations

Biological concordance — PPAR activation, leading to increased replication in hepatocytes and increased hepatic tumours, is a well-recognized MOA. Increases were observed in testicular (Leydig cell), pancreatic, and hepatocellular tumours in rats (Biegel et al., 2011), which is a recognized tumour triad for the peroxisome proliferation MOA (Corton et al., 2012); pancreatic acinar cell proliferation and hyperplasia were also observed to be increased in rats (Biegel et al., 2011). However, inconsistencies in this observation arise as the tumour triad was not observed at a similar dose in another two-year study in rats (Butenhoff et al., 2012b). Studies of peroxisome proliferation and tumour development in these cells in mice (which are more sensitive to peroxisome proliferation than rats) would potentially provide more useful information for the MOA analysis.

Essentiality of key event — Studies of PPAR-null mice (Yang et al., 2002; Abbott et al., 2007; Wolf et al., 2008; Nakagawa et al., 2012) provided information to evaluate the essentiality of the key events for hepatic effects; no studies of PPAR-null rats exposed to PFOA could be found. In the Abbott et al. (2007) study, PPAR-null mice had decreased sensitivity to liver weight effects, which lends some support to the MOA for this adverse outcome; however, liver weight effects still occur (albeit at higher doses) in PPAR-null mice, and hepatomegaly is induced to the same extent in wild-type and PPAR-null mice in other studies (Yang et al., 2002; Wolf et al., 2008; Nakagawa et al., 2012). The increase hepatocyte proliferation (as measured by increase in labelling index) was also similar between wild-type and PPAR-null mice (Wolf et al., 2008). Moreover, despite an absence of increased expression of PPAR-related genes in PPAR-null and humanized PPAR mice, increases in liver weight were similar among these strains and wild-type mice (i.e., mice with increased PPAR expression) (Nakagawa et al., 2012). Despite these quantitative similarities between strains for non-cancer liver effects, qualitative differences were observed—including differences in microscopic appearance and ultrastructure of hepatic cells (Wolf et al., 2008; Minata et al., 2010) Further studies that expose PPAR-null mice at lower doses and investigate other adverse outcomes, as well as studies of PPAR-null rats, would help to better evaluate the MOA.

Temporal and dose–response concordance — Some dose–response concordance was observed for the MOA, as PPAR activation precedes hepatocyte proliferation in rats; however, hepatocyte proliferation was absent at tumour-relevant doses in rats (Biegel et al., 2001), and occurred only at higher levels than those resulting in hepatocellular hypertrophy and increased liver weight (Elcombe et al., 2010). The sole study of hepatocyte proliferation in mice indicates its occurrence only at doses above those at which increases in hypertrophy and liver weight were observed (Wolf et al., 2008). Moreover, the absence of data on altered cell growth pathways precludes the evaluation of whether this key event is triggered by PPAR activation and is a precursor for hepatocyte proliferation.

The first key event (PPAR activation) does not appear to precede the adverse hepatic outcomes in rats. Both increased liver weight and hepatocellular hypertrophy were observed either at or below doses where an absence of PPAR activation was observed.

Consistency (across species, strains, organs, and test systems) — PPAR activation begins at lower doses in mice than rats and monkeys, as is expected, based on knowledge of PPAR biology (Corton et al., 2014). However, in monkeys, PPAR activation is not consistent, is not accompanied by cell proliferation, and occurs only at higher doses than adverse liver effects.

Analogous compounds — The tumour triad observed in male rats, along with an increase in serum estradiol, was observed similarly in both PFOA and a model peroxisome proliferator, WY. However, hepatic effects in PFOS-exposed rats appears to occur in absence of peroxisome proliferation, and the tumour triad was not observed in PFOS-exposed rats.

Some evidence in rats and mice supports the occurrence of peroxisome proliferation as a mode of action for hepatocellular hypertrophy. The characteristic tumour triad of peroxisome proliferators (cancers of the testes, pancreas, and liver) was observed in rats, and the doses at which hepatocellular tumours are observed are higher than earlier key events in the peroxisome proliferation MOA. However, increases in liver weight and hepatocellular hypertrophy appear to occur at lower doses than PPAR activation in rats; therefore, although PPAR activation does occur in rats, it does not appear to be the sole driver for these two effects. . Studies of PPAR-null mice indicate that peroxisome proliferation might play a role in observed hepatocellular hypertrophy and liver weight increases, but despite qualitative (i.e., appearance) differences between the strains, the quantitative similarities in the changes in PPAR-null vs. wild type mice indicate that other MOAs play a large role in the development of the effects. Because the peroxisome proliferation MOA does not seem to be the sole MOA involved, human relevance of PFOA-induced non-carcinogenic hepatic effects cannot be ruled out. Conversely, a detailed MOA analysis has concluded that the weight of evidence for the peroxisome proliferation MOA for PFOA-induced liver tumours was strong. The relevance of these tumours to humans is limited, as PPARα activation by PFOA is weaker in humans than in rats. Moreover, PPARα activation by various compounds in does not appear to result in hepatocellular proliferation and tumours (Corton et al., 2012; Klaunig et al., 2012).

9.3.3 Sex hormone disruption

Sex hormone disruption is a potential MOA that should be considered for mammary gland development delays in mice, obesity in prenatally exposed mice, and Leydig cell tumours in rats. Insufficient data exist to be able to perform a quantitative analysis of sex hormone disruption; however, a few different observations that could be relevant to the sex hormone MOA have been reported, including the muting of uterine effects when PFOA was co-administered with estradiol (Dixon et al., 2012), an enhancement of the effects of 17β-estradiol in a variety of *in vitro* assays, but with an absence of direct estrogenic activity (Sonthithai et al., 2015), the reversal of mammary gland development delays with the supplementation of physiological levels of estradiol or progesterone (Zhao et al., 2012), an increase in serum estradiol concentrations in male rats exposed for 1–12 months (Biegel et al., 2001), changes in estradiol genesis (decrease at lower doses and increase at higher doses) in an *in vitro* steroidogenesis assay (Rosenmai et al., 2013), an absence of PFOA binding to or activating human estradiol receptors *in vitro* (Ishibashi et al., 2007), and decreases in cholesterol levels, which might disrupt testosterone synthesis (Li et al., 2011). If more in-depth studies on the effect of PFOA on sex hormone disruption are performed, this potential MOA could be further investigated.

9.3.4 Other MOAs

Insufficient data exist to allow for the assessment of other potential MOAs considered in the MOA analysis. Some data—particularly in regards to PPAR activation/peroxisome

proliferation—exist for other endpoints that were not included in the MOA analysis (i.e., effects that were observed only at higher PFOA exposure levels).

10.0 Classification and assessment

PFOA and its salts have been classified as possibly carcinogenic to humans (Group 2B) by IARC, based on limited epidemiological evidence demonstrating associations between PFOA and testicular and renal cancers, and on limited evidence in experimental animals (Benbrahim-Tallaa et al., 2014). When evaluated under CEPA legislation, PFOA, its salts and its precursors met the criteria for persistence and immediate or long-term harmful effect on the environment or its biological diversity, but were not deemed to be bioaccumulative, nor entering the environment under conditions that constitute or may constitute a danger in Canada to human life or health (Environment Canada and Health Canada, 2012).

The benchmark dose (BMD) approach was used wherever possible to calculate potential PODs, because it is derived on the basis of data from the entire dose-response curve for the critical effect rather than from the single dose group at the NOAEL (IPCS, 1994). A lower confidence limit of the benchmark dose (BMDL) has been suggested as an appropriate replacement of the NOAEL (Crump, 1984). More specifically, a suitable BMDL is defined as a lower 95% confidence limit estimate of dose corresponding to a 1–10% level of risk over background levels. Definition of the BMD as a lower confidence limit accounts for the statistical power and quality of the data (IPCS, 1994). Benchmark dose values representing a 10% increase in adverse effect over background rates (BMD_{10}) and their lower 95% confidence limits ($BMDL_{10}$) were calculated using the U.S. EPA Benchmark Dose Software (BMDS Version 2.6.0.86; U.S. EPA, 2015).

Large pharmacokinetic differences exist between animals and humans, with lower clearance (i.e., higher half-life values) in humans than in rats, mice, and monkeys. These differences result in higher target tissue doses in humans when exposed to the same external doses as animals. Default approaches for interspecies extrapolation (e.g., interspecies uncertainty factor of 10, allometric scaling) are therefore not considered to be sufficiently protective of humans. As described in Section 8.6, AK_{UF} values (i.e., the component of the CSAF reflecting interspecies toxicokinetic differences) were calculated with a PBPK model to address pharmacokinetic differences between animals and humans. As different AK_{UF} values were calculated for various doses, the values can also address non-linearity in pharmacokinetics. Weaknesses still exist with this approach, as outlined in detail in Section 8.6, including the use of the steady-state plasma concentration as a dose metric, rather than selecting organ-based values or exploring whether other dose metrics (e.g., peak concentrations) are more appropriate. However, despite the weaknesses, the approach was determined to be the best of the available options. This approach was selected over the use of serum concentrations as points-of-departure (PODs), because human PBPK models were determined to not be sufficiently robust for precise estimates of human exposure levels corresponding to serum-based PODs.

10.1 Cancer risk assessment

Epidemiological evidence has shown an association between exposure to PFOA and increased risk of incidence of testicular and kidney cancers (see Section 9.1.3). The associations were observed in large-scale epidemiology studies in a community with elevated PFOA concentrations in water (C8 project). However, causality and a point-of-departure cannot be determined from these studies due to the lack of consistency between studies (no association found in some prospective studies in Denmark and the U.S.). Limitations were also observed in

the studies that found a positive association, including the risk of residual confounding (because not all covariates and exposures to other contaminants were included in the model), the small case numbers, the uncertainties in exposure characterization (rough estimates based on residency within a certain area), and the high number of outcomes included in the models, increasing the likelihood of chance findings.

Two chronic duration studies identified testicular Leydig cell adenomas in male Crl:CD BR (CD) rats exposed to PFOA for 2 years. The first study observed these adenomas at 13.6 mg/kg bw per day (the only dose tested in the study; Biegel et al., 2001); the other study observed a dose-related increase in incidence of adenomas, with significance achieved at the high dose (14.2 mg/kg bw per day; 3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b). The Leydig cell adenomas were accompanied by hyperplasia of Leydig cells and proliferation and adenomas of pancreatic acinar cells in the Biegel et al. (2001) study. A dose-dependent increase in mammary fibroadenomas was observed in female rats in the Butenhoff et al. (2012b) study, but were not considered proliferative lesions using current diagnostic criteria.

Although the mode of action for PFOA-induced tumours has not yet been elucidated, the weight of evidence more strongly suggests that PFOA is a non-mutagenic compound (see Sections 9.2.4 and 9.3). For this reason, the tolerable daily intake (TDI) approach is the most appropriate method for deriving a health-based value (HBV) for cancer.

The selected key study for the cancer risk assessment is Butenhoff et al. (2012b), as it is the only chronic study with more than one dose level. Incidence of Leydig cell tumours was 0, 2, and 7, in rats exposed to 0, 1.3, and 14.2 mg/kg bw per day, respectively. As significance was only observed at the high dose, the NOAEL and LOAEL for Leydig cell tumours in this study are 1.3 and 14.2 mg/kg bw per day, respectively. The use of benchmark dose modelling is not typically recommended for studies containing only two dose groups (U.S. EPA, 2012); however, the approach was performed for comparison with the NOAEL. Three models (Log Logistic, Log Probit, and Multistage) had the best fit (all models had the lowest Akaike information criterion [AIC] among all considered models). The $BMDL_{10}$ values for these three models ranged from 1.06 to 1.26 mg/kg bw per day, and were therefore similar to the NOAEL of 1.3 mg/kg bw per day, which is used as the POD for the analysis.

To reflect the large interspecies differences in pharmacokinetics, the human-equivalent point-of-departure (POD_{HEQ}) can be calculated by dividing the $BMDL_{10}$ by the AK_{UF}, as follows:

$$POD_{HEQ} = \frac{1.3 \text{ mg/kg bw per day}}{17}$$

$$= 0.076 \text{ mg/kg bw per day}$$

where:

- 1.3 mg/kg bw per day is the $BMDL_{10}$ for Leydig cell tumours in male rats (Butenhoff et al., 2012b); and
- 17 is the dose-specific AK_{UF} for rats in the 1 mg/kg bw per day range (as described in Section 8.6.2)

Using the calculated POD_{HEQ}, the cancer TDI was calculated as follows:

$$TDI = \frac{0.076 \text{ mg/kg bw per day}}{25}$$

$$= 3 \text{ mg/kg bw per day}$$

where:

- 0.076 mg/kg bw per day is the POD_{HEQ} associated with the NOAEL for Leydig cell tumours in male rats (Butenhoff et al., 2012b); and
- 25 is the composite uncertainty factor, as described below

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (×2.5) and intraspecies uncertainty factor (×10). A value of 2.5 is used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. A default value of 10 was applied for the intraspecies uncertainty factor The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOA excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. Average half-life values calculated from longitudinal data for different populations previously exposed to PFOA were similar (averages for each population ranged from 2.3–3.8 years; Olsen et al., 2007; Bartell et al., 2010; Brede et al., 2011); however, studies providing ranges indicated that there was approximately a 10-fold difference between the lowest and highest estimates of half-life. If further studies of PFOA consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed.

Using this TDI, the HBV for drinking water can be calculated as follows:

$$HBV = \frac{0.003 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= 0.028 \text{ mg/L}$$

$$\approx 0.03 \text{ mg/L (30 µg/L)}$$

where:

- 0.003 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7)

10.2 Non-cancer risk assessment

Although epidemiological evidence has shown an association between the exposure to PFOA and multiple health outcomes, such as dysfunctions of the immunological system and alterations in birth weight and lipid levels (see Section 9.1.3), a POD cannot be derived from these studies due to limitations, including in terms of study design, bias and confounders,.

The lowest LOAELs for PFOA were for reproductive and developmental effects in mice, with effects observed at levels as low as 0.001–0.01 mg/kg bw per day for delayed mammary gland development (Macon et al., 2011; White et al., 2011; Tucker et al., 2015), at 0.01 mg/kg bw per day for estrogenic effects in the uterus (Dixon et al., 2012) and weight changes in adult females exposed prenatally (Hines et al., 2009), and at 0.6 mg/kg bw per day for delayed eye opening (Abbott et al., 2007). These endpoints were not used as the basis of the risk assessment for several reasons. Estrogenic effects in the uterus (endometrial edema, hyperplasia of endometrial mucosa and glands, hypertrophy and hyperplasia of myometrium, and increase in weight in the uterotrophic assay) were excluded from the assessment because they did not occur in a dose–related manner—significant increases were observed in mice exposed only to 0.01 mg/kg bw per day, and not at higher levels (0.1 or 1 mg/kg bw per day; Dixon et al., 2012). A non-monotonic response was also observed for body weight changes in adult female mice exposed *in utero*, with increased body weight at 0.01–0.3 mg/kg bw per day (not 1 mg/kg bw per day) and in serum leptin and insulin at 0.01 and 0.1 mg/kg bw per day (not 0.3 or 1 mg/kg bw per day; Hines et al., 2009). Moreover, slight changes (although significant) in mammary gland development and bodyweight are indicative of treatment-related changes, but not necessarily adversity—there was no evidence of insufficient milk intake or inability to thrive in pups of dams with MGD changes, and weight changes were low (measured at <10%). The observation of delayed eye opening at ≥0.6 mg/kg bw per day in mice (Abbott et al., 2007) was not corroborated in other studies, as the effect had a LOAEL of 3 mg/kg bw per day (NOAEL=1 mg/kg bw per day; Lau et al., 2006), and was not observed at 3 mg/kg bw per day in another study (Albrecht et al., 2013). Mammary gland development effects might also be affected by strain sensitivity—the majority of the low-dose effects have only been observed in CD-1 mice exposed *in utero*, and other strains were typically only studied at higher doses and in peripubertal mice. A recent *in utero* study comparing MGD in both CD-1 and C57Bl/6 mice at doses of 0.01–1 mg/kg bw per day potentially provided support for low dose effects in a second strain of mice, albeit at slightly higher doses (LOAEL = 0.01 vs. 0.3 mg/kg bw per day in CD-1 and C57Bl/6 mice, respectively); however, a small sample size at low doses for C57Bl/6 mice (as few as two pups) might have precluded the observation of significant changes at similar doses to CD-1 mice. Finally, species sensitivity might be occurring for these effects, as one- and two-generation studies in rats identified similar effects only at much higher doses, if at all; the NOAELs for body weight changes and delayed sexual maturation in pups were around 3 mg/kg bw per day (Staples et al., 1984; Butenhoff et al., 2004b) and 10 mg/kg bw per day (Butenhoff et al., 2004b), respectively, and no effects on lactation index were observed up to 30 mg/kg bw per day (Butenhoff et al., 2004b). Further support for the potential for species sensitivity is provided in studies using PPARα-knockout mice, which were less sensitive to body weight changes and eye opening (Abbott et al., 2007) and MGD delays (Zhao et al., 2012); PPAR activation is more sensitive in mice than in other species, including rats and humans (Corton et al., 2014). Although the data from the studies described above provide indication of some reproductive and developmental effects at low doses, the data are not currently considered to be an appropriate basis for quantitative risk assessment; however, if further studies demonstrate consistency of these effects in other species or their relevance to humans, the endpoint could become a more appropriate basis for the PFOA evaluation.

Few epidemiological studies have investigated the developmental effects described above, which limits the ability to conclude on the relevance of these effects in humans. The human observations related to weight gain in adulthood after developmental PFOA exposures were increased odds of women being overweight and having increased biomarkers of adiposity at 20 years of age after *in utero* exposures (with maternal serum levels of 5.8 ng/mL, as compared with levels of 2.3 ng/mL) (Halldorsson et al., 2012). Estrogenic observations were limited to delayed puberty in girls, and slight associations between PFOA concentration and shorter duration of breastfeeding. As previously discussed, care should be taken before concluding on health effects based on these epidemiological studies. The nature of the observed associations between PFOA exposure and the developmental outcomes need to be investigated further because of the lack of consistency across studies, the non-specificity of the outcomes, the misunderstanding of the mechanism of action, the borderline significance and lack of strength and dose-response of many results, and the presence of various limitations inherent to the study design, such as the possibility of residual confounding, biases due to errors in outcome measurements, and chance.

Hepatic effects were observed at slightly higher levels than reproductive effects, but observations of changes were still made at PFOA doses of ≤0.3 mg/kg bw per day. Increased relative liver weight was observed at ≥0.1 mg/kg bw per day in prenatally-exposed mouse pups (Abbott et al., 2007; Macon et al., 2011) and at ≥0.15 mg/kg bw per day in adult mice (Kennedy, 1987; Loveless et al., 2006, 2008). Dose-related increases in incidence and severity of hepatocellular hypertrophy were observed at ≥0.3 mg/kg bw per day in rats (Perkins et al., 2004; Loveless et al., 2008) and mice (Loveless et al., 2008) exposed subchronically to PFOA. Although increases in hepatocellular hypertrophy and liver weight were observed at slightly lower levels in other studies, Perkins et al. (2004) was selected as a key study that was representative of the database for the endpoint. Hepatocellular hypertrophy was observed in male rats in the Perkins study at ≥0.64 mg/kg bw per day, which is on the same order of magnitude as the studies demonstrating LOAELs of 0.1–0.3 mg/kg bw per day. A major advantage presented by the Perkins study is that a NOAEL was observed (0.06 mg/kg bw per day), whereas the LOAELs in the majority of other low dose studies were the lowest administered doses. A similar NOAEL of 0.05 mg/kg bw per day can be obtained from Kennedy et al. (1987) when Health Canada (1994) assumptions for food intake and bodyweight in rats (Health Canada, 1994) are used, but the authors did not provide actual values of measured doses. A further advantage of the Perkins study over the other low-dose studies is that the study duration was longer, with exposure durations of up to 13 weeks; moreover, in addition to *ad libitum* controls, the study provided pair-fed controls to ensure that effects did not result from food consumption quantities. Finally, PPAR-α activity was measured in the Perkins study, and was only increased at ≥1.94 mg/kg bw per day; because this suggests that hepatocellular hypertrophy was not resulting from peroxisome proliferation, human relevance of this endpoint cannot be excluded. A NOAEL of 0.06 is also supported by the most conservative NOAEL for hepatic biochemical effects, which was estimated at 0.055 mg/kg bw per day in male rats demonstrating increased alkaline phosphatase levels in conjunction with increased liver weight (Kennedy et al., 1986), using default assumptions for bodyweight and inhalation rates (Health Canada, 1994), and linearly scaling from periodic to continuous exposure. The NOAEL is also approximately 10-fold lower than the NOAEL and 30-fold lower than the LOAEL for hepatic necrosis (0.56 and 1.72 mg/kg bw per day, respectively) observed in rats exposed for 90 days (Goldenthal et al., 1978a).

Although increased liver weight and hepatocellular hypertrophy can sometimes be considered effects that are adaptive rather than adverse in their own right, evidence of other histological effects in the liver at higher concentrations provide an indication of their progression upon continued exposure (ECETOC, 2002; Hall et al., 2012). An adverse histological effect

(portal mononuclear cell infiltrate) was observed in livers of male rats at the same dose where significant increases in hepatocellular hypertrophy were observed (14.2 mg/kg bw per day of PFOA for 2 years; Butenhoff et al., 2012b). Although this dose is much higher than the lowest points of departure for increased liver weight and hepatocellular hypertrophy observed in subchronic studies, the latter effects are proposed as critical effects for this assessment, as they might be sensitive indicators of the potential for the progression of adverse histological effects. Additional histological effects observed in rats in studies of shorter duration included necrosis at ≥1.72 mg/kg bw per day (Goldenthal et al., 1978a; Loveless et al., 2008), cytoplasmic vacuolation at ≥5 mg/kg bw per day (Cui et al., 2009), and fatty change, angiectasis, congestion, and acidophil lesion at 20 mg/kg bw per day (Cui et al., 2009). Therefore, increased liver weight and hepatocellular hypertrophy are considered in the dose–response assessment—despite their potential to be adaptive, rather than adverse, effects—as a means of preventing the more serious histological effects observed in other studies or at higher doses. The use of conservative endpoints for liver effects is also somewhat supported by epidemiology studies, in which some associations between PFOA exposure and increases in liver enzymes (including AST, ALT, and GGT) were observed; however, the associations between serum PFOA levels and liver effects cannot be used to draw definitive conclusions in humans because of limitations. These limitations include the lack of consistency and specificity of the outcomes, the weakness of the effects, and the study designs presenting many limitations (e.g., do not allow for verification of temporality). Serum levels at which these effects were observed in humans were on the order of 1,000 ng/mL in occupational studies and <10 ng/mL in environmental studies, which were lower than serum concentrations associated with the NOAEL and LOAEL for the 13-week Perkins study (7,100 and 41,000 ng/mL, respectively).

Changes in serum lipid levels were also observed around the levels at which hepatic effects occur. The lowest dose at which serum lipid changes were observed was 0.3 mg/kg bw per day in rats exposed for 14 days (decreased total cholesterol; Loveless et al., 2006) or 29 days (decreased total and HDL cholesterol; Loveless et al., 2008). Typical observed changes were decreases in total cholesterol, HDL, and triglycerides. These effects are important for consideration during the assessment of PFOA risks, as epidemiology studies generally demonstrated positive associations between PFOA and serum cholesterol levels. Inconsistencies in effect were observed not only in between the two databases, but also within both the toxicology (see Section 9.2.2.2) and epidemiology (see Section 9.1.2.2) databases. Clear dose–response relationships also tended to be absent in the animal studies. Due to these weaknesses, quantitative assessments were not performed for serum lipid effects; however, based on the present database, a TDI based on liver effects is assumed to be sufficiently protective of lipid changes.

To reflect the large interspecies differences in pharmacokinetics, a human-equivalent point-of-departure (POD_{HEQ}) was calculated for hepatocellular hypertrophy as follows:

$$POD_{HEQ} = \frac{0.06 \text{ mg/kg bw per day}}{96}$$

$$= 0.000625 \text{ mg/kg bw per day}$$

where:

- 0.06 mg/kg bw per day is the NOAEL for hepatocellular hypertrophy in rats from Perkins et al. (2004), which was selected to represent the hepatocellular hypertrophy and liver weight increase database; and

- 96 is the dose-specific AK_{UF} for rats in the 0.01 mg/kg bw per day range (as described in Section 8.6.2)

Using the calculated POD_{HEQ}, the non-cancer TDI was calculated as follows:

$$\text{TDI} = \frac{0.000625 \text{ mg/kg bw per day}}{25}$$

$$= 0.000025 \text{ mg/kg bw per day}$$

where:

- 0.000625 mg/kg bw per day is the POD_{HEQ} calculated for hepatocellular hypertrophy in rats, as described above; and
- 25 is the composite uncertainty factor, as described below

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (×2.5) and intraspecies uncertainty factor (×10). An interspecies uncertainty factor of 2.5 was used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. Likewise, a default value of 10 was applied for the intraspecies UF. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOA excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. Average half-life values calculated from longitudinal data for different populations previously exposed to PFOA were similar (averages for each population ranged from 2.3–3.8 years; Olsen et al., 2007; Bartell et al., 2010; Brede et al., 2011); however, studies providing ranges indicated that there was approximately a 10-fold difference between the lowest and highest estimates of half-life. If further studies of PFOA consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed. No UF for subchronic-to-chronic extrapolation was used, as liver effects were investigated in a chronic study (Butenhoff et al., 2012b), and increasing duration of exposure did not appear to worsen the effects in the key study (Perkins et al., 2004).

Using this TDI, the HBV for drinking water can be calculated as follows:

$$\text{HBV} = \frac{0.000025 \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= 0.00023 \text{ mg/L}$$

$$\approx 0.0002 \text{ mg/L (0.2 µg/L)}$$

where:

- 0.000025 mg/kg bw per day is the TDI derived above,;
- 70 kg is the average body weight of an adult;

- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7)

10.3 Comparison of cancer and non-cancer risk assessment

The HBV for the non-cancer assessment, which was 0.0002 mg/L for hepatocellular hypertrophy in rats, is more conservative than the HBV for Leydig cell tumours of 0.03 mg/L. The proposed HBV of 0.0002 mg/L that was derived for non-cancer effects is therefore considered to be sufficiently protective of the carcinogenic effects of PFOA.

10.4 International considerations

A memorandum published in 2009 by the U.S. EPA Office of Water indicates a Provisional Health Advisory (PHA) of 0.4 µg/L (0.0004 mg/L) for PFOA (U.S. EPA, 2009b). This PHA was derived from a $BMDL_{10}$ of 0.46 mg/kg bw per day for increased maternal liver weight at term in mice exposed to PFOA on GD 1–17 by gavage (Lau et al., 2006). This $BMDL_{10}$ is within the range of $BMDL_{10}$ values for increased liver weight in mice and rats (0.29–0.74 mg/kg bw per day) (EFSA, 2008, U.S. EPA, 2009b). An uncertainty factor of 2,430 (10 for intraspecies differences, 3 for interspecies toxicodynamic differences and 81 for interspecies toxicokinetic differences) was applied to the $BMDL_{10}$, resulting in a reference dose rounded at 200 ng/kg bw per day (0.2 µg/kg bw per day) (U.S. EPA, 2009b). This reference dose (RfD) was also indicated in a memorandum emitted in 2009 by the U.S. EPA Office of Solid Waste and Emergency Response (U.S. EPA, 2009c). Based on U.S. EPA policy, the PHA (0.4 µg/L; 0.0004 mg/L) was further derived for a 10-kg child consuming 1 L water per day using a default assumption that drinking water contributes 20% of total exposure to PFOA (U.S. EPA, 2009c).

The New Jersey Department of Environmental Protection derived a preliminary health-based guidance for PFOA in drinking water of 0.04 µg/L (0.00004 mg/L) from the NOAEL of 1.6 mg/kg bw per day obtained in rats exposed chronically (Sibinski, 1987). At the higher dose (16.1 mg/kg bw per day), decreases in body weight gain, hematocrit, erythrocyte counts and hemoglobin concentration were observed in female rats. Using pharmacokinetic modelling, it was determined that a dose of 1.6 mg/kg bw per day was equivalent to a mean serum PFOA concentration of 1,800 ng/mL in rats. An uncertainty factor of 100 for inter- and intraspecies variation was applied, resulting in a target maximum human serum PFOA concentration of 18 ng/mL. Using data from an epidemiology study (Emmett et al., 2006a), which noted that ingestion of PFOA in drinking water resulted in a blood PFOA concentration approximately 100 times greater than the water concentration, it was estimated that a water concentration of 0.18 ng/mL (0.18 µg/L or 0.00018 mg/L) would result in the target serum PFOA concentration. Using a default assumption that drinking water contributes 20% of total exposure to PFOA, the preliminary health-based guidance for PFOA in drinking water was set at 0.04 µg/L (State of New Jersey, undated).

The Minnesota Department of Health (MDH, 2008c, 2008d) derived a health risk limit (HRL) of 0.3 µg/L (0.0003 mg/L). This value was based on the increased liver weight observed in monkeys exposed to ≥ 3 mg/kg bw per day (Thomford, 2001a; Butenhoff et al., 2002). More precisely, the benchmark dose ($BMDL_{10}$) for these effects was estimated at 23,000 ng/mL PFOA in monkey serum. A human equivalent dose (HED) of 2,300 ng/kg bw per day (2.3 µg/kg bw per

day) was calculated based on the elimination of PFOA in humans (using human half-life data to estimate clearance). An uncertainty factor of 30 (10 for human variability and 3 for interspecies toxicodynamic differences) was applied to the HED, resulting in a reference dose of 77 ng/kg bw per day (0.077 µg/kg bw per day). Steady-state uptake/elimination was estimated to occur after 19 years of exposure, therefore a time-weighted 95th percentile intake for the first 19 years of life (0.053 L/kg bw per day) was used as the daily water ingestion. This, along with a relative source contribution of 20%, resulted in a HRL rounded at 0.3 µg/L (MDH, 2008c, 2008d).

A drinking water guideline of 10 µg/L (0.01 mg/L) was derived by the UK Health Protection Agency (UK HPA, 2007, 2009) based on a TDI of 3,000 ng/kg bw per day (3 µg/kg bw per day) previously derived by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (UK COT, 2006). This TDI was based on a POD of 0.3 mg/kg bw per day, corresponding to the lowest $BMDL_{10}$ for increased liver weights in rats exposed for 13 weeks (data from Palazzolo, 1993 and Perkins et al., 2004); this value was similar to the $BMDL_{10}$ (0.31 mg/kg bw per day) for hepatic necrosis in F0 and F1 male rats (data from Butenhoff et al., 2004b). An uncertainty factor of 100 (for intra- and inter-species variation) was applied. The drinking water guideline (10 µg/L) was derived from the TDI using an allocation factor of 50%, a body weight of 5 kg and a water ingestion rate of 0.75 L per day for bottle-fed infants (UK HPA, 2007).

In their scientific opinion document on contaminants in the food chain, the CONTAM panel under the European Food Safety Authority derived a TDI of 1,500 ng/kg bw per day (1.5 µg/kg bw per day) based on a $BMDL_{10}$ of 0.3 mg/kg bw per day in rats (EFSA, 2008). This value refers to the lowest $BMDL_{10}$ identified for effects on the liver (Palazzolo, 1993; Butenhoff et al., 2004b; Perkins et al., 2004) among those (0.3–0.7 mg/kg bw per day) derived from a number of studies in mice (Lau et al., 2006) and male rats (Sibinski, 1987; Palazzolo, 1993; Butenhoff et al., 2004b; Perkins et al., 2004). The $BMDL_{10}$ was divided by an uncertainty factor of 200 (10 for interspecies differences, 10 for intraspecies differences and 2 to compensate for uncertainties relating to the internal dose kinetics).

11.0 Rationale

PFOA is an anthropogenic compound used in the manufacture of stain/water-resistant coatings for various consumer products. Environmental concentrations, and therefore potential exposure levels, may be higher in areas near facilities using high amounts of PFOA and near locations with extinguished fires if PFOA-containing fire-fighting foams were used. Canadians can be exposed to PFOA in food, consumer products, dust, and drinking water. The major sources of PFOA are expected to be food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Based on its physico-chemical properties, exposure to PFOA via inhalation and dermal routes during showering or bathing is expected to be negligible.

Chronic exposure to PFOA has been associated with both cancer and non-cancer effects in animals and humans. HBVs for both endpoints have been calculated, with the non-cancer effects resulting in a lower, more conservative HBV.

Epidemiological studies have shown associations between exposure to PFOA and multiple non-cancer health outcomes, such as dysfunctions of the immunological system and alterations in birth weight and lipid levels. However, these studies cannot be used to derive the non-cancer HBV for PFOA due to limitations in terms of design, bias, confounding, and possibility of chance findings. In animals, non-cancer effects observed at the lowest levels of exposure include

reproductive and developmental effects, liver effects and changes in serum lipid levels. For various reasons described in section 10.2, the most appropriate endpoint to derive a HBV for PFOA is hepatocellular hypertrophy (liver effects) in rats, occurring at the same levels as the changes in serum lipid levels. Using a TDI approach, a HBV of 0.0002 mg/L (0.2 µg/L) has been calculated for the non-cancer effects of PFOA based on liver effects in rats. This HBV is considered to be sufficiently protective of both cancer and non-cancer effects of PFOA.

A MAC of 0.0002 mg/L (0.2 µg/L) is proposed for PFOA in drinking water. The proposed MAC for PFOA can be measured by available analytical methods and is achievable by municipal and residential treatment technologies. As part of its ongoing guideline review process, Health Canada will continue to monitor new research and recommend any change to the guideline that is deemed necessary.

12.0 References

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Appendix A: Reported full-scale drinking water treatment plant PFOS/PFOA removal data[1]

Water Source	Treatment Train[2]	Influent concentration (ng/L)	Effluent concentration (ng/L)	% Removal of PFOS	Reference
Groundwater	DBF, UV, Cl_2	10	9.4	6	Quinones and Snyder, 2009
Surface water	O_3, COA/FLOC, DBF, Cl_2	1.4	1.4	0	Quinones and Snyder, 2009
Surface water	PAC, CHLM, DBF	1.7	1.9	-12	Quinones and Snyder, 2009
Surface water	Cl_2, COA/FLOC, DBF, UV	22	22	0	Quinones and Snyder, 2009
Planned potable indirect reuse facility	MF/RO, UV/H_2O_2, SAT	41	ND	100	Quinones and Snyder, 2009
Planned potable indirect reuse facility	Cl_2, DL, SAT	29	57	-97	Quinones and Snyder, 2009
River water	RSF, O_3, GAC, Cl_2	1.0 (Summer)	0.93 (Summer)	7	Takagi et al., 2008
River water	RSF, O_3, GAC, Cl_2	0.87 (Summer) 3.2 (Winter)	2.8 (Summer) 1.6 (Winter)	-222 (summer) 5 (winter)	TakagiTakagi et al., 2008
River water	RSF, O_3, GAC, Cl_2				Takagi et al., 2008
Lake water	RSF, GAC, Cl_2	4.6 (Summer) 4.5 (Winter)	0.16 (Summer) <0.1 (Winter)	97 (summer) >98 (winter)	Takagi et al., 2008
River, lake, subsoil and groundwater (7 plants)	RSF, Cl_2	0.56 – 22 (Sum) 0.54 – 4.2 (Win)	0.45 – 22 (Sum) 0.37 – 4.5 (Win)	20 – 0 (summer) 31 – 0.7 (winter)	Takagi et al., 2008
River water	Membranes, Cl_2	0.37 (Summer) 0.26 (Winter)	0.29 (Summer) 0.20 (Winter)	22 (summer) 23 (winter)	Takagi et al., 2008
Lake water	SSF, Cl_2	2.7 (Summer) 1.8 (Winter)	2.3 (Summer) 1.9 (Winter)	15 (summer) -6 (winter)	Takagi et al., 2008
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.3 (Summer) 3.3 (Winter)	3.7 (Summer) 1.3 (Winter)	-185 (summer) 60 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.6 (Summer) 3.3 (Winter)	2.3 (Summer) 1.7 (Winter)	44 (summer) 48 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.2 (Summer) 2.8 (Winter)	1.6 (Summer) 1.9 (Winter)	-33 (summer) 32 (winter)	Takagi et al., 2011
River water	SED, O_3, GAC, Cl2, SF	1.4 (Summer) 3.3 (Winter)	2.2 (Summer) 2.0 (Winter)	-57 (summer) 39 (winter)	Takagi et al., 2011
Lake water	COA/FLOC/SED, SF, GAC (reactivated), Cl_2	4.4 (Summer) 4.1 (Winter)	<0.5 (Summer) <0.5 (Winter)	>89 (summer) >88 (winter)	Takagi et al., 2011
Ground water	UF, Cl_2	16	16	0	Atkinson et al., 2008
Ground water	GAC (not in operation), super chlorination and dechlorination	135	130	3	Atkinson et al., 2008
Ground water	GAC (2 parallel GAC trains each having 6 beds; contactors are mature and act as biological contactors; not been	42	45	-7	Atkinson et al., 2008

Water Source	Treatment Train[2]	Influent concentration (ng/L)	Effluent concentration (ng/L)	% Removal of PFOS	Reference
	regenerated for some years), Cl_2				
Ground and surface water (60:40)	SSF, O_3, GAC (6 beds-no regeneration for several years), Cl_2using NaOCl	20.6	25	-21	Atkinson et al., 2008
Ground water	Cl_2 using NaOCl				Atkinson et al., 2008
River water	COA/FLOC/SED, O3, GAC, RSF	5.3 (Aug) 5.8 (Oct)	9.4 (Aug) 6.4 (Oct)	-77 (Aug) -10 (Oct)	Shivakoti et al., 2010)
River water	COA/FLOC/SED, O3, GAC, RSF	5.8 (Aug) 8.8 (Oc)	3.9 (Aug) 4.2 (Oct)	33 (Aug) 53 (Oct)	Shivakoti et al., 2010)
Treated wastewater	De-nitrification, pre-O_3, COA/FLOC/SED, DAF, O_3, GAC (acts as biological contactor), O_3	2.2 (Oct) 3.7 (Nov) 3.6 (Nov)	<LOR (0.3 ng/l) (Oct) 0.6 (Nov) 0.7 (Nov)	100 (Oct) 84 (Nov) 81 (Nov)	Thompson et al., 2011b
River water	COA/FLOC/SED, RSF, Cl_2	5.02	0.73	85	Kunacheva et al., 2010)
Treated wastewater	Clarifier/lamellar settler ($FeCl_3$&$(NH_4)_2SO_4$, NaOCl addition), UF, RO, UV+H_2O_2, stabilization/disinfection (addition of lime, CO_2, NaOCl)	38 39 23	<LOR (0.5 ng/L) ND <LOR (0.2 ng/L	100 100 100	Thompson et al., 2011
River water	COA/FLOC, RSF, O_3, GAC, SSF	8.2	<0.23	<97	Eschauzer et al., 2012
River water	Cl_2, COA/FLOC, RSF, O_3, GAC	116	33	69	Flores et al., 2013
River water	Cl_2, COA/FLOC, RSF, O_3, GAC, UF, RO	86	13	86	Flores et al., 2013

[1]developed from Rahman et al. (2014) Table 3

[2] COA/FLOC/SED = coagulation/flocculation sedimentation; DAF = dissolved air flotation; GAC = granular activated carbon; RSF = rapid sand filtration; SSF = slow sand filtration; SF = sand filtration; NaOCl = sodium hyochlorite; Cl2 = chlorine; RO = reverse osmosis; UF = ultrafiltration; IX = ion exchange; SF = sand filtration; UV/H_2O_2= ultraviolet irradiation/hydrogen peroxide; SAT = soil aquifer treatment; CHLM = chloramines

Appendix B: List of Acronyms

AFFF	aqueous film-forming foam
ALT	alanine transaminase
APFO	ammonium perfluorooctanoate
BMD	benchmark dose
BMDL	lower confidence limit on the benchmark dose
$BMDL_{10}$	lower 95% confidence limit on the benchmark dose for a 10% response
BV	bed volume
CAS	Chemical Abstracts Service
CI	confidence interval
CSAF	chemical specific adjustment factor
DI	direct injection
DL	detection limit
EBCT	empty bed contact time
ESI	electrospray ionization
GAC	granular activated carbon
GD	gestational day
GM	geometric mean
HBV	health-based value
HPLC	high performance liquid chromatography
IT	ion-trap
LC	liquid chromatograph
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantitation
LCMRL	lowest concentration minimum reporting level
LLE	liquid-liquid extraction
MAC	maximum acceptable concentration
MDL	method detection limit
MGD	mammary gland development
MG/D	million gallons per day
MOA	mode of action
MRL	minimum reporting level
MS/MS	tandem mass spectrometry
NF	nanofiltration
NOAEL	no-observed-adverse-effect level
NOM	natural organic matter
PAC	powdered activated carbon
PBPK	Physiologically-based pharmacokinetic
PEFT	polytetrafluoroethylene
PFA	perfluoroalkyl
PFAA	perfluorinated alkyl acid
PFAS	perfluoroalkyl substance
PFCA	long-chain perfluorocarboxylic acids
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate

PND	postnatal day
POD	point of departure
POD_{HEQ}	human-equivalent points-of-departure
PTFE	polytetrafluoroethylene
RBF	river bank filtration
RO	reverse osmosis
SPE	solid phase extraction
TDI	tolerable daily intake
TDS	total diet study
UCMR3	third Unregulated Contaminant Monitoring Rule
WAX	weak anion exchange

Appendix C: Provincial/territorial cost estimates

Prince Edward Island

Newfoundland and Labrador

Nova Scotia

New Brunswick

Quebec

Ontario

Manitoba

Saskatchewan

Alberta

British Columbia

Yukon

Northwest Territories

Nunavut

Fishwick, David HLTH:EX

From: Anne Vezina <anne.vezina@hc-sc.gc.ca>
Sent: October 9, 2015 11:16 AM
To: POLEGAAR@gov.ns.ca; Caroline.Robert@mddelcc.gouv.qc.ca; Fishwick, David HLTH:EX; donald.reid@gov.ab.ca; Peter_Workman@gov.nt.ca; ghsomers@gov.pe.ca; hkhan@gov.nl.ca; Kevin.Gould@gnb.ca; Kim.Philip@gov.mb.ca; pat.brooks@gov.yk.ca; sam.ferris@wsask.ca; Satish.Deshpande@ene.gov.on.ca; MLeBlanc-Havard@GOV.NU.CA
Cc: WQHB@hc-sc.gc.ca; kristina.taracha@hc-sc.gc.ca; Rocio Aranda-Rodriguez; Anca-Maria Tugulea; doug.spry@ec.gc.ca; Gary.OToole@gov.ns.ca; philippa.cureton@ec.gc.ca
Subject: Information package - upcoming CDW meeting
Attachments: Cdw2015-11 (agenda package) 2015-1009.pdf

CDW members and secretariat,

Please find attached the information package for the upcoming CDW meeting. The draft guideline technical document on manganese **has not been professionally edited** so please focus on the content as opposed to editing related comments when you review the document.
(See attached file: Cdw2015-11 (agenda package) 2015-1009.pdf)

We will be sending the remaining documents prior to the meeting, starting next week with PFOS and PFOA.
Our apologies for sending you these documents less than 4 weeks prior to the meeting - we are doing the best we can.

Have a great weekend and
Happy Thanksgiving!
Anne

Anne Vézina
Coordinator of the F/P/T Committee on Drinking Water
Coordonatrice du Comité F/P/T sur l'eau potable
Water and Air Quality Bureau
Bureau de la qualité de l'eau et de l'air
Safe Environments Directorate
Direction de la sécurité des milieux
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Health Canada
Santé Canada

Healthy Environments and Consumer Safety Branch
Direction générale, Santé environnementale et sécurité des consommateurs

Your file Votre référence

Our file Notre référence

Federal-Provincial-Territorial Committee on Drinking Water Technical Secretariat
269 Laurier Avenue West (Locator 4903 D)
OTTAWA, Ontario K1A 0K9

Secrétariat technique du Comité fédéral-provincial-territorial sur l'eau potable
269 ave Laurier ouest (indice d'adresse 4903 D)
Ottawa (Ontario) K1A 0K9

October 9th, 2015

le 9 octobre 2015

DISTRIBUTION

DISTRIBUTION

FEDERAL-PROVINCIAL-TERRITORIAL COMMITTEE ON DRINKING WATER

Enclosed you will find information for the next meeting of the Federal-Provincial-Territorial Committee on Drinking Water (CDW).

CDW meeting will be held November 4, 5 and 6, 2015 at 269 Laurier Ave W., Ottawa, Ontario. The meeting will be held in room 7-086 and will start at 9 am on each day.

If you have any questions, please contact me at (613) 957-3130.

COMITÉ FÉDÉRAL-PROVINCIAL-TERRITORIAL SUR L'EAU POTABLE

Vous trouverez ci-inclus de l'information concernant la prochaine réunion du Comité fédéral-provincial-territorial sur l'eau potable (CEP).

La réunion du CEP aura lieu les 4, 5 et 6 novembre 2015, au 269 ave Laurier O., Ottawa, Ontario. La réunion se déroulera dans la salle 7-086 et débutera à 9 h à chaque jour.

Pour de plus amples renseignements, veuillez communiquer avec moi au (613) 957-3130.

Anne Vézina
Committee Coordinator / Coordonnatrice du comité

Canada

Federal Provincial Territorial Committee on Drinking Water

Fifty-sixth Meeting
November 4, 5 & 6, 2015
Ottawa, ON

AGENDA PACKAGE

Federal Provincial Territorial Committee on Drinking Water
Fifty-sixth meeting –November 4, 5 & 6, 2015
Ottawa, ON
AGENDA PACKAGE

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1-A Opening

Reference/Action:

- Introduce CDW Members and Observers
- Attached, October 2015 CDW Membership List
- Members to update the membership list

Notes:

CDW MEMBERSHIP LIST - LISTE DES MEMBRES DU CEP

VOTING MEMBERS – MEMBRES VOTANTS

Jurisdiction Compétence	**Member & Affiliation** Membre & Affiliation	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* / NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Newfoundland and Labrador / Terre-Neuve et Labrador	Mr. Haseen Khan, P. Eng., Director, Water Resources Management Division Department of Environment and Conservation	P.O. Box 8700 St. John's, NL A1B 4J6	Phone: 709 729-2563 Fax: 709 729-0320	Emergencies: 709 729-3703 / 709 772-2083 NEEC: 709 772-7745	Email: hkhan@gov.nl.ca Website: www.gov.nl.ca/env/water
Prince Edward Island / Île-du-Prince-Édouard	Mr. George Somers, Manager Drinking Water and Wastewater Management Environment Division Department of Environment, Labour and Justice	11 Kent Street, 4th Floor P.O. Box 2000 Charlottetown, PEI C1A 7N8	Phone: 902 368-5046 Fax: 902 368-5830	Emergencies: 902 426-6030 NEEC: 902 426-6200	Email: ghsomers@gov.pe.ca Website: www.gov.pe.ca/infopei/Environment_and_Land/Water_Resources/Drinking_Water/
New Brunswick / Nouveau-Brunswick	Mr. Kevin Gould, P.Eng Public Health Engineer Office of the Chief Medical Officer of Health Healthy Environments Branch New Brunswick Department of Health	520 King Street, 2nd Floor, HSBC Place Fredericton, NB E3B 5G8	Phone: 506 444-4096 Fax: 506 453-8702	Emergencies: 506 453-2133 NEEC: 902 426-6200	Email: kevin.gould@gnb.ca Website: http://www.gnb.ca/health
Nova Scotia / Nouvelle-Écosse	Ms. Angelina Polegato, Supervisor Drinking Water Management Unit, Science Division Nova Scotia Environment	1894 Barrington Street, Suite 1800 P. O. Box 442 Halifax, NS B3J 2P8	Phone: 902 424-1583 Fax: 902 424-0501	Emergencies: 902 426-6030 NEEC: 902 426-6200	Email: angelina.polegato@novascotia.ca Website: http://www.gov.ns.ca/nse/water/drinking.water.asp
Quebec / Québec	Ms. Caroline Robert (Vice-Chair) Chef de la division de l'eau potable Direction des eaux municipales Ministère du Développement durable, de l'Environnement et de la Lutte aux Changements Climatiques	Édifice Marie Guyart, 8e Étage 675 blvd René-Lévesque Est Québec, QC G1R 5V7	Phone : 418 521-3885 (ext 4938) Fax : 418 644-2003	Emergencies: 866 694-5454 / 418 643-4595 NEEC: 866 283-2333 / 418 317-0513	Email: caroline.robert@mddelcc.gouv.qc.ca Website: www.mddelcc.gouv.qc.ca/eau/potable/

Jurisdiction Compétence	**Member & Affiliation** Membre & Affiliation	**Address** Adresse	**Phone / FAX /** Téléphone / Télécopieur	**Emergencies* / NEEC** (24hr)** Urgences* / CNUE (24 hres)	**Email / Website** Courriel / Site Web
Ontario	Mr. Satish Deshpande, Team Leader, Water Standards Section Standards Development Branch, Ministry of the Environment	40 St. Clair Ave W, 9th Floor Toronto, ON M4V 1M2	Phone: 416-327-4689 Fax: 416-327-2936	Emergencies: 800 268-6060 NEEC: 416 994-2126	Email: Satish.Deshpande@ontario.ca Website: www.ene.gov.on.ca/water.htm
Manitoba	Ms. Kim Philip, Director Office of Drinking Water Manitoba Conservation and Water Stewardship	1007 Century Street Winnipeg, MB R3H 0W4	Phone: 204 945-7010 Fax: 204 945-1365	Emergencies: 204 944-4888 NEEC: 819 997-3742	Email: Kim.Philip@gov.mb.ca Website: www.manitoba.ca/drinkingwater/
Saskatchewan	Mr. Sam Ferris (Chairperson) Executive Director Environmental & Municipal Management Services Division Saskatchewan Water Security Agency	420, 2365 Albert Street Regina, SK S4P 4K1	Phone: 306 787-6193 Fax: 306 787-0197	Emergencies: 800 667-7525 NEEC: 306 536-9991	Email: sam.ferris@wsask.ca Website: www.saskh2o.ca/browser.htm
Alberta	Dr. Donald Reid Drinking-water Quality Regulator Drinking-water and Wastewater Section Provincial Programs Branch Operations Division, Environment and Sustainable Resource Development Alberta Environment	1504, 15th Floor, 9820-106 Street Edmonton, AB T5K 2J6	Phone: 780 644-8061 Fax : 780 422-4086	Emergencies: 800 222-6514 NEEC: 780 977-1559	Email: donald.reid@gov.ab.ca Website: www.environment.gov.ab.ca
British Columbia / Colombie Britannique	Mr. David Fishwick Drinking Water Manager, Ministry of Health Province of British Columbia	4-2, 1515 Blanshard Street Victoria, BC V8W 3C8	Phone: 250 952-1110 Fax: 250 952-1713	Emergencies: 800 663-3456 NEEC: 604 666-6100	Email: david.fishwick@gov.bc.ca Website: www2.gov.bc.ca/
Yukon	Ms. Patricia Brooks, Drinking Water Program Coordinator Health and Social Services, Environmental Health Services Government of Yukon	2 Hospital Road Whitehorse, YT Y1A 3H8	Phone: 867 667-8351 Fax: 867 667-8322	Emergencies: 867 667-7244 NEEC: 867 667-7244	Email: pat.brooks@gov.yk.ca
Northwest Territories / Territoires du Nord-Ouest	Mr. Peter Workman, Chief Environmental Health Officer Department of Health & Social Services Government of the Northwest Territories	102-5204, 50th Ave P.O. Box 1320 Yellowknife, NT. X1A 2L9	Phone: 867 873-2183 Fax: 867 669-7517	Emergencies: 867 920-8130 NEEC: 867 920-8130	Email: peter_workman@gov.nt.ca Website: www.hss.gov.nt.ca

Jurisdiction Compétence	Member & Affiliation Membre & Affiliation	Address Adresse	Phone / FAX / Téléphone / Télécopieur	Emergencies* / NEEC** (24hr) Urgences* / CNUE (24 hres)	Email / Website Courriel / Site Web
Nunavut	Ms. Michele LeBlanc-Havard, Environmental Health Specialist Department of Health Government of Nunavut	Box 1000 Station 1000; 1107 Sivummut Bldg. Iqaluit, NU X0A 0H0	Phone: 867 975-5943 Fax: 867 975-5755	Emergencies: 867 222-0256 NEEC: 867 222-0256	Email: mleblanc-havard@gov.nu.ca Website: www.gov.nu.ca
Canada	Dr. John Cooper, Director Water & Air Quality Bureau Safe Environments Directorate Healthy Environments & Consumer Safety Branch, Health Canada	269 Laurier Ave West A.L. 4903D Ottawa, ON K1A 0K9	Phone: 613 948-2568 Fax: 613 952-2574	Emergencies: 613 954-6651	Email: john.cooper@hc-sc.gc.ca Website: http://www.hc-sc.gc.ca/ewh-semt/water-eau/index_e.htm

**Telephone number for emergencies ONLY that may impact drinking water quality (e.g., toxic chemical spill into source water). Numéro de téléphone à utiliser SEULEMENT pour les urgences pouvant avoir des répercussions sur la qualité de l'eau potable (p.ex. déversement de substances toxiques dans une eau d'approvisionnement).*
*** NEEC - Environment Canada's National Environmental Emergencies Centre. CNUE – Centre National des Urgences Environnementales.*

CDW LIAISONS MEMBERS – MEMBRES LIAISONS DU CEP

Liaison	Member & Affiliation	Address Adresse	Phone / FAX / Téléphone / Télécopieur	Emergencies* /NEEC** (24hr) Urgences* / CNUE (24 hres)	Email / Website Courriel / Site Web
Environment Canada Environnement Canada	Dr. Doug Spry, Manager Science & Risk Assessment Directorate Emerging Priorities Division National Guidelines and Standards Office Environment Canada	9th Floor Fontaine Building 200 Sacre-Coeur blvd, Gatineau, QC K1A 0H3	Phone: 819 938-3359 Fax: 819 994-3120	NEEC: 819 997-3742	Email: doug.spry@ec.gc.ca
CHE Committee Comité CSE	Mr. Gary O'Toole, Director, Environmental Health Nova Scotia Health and Wellness	PO Box 488, 1894 Barrington Street Halifax, NS B3J 2R8	Phone: 902 424-1262 Fax: 902 424-4716	N/A	Email: Gary.otoole@gov.ns.ca

Liaison	Member & Affiliation	Address Adresse	Phone / FAX / Téléphone / Télécopieur	Emergencies* /NEEC** (24hr) Urgences* / CNUE (24 hres)	Email / Website Courriel / Site Web
FNIHB (HC) DGSPNI (SC)	Ms. G. Kristina Taracha, Manager Public Health Engineering Section Environmental Public Health Division Drinking Water Safety Program Interprofessional Advisory Program Support Directorate First Nations and Inuit Health Branch, Health Canada	Jeanne-Mance Building, A.L. 1979D Tunney's Pasture Ottawa, ON K1A 0K9	Phone: 613 941-5750 Fax: 613 952-8639	N/A	Email: kristina.taracha@hc-sc.gc.ca
RPB (HC) BRP (SC)	Dr. Jing Chen Radiation Health Assessment Division Radiation Protection Bureau Healthy Environmental & Consumer Safety Branch Health Canada	2720 Riverside drive, 4th floor A.L. 6604C Ottawa, ON K1A 0K9	Phone: 613 941-5191 Fax: 613 960-5604	N/A	Email: jing.chen@hc-sc.gc.ca
HPFB (HC) DGPSA (SC)	Diane Fournier, Senior Advisor Food Regulatory Program Food Directorate Health Products and Food Branch Health Canada	Banting Building A.L. 2203B Tunney's Pasture Ottawa ON K1A 0K9	Phone: 613 957-1751 Fax : 613 941-6625	N/A	Email: diane.fournier@hc-sc.gc.ca
EHSRB (HC) BSRSE (SC)	Dr. Rocio Aranda-Rodriguez Exposure and Biomonitoring Division Environemental Health Science and Research Bureau Healthy Environments and Consumer Safety Branch Health Canada	Environmental Health Centre Room B-5 Tunney's Pasture Ottawa ON K1A 0K9	Phone: 613 941-5423 Fax: 613 946-3573	N/A	Email: rocio.aranda-rodriguez@hc-sc.gc.ca

TECHNICAL SECRETARIAT ADDRESS / ADRESSE DU SECRÉTARIAT TECHNIQUE

Health Canada
Santé Canada
Water & Air Quality Bureau, Safe Environments Directorate
Bureau de la qualité de l'eau et de l'air, Direction de la sécurité des milieux
Healthy Environments & Consumer Safety Branch, Health Canada
Santé environnementale et sécurité des consommateurs
269 Laurier Avenue West ave Laurier Ouest (A.L / I.A. 4903D)
Ottawa, ON K1A 0K9
Emergencies / Urgences (24hr): 613 954-6651
Email / Courriel : water_eau@hc-sc.gc.ca
FAX / Télécopieur #: 613 952-2574

TECHNICAL SECRETARIAT MEMBERS / MEMBRES DU SECRÉTARIAT TECHNIQUE

Secretariat member / Membre du secrétariat	Phone / Téléphone	Email / Courriel (@hc-sc.gc.ca)
Ms. Véronique Morisset, Manager, Water Quality Program Division Mme Véronique Morisset, Gestionnaire, Division du programme de la qualité de l'eau	613 957-1506	veronique.morisset
Ms. France Lemieux, Head, Materials & Treatment Mme France Lemieux, Chef, Matériaux et traitement	613 941-3166	france.lemieux
Ms. Michèle Giddings, Manager, Water Quality and Science Division Mme Michèle Giddings, Gestionnaire, Division Qualité de l'eau et de la science	613 952-2594	michele.giddings
Ms Stéphanie McFadyen, Head, Microbiological Assessment M. Stéphanie McFadyen, Chef, Évaluation microbiologique	613 948-2416	stephanie.mcfadyen
Mr. Richard Carrier, Head, Chemical Assessment M. Richard Carrier, Chef, Évaluation chimique	613 946-7266	richard.carrier
Ms. Anne Vezina, CDW Coordinator Ms. Anne Vézina, Coordonatrice CEP	613 957-3130	anne.vezina

2- Agenda/Minutes

2-A Adoption of Agenda

Reference/Action:

- Tentative meeting agenda
- Attached, schedule for tentative meeting agenda
- CDW to approve agenda

Notes:

Draft Agenda

FPT Committee on Drinking Water - November 2015 (269 Laurier West, Ottawa, Ontario)			
	Wednesday November 4th, 2015	**Thursday November 5th, 2015**	**Friday November 6th, 2015**
9:00 am	1-A Opening 2-A Adoption of agenda 2-B Approval of minutes 2-C CDW status/checklist 2-D CDW priority list/old guidelines	4-C PFOS, PFOA and chemical specific adjustment factors 4-D Chromium	6-C FNIHB report 6-D WHO report 6-E CHE report 6-F CCME report 7-A Member's reports
10:30 am	Break	Break	Break
11:00 am	3-A Protozoa 3-B Viruses 3-C Other microbiological (QMRA, *enterococcus*, etc.) 5-A PHAC project on waterborne disease	4-E B(a)P 4-F Uranium 4-G Strontium	5-I Safe Drinking Water for First Nations Act 8-A Future meetings
12:00 am	Lunch	Lunch	End of meeting
1:00 pm	5-B Antimicrobial resistance 4-A Manganese	4-H Copper 4-I TOC 5-E Update on CNPHI tools	
2:30 pm	Break	Break	
2:45 pm	5-C Certification and standards 6-A CRCP/CACP report 6-B Certification body reports 4-B Lead 5-D National drinking water conference	4-J Microcystins 4-K Other chemical/radiological (2,4-D, atrazine, etc) 5-F Hydraulic fracturing 5-G Criteria for sampling list of pharmaceuticals for the next NDWS 5-H GRC conference on DBPs update	
5:00 pm	End of meeting	End of meeting	
NB: Meeting will be held in room 7-086 and will run from 9:00 AM to Noon and from 1:00 PM to 5:00PM (ending at noon on Friday). The social dinner will be held on Wednesday.			

2- Agenda/Meeting

2-B Approval of Minutes

Reference/Action:

- Attached, draft May 2015 meeting minutes
- CDW to approve the minutes

Notes:

Federal-Provincial-Territorial Committee on Drinking Water

Fifty-sixth Meeting
May6-7, 2015
Ottawa, ON

Draft Minutes

Draft minutes prepared by J. A. MacDonald, May2015
Draft minutes revised by A. Vézina and V. Morisset, June 2015
Minutes finalized, ? 2015

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FEDERAL-PROVINCIAL-TERRITORIAL COMMITTEE ON DRINKING WATER – 56th MEETING

May 6-7, 2015
Ottawa, Ontario

Members Present

Mr. S. Ferris, Saskatchewan - Chair
Ms. C. Robert, Quebec - Vice Chair
Dr. J. Cooper, Health Canada
Mr. P. Workman, Northwest Territories
Mr. D. Fishwick, British Columbia
Ms. K. Philip, Manitoba
Mr. K. Gould, New Brunswick
Mr. H. Khan, Newfoundland and Labrador
Ms. P. Cureton, Environment Canada
Ms. M. Leblanc-Havard, Nunavut
Dr. D. Reid, Alberta
Dr. S. Deshpande, Ontario
Mr. G. Somers, Prince Edward Island
Ms. A. Polegato, Nova Scotia
Mr. G.O'Toole, CHE Liaison (phone)
Ms. P. Brooks, Yukon

Secretariat

Mr. R. Carrier, Health Canada
Ms. F. Lemieux, Health Canada
Ms. V. Morisset, Health Canada
Ms. A. Bevan, Health Canada (FNIHB)
Ms. A. Vézina, Health Canada (Coordinator)
Ms. J. MacDonald, Health Canada (Reporter)
Ms. M. Giddings, Health Canada
Ms. S. McFadyen, Health Canada
Dr. A-M.Tugulea, Health Canada
Dr. R-A. Rodriguez, Health Canada
Water Quality Staff, Health Canada

Observers

Dr. Anna Majury, Public Health Ontario
Laura Gibson, Public Health Ontario
Ms. J. MacKinnon (AANDC)
Mr. J. Lafontaine, Health Canada (FNIHB)

1 Opening

The Chair called the 56th meeting to order and welcomed everyone to Ottawa. Members, alternates and observers introduced themselves. The Coordinator noted that the membership list is circulating and asked members to update their information. The Coordinator reviewed administrative details.

Decision/Action:

- **Members to update the membership list.**

2 Agenda/Meeting

2-A Adoption of agenda

The meeting agenda was reviewed and approved.

Decision/Action:

- **Members approved the meeting agenda.**

2-B Approval of minutes

The meeting minutes were discussed. D. Fishwick noted that under the British Columbia report, the "University of Victoria" should be changed to "Sustainable Infrastructure Society". K. Philip provided changes for the Manitoba report. Members approved the minutes as revised.

Decision/Action:

- **Members approved the minutes as revised.**

2-C CDW Status/ROD/Checklist

The Coordinator reviewed the status of documents and highlighted guidelines that have been recently published. Guidelines that are expected to be presented to CDW in November 2015 and May 2016 were highlighted. C. Robert asked for an update on the appendix that was to be developed for the boil water advisory guideline. V. Morisset indicated that the appendix was being prepared. The Coordinator presented the guideline approval spreadsheet and the guideline status file. A summary of CHE approvals was also presented. The Coordinator asked members to stay in touch with their CHE representatives so they are aware of documents that require approval. K. Gould asked for clarification on the New Brunswick information. A. Vézina explained the process and noted that CHE members should respond to emails from V. Marshall to approve guideline documents. The Coordinator summarized the priority list and noted it is on the agenda for discussion. The Coordinator noted that the checklist summarizing the status of meeting action items is included in the meeting material.

Decision/Action:

- **Secretariat to circulate the appendix for the boil water advisory guideline.**

2-D Priority list

V. Morisset distributed a table which lists all guidelines that have been developed by the Committee over the past 40 years and are still on the books and explained that the legend notes which parameters are being worked on, which are on the priority list and which are inactive. A process is being initiated to determine whether older guidelines should be withdrawn or updated to include them in priority lists. A data request will be made to assess exposure as part of the process. The Coordinator asked if jurisdictions would like one data request for all parameters or several requests. Members preferred to receive one data request for all parameters. M. Giddings gave a presentation on the pesticides that are part of the review. Although some pesticides were re-affirmed in 2005, consideration is being given to withdrawing a number of guidelines. Health

Canada is working with PMRA and has requested any exposure data they may have. J. Cooper and S. Ferris noted that caution is required for those pesticides that have just been de-registered as it can take time to use up inventory. S. Ferris asked about environmental fate. M. Giddings indicated that Health Canada is working with PMRA to determine if compounds are found in source water. C. Robert noted that when Quebec considered metholachlor, they found s-metholachlor was still in use; she asked that associated compounds also be considered as part of the process. S. Deshpande noted that confidence in the guideline limit is low for older guidelines. He also noted that some of the older guidelines may have some use as landfills are starting to leak. However, he recognizes that a drinking water guidance value could be developed for that purpose. P. Brooks noted that the Yukon is unlikely to have data for regulated drinking water systems but some environmental monitoring may be available. She asked if this data should be provided as part of the request. V. Morisset indicated that this data would be useful. S. Ferris asked when the data request would be made and would it be for individual pesticides. It was agreed that one data request will be made for specific pesticides. It was agreed that two months was adequate to provide the data.

Decision/Action:

- **Secretariat to send the data request to members for exposure levels of requested pesticides and other chemicals.**

3 Parameters: Microbiological

3-A *Enterococcus*

G. Yasvinski gave a presentation on the possible paths forward for *enterococcus*.A discussion ensued on whether a guideline or guidance document should be prepared. D. Reid noted that there is a strong support for an*enterococcus*guideline in Alberta; it would support the recreational water guideline and is considered a better indicator for groundwater. K. Gould asked for clarification of the presented results; G. Yasvinski provided additional information. K. Philip noted that Manitoba is neutral. P. Workman noted that the Northwest Territories is neutral. P. Brooks noted that Yukon doesn't have a strong opinion as routine monitoring for *enterococcus*wouldn't be implemented. K. Gould indicated that New Brunswick labs are not currently offering the test. K. Gould asked D. Reid why there is support in Alberta. D. Reid indicated that *enterococcus*would not replace *E. coli* but rather both would be required and labs that offer recreational water tests will be ramping up for *enterococcus*. A discussion ensued on whether *enterococcus*is a more appropriate indicator for groundwater. G. Yasvinski indicated that *enterococcus*may be detected in groundwater when *E. coli* is not. D. Fishwick indicated that he viewed *enterococcus* as another tool – you can use it if you want. C. Robert indicated that Quebec is testing for and detecting*enterococcus*in groundwater. S. McFadyen noted that the report prepared for the Committee indicated that the more indicators you have for groundwater, the better; *enterococcus* is not necessarily better than *E. coli* – it is an additional tool as noted by D. Fishwick. She noted that the Secretariat is looking for clear direction from the Committee on what form the document should take. H. Khan indicated that Newfoundland and Labrador is neutral as changes won't be made to their regulatory framework. A discussion ensued on the cost of the test. G. Somers indicated that it's not a question of whether the indicator is useful but whether it should be a guideline or guidance document. M. Leblanc-Havard indicated Nunavut is neutral due to the lack of groundwater supplies. The Committee agreed that an *enterococcus* guideline should be developed. S. Deshpande noted that some questions that should be addressed in the document include: what do the results mean, when should one be monitoring *enterococcus*, what is rationale for using *enterococcus*, what other suite of organisms could be

considered. G.Yasvinski noted that *enterococcus*is a fecal indicator but not a lot of data exists; it is discussed in some literature related to distribution system. A discussion ensued on whether UK data would be useful. D. Reid noted that *enterococcus* has been an EU requirement since 1998. G. Yasvinski will begin to pull information together. D. Reid indicated that the data from Quebec and from Foodnet may be useful.

Decision/Action:

- **Members approved moving forward with a guideline technical document for *enterococcus*.**

3-B Total coliforms

G. Yasvinski gave a presentation on the possible paths forward for total coliforms. A discussion ensued on the options – a guideline document with a maximum acceptable concentration (MAC), a guideline document without a MAC or a guidance document. A. Polegato indicated that Nova Scotia requires a guideline document with a MAC for its regulatory framework. D. Fishwick asked for more information on the guideline without a MAC option. G. Yasvinski indicated the information would be the same but it would be a goal instead of a MAC. K. Philip noted it is similar to turbidity which is not necessarily a health parameter; she indicated Manitoba prefers a guideline document with a MAC. P. Brooks noted some challenges she had with turbidity in the Yukon and would prefer a guideline document with a MAC for total coliforms. S. Deshpande indicated that he consulted with his engineering and health groups, and that they noted that total coliforms are system-related; he indicated that Ontario prefers a guideline document with a MAC. F. Lemieux noted that if there is no MAC, it would become an operational guideline that can be implemented as required by the jurisdiction. D. Reid indicated that even if there is no MAC, the presence of total coliforms would still trigger an investigation; he indicated that if there are few samples taken, monitoring for total coliforms becomes a false crutch that people rely on. K. Gould indicated that New Brunswick is supportive of removal of the MAC from the guideline document since it is not a health-based value. However, K.Gould noted that NB is flexible on whatever decision is made by CDW provided that the technical advice remains in the document and that the document remains part of the regularly reviewed micro documents. K. Gould said he understands the points made by S. Deshpande. S. Deshpande noted that for small systems, reporting the presence of total coliforms ensures adequate oversight. S. Ferris agreed that if there is no MAC, attention to small systems may diminish. S. Ferris asked A. Polegato for more detail on Nova Scotia requirements. A. Polegato noted that the MAC triggers follow-up. G. Somers noted that his health colleagues are concerned with the absence of a MAC. P. Workman noted that the Northwest Territories can support a guideline document with a MAC. G. Somers indicated that it would be helpful to remove the percent of samples for the systems that need follow-up, however D. Reid noted that Alberta would have concerns if the percent of samples is removed. G. Yasvinski indicated that most likely a "change in water quality" approach will be used. D. Reid noted that if there aren't enough samples taken, a "change in water quality" may not be appropriate. G. Somers noted that total coliforms remains the best tool at the moment regardless of the number of samples. F. Lemieux asked if D. Reid was suggesting a minimum number of samples. D. Reid indicated yes, but for larger systems. S. McFadyen indicated that the comments raised by the Committee will be considered in the next review. The Secretariat will look at what is necessary to generate reliable monitoring information versus what we can be reasonably achieved.

Decision/Action:

- **Members approved moving forward with a guideline technical document for total coliforms with a MAC.**

3-C Other microbiological (QMRA, viruses, protozoa, etc.)

S. McFadyen re-iterated the timelines for the protozoa document (November 2015) and virus document (May 2016). The project to update the QMRA model (with the Water Research Foundation) is progressing; a revised model will be available this spring and project reports will be available this fall. A manuscript has been submitted for publication for the PHAC project with Dr. K. Pintar regarding the burden of acute gastrointestinal disease attributable to drinking water. The anti-microbial resistance report should be circulated later this Fall. The recreational water guideline will require updating to reflect the new microcystin toxins information. Other topics that staff is monitoring include: premise plumbing and opportunistic pathogens, *N. fowleri*, ebola, prions, non-polio enteric viruses. Staff is also working with the treatment group on rainwater harvesting work, and is keeping track of reclaimed water quality issues. D. Fishwick asked about metagenomic testing. S. McFadyen noted that this is another project that staff is involved with. K. Gould requested the update in an email.

Decision/Action:

- **For information.**

4 Parameters: Chemicals under Assessment

4-A Lead

F. Lemieux and A. Vézina gave a presentation on the lead document. D. Reid noted that Alberta supports approving the document for public consultation but will be providing comments during the process on the need for the use of hot acid digestion for sample analysis. A discussion ensued on how to explain the risk associated with lead. A. Vézina indicated that the health impact (drop in IQ) was considered on a population health basis. It was agreed that a graph would help explain the risk assessment. K. Philip asked if there are any recommendations on the number of homes that should be monitored. F. Lemieux indicated that there aren't specific recommendations. K. Philip asked about percentages. F. Lemieux indicated it should be based on the utility's sampling plan. K. Philip noted that sampling is necessary at the tap for lead and guidance would be helpful. K.Gould noted that he is unclear how the MAC will be enforced. It will have huge infrastructure cost implications. He re-iterated that to be in compliance with this guideline requires sampling in homes which is not currently done in New Brunswick – utilities sample in the distribution system. F. Lemieux indicated this would not be representative of the risk to the population. D. Fishwick noted that the document indicated that every tap in every school should be sampled every year. F. Lemieux indicated that the intent is to sample every tap where children are drinking. S. Ferris asked if members would approve the document for public consultation subject to the following changes: Include a graphical representation of risk, and clarify that taps in schools where children drink are to be sampled. A. Vézina noted that a graph would be included only if an appropriate one is published in the literature. Members approved this path forward. C. Robert noted that Quebec is supportive of lowering the value but expects a large impact to implement; she asked if impact statements are to be included. It was agreed that jurisdictions should provide impact statements. C. Robert asked if NSF will lower the standard for residential treatment units to 5.0. F. Lemieux responded in the affirmative and indicated that some units are already capable of meeting 5.0.

Decision/Action:

- **Members approved the document in principle for public consultation, subject to the above noted changes being made.**
- **Members to submit impact statements.**

4-B Manganese

J. MacAulay, A. Cherry and S.J. Payne gave a presentation. D. Reid asked for clarification regarding the form of manganese used in the health studies. J. MacAulay noted that manganese is never found on its own and solubility is high so it quickly disassociates. D. Reid asked if epigenetic effects are being considered. J. MacAulay indicated that she looked for papers on this topic following the last meeting and found little information. D. Reid offered to forward several references to A. Vézina for consideration. D. Reid asked for more information on the speciation of manganese. A. Cherry indicated that identifying total, dissolved and colloidal fractions would be useful to inform treatment strategies but not for MAC interpretation; this will be made clear in the document. K. Gould asked for confirmation that the MAC will be for total manganese. S. Deshpande asked if there is any indication what the limit will be. J. MacAulay indicated that the screening value that was prepared was 100 µg/L but the MAC maybe lower. D. Reid asked when the value will be known. A discussion ensued on the basis for the screening value and the schedule to complete the guideline analysis. F. Lemieux suggested using the value recommended in the Water Research Foundation report for minimizing colour events be used in the interim (15 µg/L).

Decision/Action:

- **D. Reid to forward epigenic references to A. Vézina.**

4-C 1,4-Dioxane

I. Moffat and A. Cherry gave a presentation. C. Robert requested information on uncertainty. S. Deshpande asked for additional clarification. I. Moffat noted that the EPA looked at both the non-linear and linear approach, however, the mode of action was unknown at the time. There is more information available at this time to inform the guideline development process. S. Deshpande indicated that it would be helpful if this guideline document could include some historical context since the IRIS work completed in the 1970s may not be comparable to the more recent studies. A. Vézina asked which members have exposure data for this compound. C. Robert and S. Deshpande indicated that they had data. A discussion ensued on the potential to detect 1,4-dioxane in groundwater around landfills.

Decision/Action:

- **For information.**

4-D Pesticides

R. Charron gave a verbal update. The Secretariat has been approached by PMRA for guidance on deriving health-based drinking water values for pesticides using PMRA's ADI. S. Deshpande asked for additional clarification on the Secretariat's approach for assessing pesticides. R. Charron confirmed that the Secretariat would use the ADI developed by PMRA but that the uncertainty factor could be adjusted (upon review by the PMRA) when calculating health-based values for drinking water. A discussion ensued on whether formulants (including surfactants and solvents) are considered. F. Lemieux indicated that they are considered in the overarching approach. R. Charron indicated that this would be clarified with PMRA. More information will be provided as progress is made.

Decision/Action:

- **Secretariat to follow-up with PMRA regarding how formulations are considered.**

4-E Uranium

J. Carney and N. Martinova gave a presentation on uranium. C. Robert asked what the source of exposure is for infants under 3 months. J. Carney indicated that the data came from the Canadian diet study but it does not specify the source of exposure. S. Deshpande asked if the document would discuss the linkage to gross alpha. F. Lemieux noted that gross alpha is used for radiological parameters rather than chemicals. N. Martinova indicated that there is a conversion factor that can be discussed. P. Brooks asked if there is any Canadian residuals management information. F. Lemieux indicated that it's complicated because it's a provincial issue. A discussion ensued on the need to discuss residential-scale ion exchange units and the perception that they generate low level nuclear waste. K. Gould asked if there is an indication of what the value will be. J. Carney noted that the guideline development process is still ongoing but the value may stay the same or go up.

Decision/Action:

- **For information.**

4-F pH

F. Lemieux gave a presentation on the pH document after consultations. She explained that the upper bound of the pH range was set at 10.5based on Rhode Island's experiences. They have used a finished water pH range of 10.2 to 10.4 since 1994 for corrosion, manganese and iron control. In 2006 the utility decided to use a finished water pH of 9.6 but significant lead releases resulted. In 2011 the utility went back to 10.3 to 10.4 to reduce lead releases. Rhode Island's raw water would be similar to Nova Scotia's. An upper bound as high as 10.5 was included to allow flexibility for those utilities that may need to go this high to control lead releases. D. Fishwick was supportive of pH being an operational guideline. C. Robert noted that her colleagues raised concerns with the upper bound; if the 10.5 is only based on one utility, Quebec may choose to set the upper bound at 10 considering that it's an operational guideline. F. Lemieux noted that iron is part of the problem for particle lead. The Rhode Island experience was published in December 2014, and that Rhode Island has not had any complaints about skin irritability. Additional information can be added to strengthen the document, which C. Robert indicated would be helpful. C. Robert noted that one of the comments submitted was regarding the well-known fact that cyanobacteria blooms result in increasing pH due to the consumption of CO_2 by the bacteria but this comment was not addressed. F. Lemieux indicated that a literature review did not identify any studies documenting this issue. C. Robert offered to forward relevant references and indicated that the information may also be in the microcystins document. She re-iterated that pH can go higher than 9 during a bloom which results in operational challenges.

Decision/Action:

- **C. Robert to forward pH references to A. Vézina.**
- **Members approved the document in principle for publication, subject to the above noted changes.**

4-G Aluminum

I. Moffat and S.J. Payne gave a presentation. F. Lemieux noted that if the health-based value is significantly higher than the operational value, efforts to meet the operational value may be lessened. A discussion ensued on whether aluminum should remain at its current priority. I. Moffat noted that the health assessment is relatively straight forward but treatment is more of an issue. F. Lemieux noted that coagulation and distribution issues will require significant resources. A. Vézina presented the prioritization process results. K. Gould asked for clarification of whether a HBV could be established. J. Cooper noted that if the science indicates that there are health effects at a certain value, that information should be included. K. Gould agreed that this was necessary for compliance from a health perspective. S. Deshpande asked about the operational nature of the guideline. A. Polegato noted that Nova Scotia has utilities with aluminum exceedances in the distribution system and a health-based value would be helpful. The discussion on priority continued. It was decided that cadmium should move ahead of aluminum as there is new health information related to cadmium whereas the driver for aluminum is treatment.

Decision/Action:

- **Members agreed switching the priority of aluminum and cadmium.**

4-H Microcystins

J. Cooper gave a presentation on the collaborative process used with the US EPA to develop a guideline on microcystins for Canada and a health advisory for the US. Differences in jurisdictional processes were highlighted. J. Cooper noted that the EPA will host a workshop on May 11 on the implementation of their health advisory (released May 6). A communication plan should be developed for Canada. K. Gould raised concerns with the text related to infants in the guideline statement as it does not reflect the fact that the current MAC is considered protective of public health and that the statement would create unnecessary fear and would erode public confidence in the drinking water supply. Further discussion was deferred until after the technical presentation by G. Yasvinski, A. Cherry and R. Charron. K. Philip raised similar concerns to those raised by K. Gould and suggested supplemental text for plants that are reliably monitoring blooms. C. Robert noted that the existing text appears to show a lack of confidence in municipal treatment and does not reflect that many plants have been optimized. A. Cherry noted that it is difficult to demonstrate what "reliably monitoring" means for treatment facilities. S. Deshpande noted that based on Ontario's surveillance no toxins were detected in treated municipal water. He raised concerns with the calculated number proposed by EPA for bottle-fed infants. D. Reid requested clarification on the status of Appendix B – is it being revised or withdrawn? It was noted that it is being revised but it will not define "reliably monitoring". J. Cooper indicated the guideline statement should allow flexibility. K. Philip noted that there are other guidelines where supplemental information is provided; the concern is how does one decide what advice to provide for bottle-fed infants without a number. V. Morisset asked if "reliably monitoring" would be part of historical data. K. Gould noted that there appears to be an abundance of caution in this case and asked if more information could be added to the guideline statement to explain that the guideline is considered protective of population health but a gap in science may exist for bottle-fed infants. D. Reid indicated that Alberta consulted internally and is content with the proposed text, however, concerns were raised with directing people to bottled water which is less regulated than drinking water. D. Fishwick noted that the guideline statement cannot be interpreted without the complete document and that it should be flexible. M. Leblanc-Havard indicated that bottled water may not always be an option. P. Brooks agreed that the issue is

complex and the complete document needs to be considered not just the guideline statement. K. Philip indicated that Manitoba can accept a more flexible guideline statement if the rationale includes the information. F. Lemieux indicated that additional information can be added to the application of the guideline. K. Gould re-iterated that it is very important to note that the committee believes the guideline is protective of the public and the precautionary advice is to fill a gap in science. K. Philip asked about monitoring. She wanted to review the decision tree; it starts with visual inspection but often only three to four samples may be collected which may not be adequate for decision-making. D. Reid noted that Alberta has a routine monitoring program. S. Deshpande indicated that in Ontario utilities develop their sampling programs which results in samples approximately every two weeks. Also, the Health Unit is assessing private wells along the shore of Lake Erie. G. Yasvinski noted that the decision tree will be in an annex. It will indicate that areas with known history of blooms should be visually monitored every two weeks; when there a resigns of a bloom, visual monitoring should occur every week and toxin monitoring should start. K. Philip noted that not all utilities are sampling for toxins when they visually monitor. G. Yasvinski indicated that the decision tree will not include a monitoring frequency. S. Ferris indicated that in Saskatchewan, if utilities fail to monitor it is written up in their inspection report and enforcement action may be taken. K. Gould asked if the scenario of the presence of toxins without a visual bloom needs to be covered. A discussion ensued on revised guideline statement wording that was presented. Members approved the new wording. J. Cooper indicated that he would like to issue a letter to committee members recommending Canada adopt the approved approach for this bloom season and possibly issue a press release. D. Reid asked what the timing would be for letter. J. Cooper indicated that it could be expected by June 15. All members were in favour. J. Cooper asked if G. O'Toole could advise CHE.

Decision/Action:

- **Members approved the document for public consultation in principle, subject to the above noted changes.**
- **Secretariat to prepare a letter for issuance to members by June 15th.**
- **G. O'Toole to update CHE.**

4-I Copper

S. Chébékoué, F. Lemieux and S. J. Payne gave a presentation. The document on copper is being drafted and will go through internal and external peer-review processes. Once the comments from these reviews are integrated, the document is expected to be presented to CDW at the fall 2015.

Decision/Action:

- **For information.**

4-J PFOS and PFOA

M. Deveau and N. Martinova gave an update on the document. C. Robert noted that the limited data indicate exposure is very low. C. Robert noted that Sebastien Sauvé at the Université de Montréal is conducting some sampling that may be useful. S. Deshpande indicated that PFOS and PFOA have been detected at some sites in Ontario, mainly at airports and Department of National Defence (DND) sites. He suggested that guidance be included on where to sample. C. Robert noted that in Quebec, PFOS and PFOA are being detected in various rivers affected by wastewater effluents, for example the St. Lawrence River and other rivers with large populations in the watershed. S. Deshpande noted that for a well contamination situation in Ontario, GAC was used for treatment. N. Martinova noted that firefighting foams can contain other

contaminants. D. Fishwick asked if PFOS and PFOA are used for forest fighting. M. Deveau reviewed the sources of exposures and indicated it was unlikely. S. Deshpande noted that most airports and DND sites have stopped using PFOS. J. Cooper noted that it is also an issue for Health Canada's contaminated sites group. A. Vézina also noted that PFOS and PFOA were detected in the population as part of the Canadian Health Measures survey. H. Khan noted that one site in Newfoundland has contamination and discussions are ongoing with Transport Canada. A number of technical reports have been prepared that he will forward to A. Vézina for consideration. C. Robet asked if PFOS and PFOA are to be banned. M. Deveau noted that PFOS is already banned. J. Cooper noted that both were declared CEPA toxic to the environment.
Decision/Action:

- **H. Khan to forward technical reports to A. Vézina.**

4-K Other chemical/radiological (chromium, B(a)P, bromate, etc.)

F. Lemieux gave a verbal update. A Water Research Foundation report on microcystins was previously shared with the Committee. Another report on Green Buildings is being commented on as it is finding water quality deterioration due to low water use. The Res'eau Water Network is looking at small systems. The work is being done in a very progressive way with community discussions. The project is going into its second five year cycle. The Network is looking to get an Ontario community engaged.More information will be provided as progress is made. It took a long time to establish the network. US EPA regulations for low lead materials are expected soon. As similar regulations do not exist in Canada, low lead requirements have been integrated into plumbing standards. Approximately six to eight provinces now have a requirement to meet low lead requirements included in their plumbing codes. The message is getting out to industry. P. Brooks asked if the National Building Code has been modified to include the weighted average. F. Lemieux indicated that fitting standards has been modified as an interim measure and back-dated to the 2010 standard. Provinces are referencing the fitting standard. C. Robert asked for an update on the arsenic speciation project. A. Vézina noted that she attempted to have an update for the Committee but is still waiting to hear from the researcher regarding the sharing of data; she will follow-up again.

Decision/Action:

- **A. Vézina to follow up regarding the sharing of arsenic speciation data.**

5 Secretariat projects

5-A National Drinking Water Conference

S. McFadyen gave a presentation on the potential paths forward for the conference. D. Reid asked if the Committee's terms of reference would need to be modified if Option D (no event) was selected. A discussion ensued on the NSERC chairs option (Option A) and that the more ideal locations would be Toronto and Montréal, although it was noted that the current proposal is for Ottawa. D. Reid suggested that for the Health Canada one day workshop option (Option C), this be tagged onto the meeting since members are traveling for as much time as they are at the meeting. D. Reid indicated that Alberta supports Option A. K. Philip asked if Health Canada staff can travel. S. McFadyen noted that approval to travel was not expected for 2016andthe Committee will need to assess how the new process works beyond that. K. Philip noted that it is critical that the event be tied to the committee meeting. J. Cooper noted that the workshop option may need to be a non-paid event for this audience only. H. Khan noted that the NSERC Chairs are only funded for a five to six year period and asked if this option is sustainable. F. Lemieux indicated that the NSERC Chairs are renewed on a five year cycle but it would be unusual to not

be renewed. A discussion ensued and it was agreed that this option has good potential for the long term. D. Reid noted that a conference would support the NSERC Chair renewal process, as well as technology/knowledge transfer. K. Gould indicated that New Brunswick can support Option A but also believes Option B (drinking water sessions at CWWA event) would not necessarily result in a watered down event for the Committee. The branding and marketing would be important. P. Brooks noted that if it's a combined event, she would have a challenge attending. A discussion ensued on the required level of technical content for the conference. H. Khan indicated that this Committee is the drinking water champion for Canada and should only team up with those agencies that are committed to drinking water. Drinking water should be the primary topic of the conference. Members raised concerns that partnering with CWWA could result in too much commercialization. S. McFadyen noted that the Committee would have a say in the program. C. Robert noted that the NSERC Chairs are not limited to treatment; their focus is source to tap and Res'eau is focusing on small systems. S. Ferris indicated that Saskatchewan can support Option A at this time and maybe CWWA in the future. G. O'Toole indicated that his preference would be for Option A. G. Somers indicated preference for Option A connected to the meeting. C. Robert noted that Option B could be problematic if members are not able to attend the event. A discussion ensued on the timing required for Option A (mid-October). Members agreed to make it work for 2016. K. Philip noted that Option A could be combined with Option C as one chair has offered to fund a knowledge transfer day. Members could submit ideas, for example, small systems or genomics. S. Ferris asked if NSERC itself was contacted. S. McFadyen noted that just the NSERC Chairs have been contacted to date. K. Gould was supportive of a workshop the day before or after. J. Cooper noted that it would make members trip to Ottawa more valuable. D. Reid indicated that an orientation session every three or four years would also be useful. P. Workman suggested contacting the National Collaborating Centre for Environment Health (NCCEH) in British Columbia. Members agreed to pursue Option A for the 2016 conference.

Decision/Action:

- **S. McFadyen to prepare financial details for an October 2016 conference with NSERC Chairs (Option A).**

5-B Hydraulic fracturing

K. Gould updated the group on activities in New Brunswick. P. Workman indicated that the Northwest Territories have updated regulations that require baseline data for groundwater and surface water, public disclosure, measures to address air quality and enhanced reporting. The regulations are expected to take effect in October. H. Khan indicated that for Newfoundland and Labrador an internal review panel report was prepared about 18 months ago; the government has now appointed an external review panel. Saskatchewan, Ontario and Nova Scotia members indicated that they have no new information to report. A-M. Tugulea noted that a paper was recently published on what is found in hydraulic fracturing effluent and offered to provide the reference to A. Vézina to circulate to members. It was agreed that hydraulic fracturing should remain on the agenda as a standing item.

Decision/Action:

- **A-M. Tugulea to forward reference on hydraulic fracturing to A. Vézina for circulation to members.**
- **Hydraulic fracturing to remain as a standing item on the agenda.**

5-C Safe Drinking Water for First Nations Act

J. Lafontaine from Health Canada's First Nations Inuit Health Branch (FNIHB) and J. MacKinnon from Aboriginal Affairs and Northern Development Canada (AANDC) gave an update on the "Safe Drinking Water for First Nations Act". Phase 1 involves the Yukon, Northwest Territories and the Atlantic Region. The analysis completed to date indicates that the Yukon likely does not need new regulations. For the Northwest Territories, staff has discussed drafting instructions with First Nations and the territorial government. Drafting instructions are being reviewed by the Department of Justice and will be shared with the Northwest Territories before being gazetted. For the Atlantic Region, drafting instructions will be developed with the Atlantic Policy Congress. Staff met with Nova Scotia Environment representatives to seek clarification on their regulations. The Department of Justice has indicated that it will take ten months to develop a first draft once the Northwest Territories material is finalized. Ministerial concurrence is being sought to proceed with British Columbia, Manitoba and Saskatchewan as Phase 2. The process to fund aboriginal partners has changed starting this fiscal year, and requires the submission of funding proposal. Some funding proposals have been received from organizations in Saskatchewan and Ontario but none from British Columbia. The funding decision is expected on June 8. An analysis has started to update the cost of compliance and enforcement; the original work was a high level analysis completed by the Institute of Governance in 2007. Nova Scotia Environment identified a number of issues to consider, such as the need for a computer system for tracking activities. A contractor is working on the costing piece. J. Cooper asked if it is still the intent to incorporate provincial standards by reference and if any consideration has been given to the provinces regulating. J. MacKinnon indicated that yes, provincial standards are being incorporated by reference and to date provinces have declined their proposal to provide funding for the province to take care of the enforcement. D. Fishwisk asked if there have been discussions with the British Columbia First Nations Health Authority. J. MacKinnon indicated that they were approached and also declined. K. Gould asked when the meeting with the Atlantic Policy Congress occurred. J. MacKinnon indicated that the meeting took place in November. A discussion paper on what would be incorporated from each province was discussed. It is expected that Justice can begin drafting instruction at the start of June. D. Fishwick asked for clarification regarding the funding proposals. J. MacKinnon indicated that there is a cap on funding to political organizations and a "single-window" application process has been put in place. No applications were received from British Columbia organizations. D. Reid asked if having the FNIHB act as the enforcer was still an option on the table. J. MacKinnon noted that internal federal discussions are still ongoing. J. Cooper asked if the regulations are being written such that when standards are updated, the regulations will automatically reference the updated standards rather than having to amend the regulations. J. MacKinnon indicated that yes, this is the intent J. Cooper asked how the provincial permitting process is being considered, for example when a treatment plant needs a permit. J. MacKinnon indicated this is still being reviewed. K. Philip asked how the decision was made to select British Columbia, Manitoba and Saskatchewan as Phase 2. J. MacKinnon indicated that it was a combination of complexity, partners and state of preparedness. P. Brooks asked what happens if a gap is found when a jurisdiction is engaged. J. MacKinnon indicated that their direction is to limit coverage to what the jurisdiction has. J. Lafontaine noted that small systems may raise some issues regarding coverage. For example, there is no trucked water system in the Atlantic region but there are in other jurisdictions so this could become a gap. G. Somers asked how complicated the enforcement will be in the Atlantic region given the mix of regulations. J. Cooper indicated that provinces won't be representing First Nations on this Committee and

asked if the future entity overseeing the First Nations regulations should sit on the Committee. K. Philip noted that implementation is often done by policy which is updated daily. She asked if there will be a mechanism to ensure policy changes are communicated to this new entity.

Decision/Action:

- **For information.**

5-D Iodo-THM formation

A-M. Tugulea gave a presentation on study results that will be published. F. Lemieux asked about the odour threshold. A.M Tugulea indicated it is very low, in the range of 0.02 µg/L. D. Reid asked about the formation of iodo-THMs in supplies with high ammonia. A-M. Tugulea indicated that iodo-THMs form before regulated THMs. K. Gould asked why this is being studied. A-M. Tugulea indicated that iodo-THMs have different formation mechanisms and they are considered more toxic than regulated THMs hence more information is being collected. C. Robert indicated that a study is ongoing in Quebec. In high bromide supplies, iodo-THMs are found at higher concentrations than regulated THMs. C. Robert offered to share the information.

Decision/Action:

- **C. Robert to share iodo-THMs information.**

5-E Scope of regulators' meeting

D. Reid indicated that the sub-group met and questions came up regarding Terms of Reference. As a result, it was decided to bring this item back to the Committee for consideration. D. Reid indicated that the original intent was that the provinces and territories could meet before or after the CDW meeting to discuss items such as compliance, enforcement, lab management, rather than to discuss regulatory frameworks. S. Ferris asked what members would like to discuss in a separate meeting. K. Philip indicated that she is more interested in discussing implementation issues than regulatory frameworks. G. Somers indicated his preference is to discuss "on the ground" activities. P. Brooks noted that practical level discussions would be most helpful. V. Morisset indicated that was originally proposed by the sub-group was administratively high. K. Philip indicated it would be helpful to consider implementation issues as part of the guideline development process. A. Vézina asked if the existing process where questions are circulated and members reply to all is working. K. Philip noted that at times there are too many emails. P. Workman noted that the email system can get bogged down with "reply-all" emails. A discussion ensued on whether the CNPHI platform could be used to facilitate communication. P. Brooks indicated that people usually ask policy questions. It was agreed that the sub-group would meet again to discuss this feedback.

Decision/Action:

- **Sub-group to re-convene and consider feedback.**

6 Committee Liaison Reports

6-A FNIHB report

A. Bevan provided a verbal update of FNIHB's activities. An interactive tool which guides operators of small systems through a questionnaire and provides useful information to fix deficiencies has been developed and will be piloted in a few First Nations systems this fiscal year. H. Khan asked if the tool was developed with operators or in isolation. A. Bevan indicated that the tool is based on New Zealand's water safety plan material, with additional work by Dalhousie University to reduce the technical language and a consultant to develop the software tool. The next phase is operator testing. A. Polegato asked if FNIHB staff tested it. A. Bevan

indicated that Dalhousie tested it with a number of communities. The objective is to keep it simple. The operator gets a list of things to look into. This can be helpful when the operator is overwhelmed. D. Reid asked if the New Zealand videos will be replicated as these are also very useful. A. Bevan advised he wasn't aware of the videos but would look into it. D. Fishwick indicated that the videos are available on Youtube. J. Cooper asked D. Reid what happened to the WHO tool that was being developed. D. Reid indicated he would find out. M. Leblanc-Havard asked if the operator has to input their system information or if the tool comes pre-loaded with some basic information. A. Bevan indicated that the tool has some basic information from the First Nations risk assessment reports but some process information still needs to be inputed.
Decision/Action:

- **D. Reid to inquire about the status of the WHO small systems tool.**

6-B WHO report

M. Giddings noted that the last WHO meeting occurred in February in Bonn, Germany. The first addendum for the 4th Edition of the WHO Guidelines is expected in Fall 2015 with the second addendum planned for 2017-18. The fifth edition is planned for publication in 2020. The WHO approved the revised guideline for nitrate and nitrite that was based on the Canadian document and accepted the changes/inclusion based on thyroid information. However, the current value of 50 mg/L for nitrate and 3 mg/L for nitrite will be kept. The WHO turbidity guideline is being updated based on the Canadian document (which they really like). Other documents under review or on priority list for updating include bromate, chromium, perchlorate, barium, manganese, chlorate/chlorite, PFOS/PFOA, microcystins and a number of pesticides. The process to assess pesticides has been significantly revised; documents will be much shorter and based on Joint Meeting Pesticide Residue reviews or on peer reviewed international assessments. Work is underway to develop a problem formulation process to address chemical mixtures (or combined exposures to multiple chemicals). Changes have been made to the approach document, to clarify the default values (basement & ceiling levels) used in deriving allocation factors. On the microbiology front, discussions were held regarding QMRA, anti-microbial resistance, vulnerable populations, reference pathogens and updating of various pathogen fact sheets.
Decision/Action:

- **For information.**

6-C CHEreport

G. O'Toole noted that the CHE met in December by teleconference. Items noted include a North American climate change workshop being proposed for the fall, the Canadian Institute for Health Research is looking at agri-food and urban development, a hydraulic fracturing roundtable and information sharing is planned for the Energy Geoscience Collaborative Open Innovation Network. A discussion ensued on how to ensure CDW and CHE are robustly connected.
Decision/Action:

- **For information.**

6-D CCME Report

P. Cureton gave an update on the Canadian Council of Ministers of the Environment (CCME) and Environment Canada initiatives.Environment Canada continues to develop environmental quality guidelines in two areas: federally, to support the Chemicals Management Plan and contaminated sites, and nationally, through CCME's Water Management Committee and Soil Quality Guideline Task Group. Water activities support the CCME Water Management

Committee's priority to improve water quality and water quantity management. Public review of the carbamazepine guideline ended April 17, 2015 and comments are under consideration. Ontario is leading this initiative. Water quality guidelines are underway for: zinc, manganese and silver. The Groundwater Sustainability Assessment Approach is being finalized. The approach and supporting document are intended to assess the sustainability of groundwater resources at a local, regional or Canada-wide scale. Activities of the CCME Soil Quality Guidelines Task Group support the CCME's priority to increase jurisdictional capacity to manage contaminated sites. The connection to CDW is that the Guidelines for Canadian Drinking Water Quality (GCDWQ) are used directly to protect groundwater as a drinking source. Since the CCME values select the lower of the ecological and human health pathways for the final guideline, a change to a GCDWQ can potentially play a role in the final soil and groundwater guidelines. Two protocols have been published: *A Protocol for the Derivation of Soil Vapour Quality Guidelines for Protection of Human Exposures via Inhalation of Vapours* (published Nov 28, 2014) and *A Protocol for the Derivation of Groundwater Quality Guidelines for Use at Contaminated Sites* (published January 9, 2015). The soil quality guideline for beryllium was published February 24, 2015. Other projects include: (1) the development of an ecological risk assessment guidance document (led by Alberta), now being revised after the public review ended April 27, 2015; (2) the development of best management practices for the beneficial reuse of excavated soils. The objective is to reuse treated and excess soil for landfill cover, on a development site or incorporated in industrial construction fill projects; (3) the development of guidance for management of contaminated sites located in permafrost and permafrost transition zones. With climate change, and a decrease in the zone of continuous permafrost, contaminants once thought contained by a permanent ice barrier may no longer be contained and transport may be more prevalent than once thought. This work is being led by the Northwest Territories. Updates to the soil quality guidelines for nickel, zinc and lead are underway. Soil quality guidelines are being developed for methanol, glycols and amines. J. Cooper noted that Health Canada's contaminated sites group in now part of the Water and Air Quality Bureau. J. Cooper asked about PFOS/PFOA and micro-beads.

Decision/Action:

- **For information.**

7 Members' Reports

Each jurisdiction provided a report on its program and legislative activities, training and outreach programs, publications and current key issues.

Alberta

The consultation on proposed drinking water regulation revisions is now closed. The input received is being evaluated and a path forward is being developed.

British Columbia

The Environmental Operators Certification Program, which is an external program that classifies systems and certifies operators, has been reviewed. The department is now re-looking at how to classify systems, certify operators and provide more transparency for Environmental Health Officers. Risk management plans are being developed, including the risk of the organization running the system from a financial and human resources perspective. This goes beyond the health role and looking at conditions that lead to problems. Work on small water systems is on-going. Subdivisions are being considered before they get built to ask if they have a finance plan,

loan programs. The program is also looking at options for nano-systems which have less than 5 users and that seem incapable of compliance, for example can a notice be put on title to encourage compliance. A tour around the province was conducted to explain the policies for groundwater at risk of containing pathogens, and the treatment expectations for supplies that require treatment. The distribution system guideline was reviewed. A discussion ensued and all members requested a copy of this document. The lack of snowfall this year could make the summer interesting, particularly from a fire fighting perspective. A. Polegato asked if all small systems are required to do an assessment. D. Fishwick noted that in some cases the supply may dispense with the assessment and decide to treat.

Manitoba
The City of Winnipeg review will be made publicly available. Investigations are pointing to sampling error as the problem. Risk assessments for sources and public and semi-public drinking water infrastructure are being updated and powers for non-potable systems are being strengthened.

New Brunswick
The province regulates drinking water supplies that provide 50 m^3or more per day. There are 71 municipal systems with operating conditions and these seem to be able to meet requirements. The program is continuing to identify more private and crown systems.

Newfoundland and Labrador
The annual water safety report was released. The annual drinking water forum was held in March 2015. Topics included: what are the challenges, what is being done right, what is not being done right. Best management practices have been posted on the website. A drinking water monitoring program and an operator training program were developed. A "one time" private water quality testing program was initiated; most issues relate to arsenic. A new fiscal framework for municipal drinking water safety proposes regional service boards to hire regional operators. A pilot program will be carried out for four years. The number of boil water advisories was reduced from 350 in 2002 to 220, but the number has remained stable for the past 10 years. Politicians are asking for progress in this area. Dam safety regulations are being developed for the over 600 dams in the province. S. Ferris noted that Saskatchewan is eliminating boil water advisories for system depressurization or minor breaks. A discussion ensued on information included in AWWA Standard C-651 regarding water main commissioning and intrusion, as well as when advisories may be needed, that may be transferrable to a boil water advisory.

Northwest Territories
Legislation is being developed for a First Nations Authority. A first draft plan for source water protection has been developed. Four out of six Environmental Health Officer positions are filled. We have a number of capacity issues. We're also looking at operator certification and SCADA systems.

Nova Scotia
Nova Scotia's public drinking water supply program was audited by the auditor general in 2014, and the auditor's recommendations continue to be implemented. Most recently, all inspection

staff and management in the Compliance Division were trained in the municipal and registered drinking water programs including protocols to be followed during an audit, sampling requirements, and follow up to identified deficiencies. The training was delivered to improve consistency in program delivery throughout the province. All municipal drinking water supply operating approvals were recently updated to include corrective actions and timelines required to comply with Nova Scotia's municipal treatment standards. These changes were implemented to ensure all municipal drinking water supplies meet the 2012 treatment standard by the year 2020. Watershed planners continue to work with municipalities to develop source water/wellhead protection plans. Currently, 89% of supplies have source water protection plans. We are working to have our water advisory data transferred to the CNPHI platform. Nova Scotia continues to work on updating well construction regulations. The policy analysis and stakeholder engagement have been completed, and new regulations are anticipated to be drafted in the next fiscal year. Nova Scotia continues to evaluate the public drinking water supply program and is currently identifying potential solutions to address issues identified during the stakeholder engagement. We are seeking approval from our Steering Committee for several changes, including to: introduce a regulation for water testing labs; develop defined treatment requirements for small drinking water systems; and develop an integrated data management system to facilitate data collection, management, analysis and decision-making. The department has met with representatives of AANDC, who had a number of program specific questions. Nova Scotia Environment has declined AANDC's request to perform regulatory audits of water and wastewater facilities in First Nation communities within the province.

Nunavut
There are a lot of challenges, but new resources have been hired, with a new Chief MOH and 6 EHOs expected. Current issues under consideration include water licenses, water regulations and the Public Health Act. An environmental manual has been drafted. Relationships are being built with operators. Each area has an audit tool that EHOs will roll-out to take an inventory of capital infrastructure. The Chief MOH is committed to sign off on every WTP. The City of Iqaluit entered into talks for issuing BWAs, and protocols are being developed to do so. An alternate source study has been completed for each community except for two. The territory is looking at standardized lab protocols for micro testing. Climate change and source protection are becoming more significant. Compliance, communication and training form the base of our requirements.

Ontario
Consultation was completed on the Great Lakes Protection Act and it should come into effect soon. Consultations were held on changing the disinfection procedure. The update is expected to be written in a Q&A format. The department has changed its name to include climate change. A cap and trade agreement has been developed. Departmental focus is on climate change.

Prince Edward Island
In the aftermath of the provincial election, there are early indications that there may be restructuring of some government departments. This might affect "on the ground" activities with respect to drinking water. Among department priorities, it is anticipated that work on a "Water Act" will take center stage, although there may not be much impact of this on drinking water standards or administration. While the scope of the act has not been defined yet, some possible areas that might be relevant to drinking water or drinking water supplies are new rules for water

allocations, source water protection. Some minor revisions are being made to the Drinking Water and Wastewater Facility Operating Regulations, primarily to fit our current approach to very small water systems. Efforts continue with registration, facilities classification and operator certification of water and wastewater systems, with a focus on small and very small systems. J. Cooper asked what the size was for a very small system. G. Somers noted that the size is 5–20 connections. They don't require a certified operator but must take a training course. A. Polegato asked about the training course. All members expressed interest in getting a copy. It was noted that NL and the Walkerton Clean Water Centre also have courses.

Quebec

A guidance manual on vulnerability assessments has been published. All municipal systems with more than 500 persons must complete a vulnerability assessment and have it updated every five years. Training is up-coming. A financial assistance program has not yet been announced. The Ombudsman released a report regarding non-municipal non-residential systems. Main priorities include the development of an action plan to review and update regulations and to determine how to rescind boil water advisories. There are a number of monitoring projects underway – groundwater with high bromide and iodide through a partnership with the Université Laval, as well as various disinfection by-products such as bromate and chlorate/chlorite. A "Partnership for Safe Water Program" for distribution systems is being piloted to accompany the existing program for treatment. Following the incident of contamination by diesel in Longueuil, which resulted in a "do not use" advisory, best management practices for distribution systems are being developed. F. Lemieux asked if the driver for the distribution system best management practices was infrastructure or water quality. C. Robert indicated the driver was water quality and agreed to share the information on disinfection by-products.

Saskatchewan

New regulations known as The Waterworks and Sewage Works Regulations will take effect on June 1, 2015. Updated standards for Saskatchewan include haloacetic acids, chlorate, chlorite, bromate, arsenic, microcystin toxins, MCPA, and the current national guideline based series of radiological parameters. It is anticipated that the Environmental Management and Protection Act, 2010 will be proclaimed at the same time. Relevant Environmental Code aspects for water management include both water main and sewer main chapters will also come into force on June 1, 2015. The Water Security Agency is currently revising policies and protocols to align with the anticipated revised/new regulatory and environmental code requirements. Compliance with regulatory requirements for bacteriological standards and disinfection requirements are highs: 98.9% compliance with bacteriological requirements 90% of the time at municipal works, and 91.4% compliance with disinfection requirements. There are a total of 1,325 water and wastewater operators currently certified by the Saskatchewan Operator Certification Board and 99.8% of waterworks classified as human consumptive systems have a certified operator as of April 1, 2015. Regional/contract operator provisions are also in place where required full certification has not been met. Compliance with health parameters (metals) is 92.2 % for the 2014-15 fiscal year, with exceedances for arsenic (29), copper (1), and uranium (8).

Yukon

The Build Canada funds has resulted in many systems being upgraded or replaced. Work is continuing on semi-public systems under the Public Health Regulations as these require safe water to be provided. The process begins with an assessment of the water source which provides

a risk assessment rating, however, a large part of the assessment relies on well records which are not available. The Water Strategy has been finalized. All departments involved in water (health and environment) have 50-plus action items to implement over the next three years, and met to discuss implementation actions. PT jurisdictional information was requested as part of the process to enhance inspection programs, however variances were found to be huge. The goal is to have more consistency and more transparency so inspection results are communicated consistently and understood by operators. For operator training and certification, The territory is using the BC-based Environmental Operators Certification Program, which offers web based testing that gives the operators their results right away. A design manual for small systems is being developed, which will include some standard basic designs. D. Fishwick asked if Res'eau was contacted regarding the design guideline as they are developing something similar for disinfection. P. Brooks noted that the Yukon manual is more about educating people about what they should look for and covers more than disinfection. J. Cooper asked if SCADA systems were being used for remote operation. P. Brooks noted that there are some but for larger systems. A discussion ensued on security requirements for SCADA systems. S. Ferris noted that Saskatchewan has a guideline for SCADA systems and on-site security. A. Polegato asked if this is something that gets audited by the inspector. C. Robert noted that Quebec has a guidance document that she will send to members.

Decision/Action:

- **D. Fishwick to send A. Vézina BC's distribution system guideline for circulation.**
- **G. Somers to send A. Vézina PEI's operator training information for circulation.**
- **C. Robert to share disinfection by-product monitoring results with the Secretariat.**
- **C. Robert to send A. Vézina Quebec's SCADA guidance document for circulation.**

8 Meetings

8-A Future Meetings

Members discussed future meeting dates. The Chair reminded members that if they would like observers to attend the meeting, the request needs to go through the Chair, the Co-Chair or the Coordinator.

Decision/Action:

- **Fall 2015: November 4-6, 2015 in Ottawa**
- **Spring 2016: May 4-6, 2016 in Ottawa with possible workshop**

2- Agenda/Meeting

2-C CDW Status / Checklist

Reference/Action:

- Oral presentation on the status of guideline/guidance documents
- Verbal update on the record of decision and checklist of action items
- Attached, record of decision sorted by subject
- Attached, checklist of action items from the May 2015 meeting
- Provided at meeting, CDW parameters status list
- For information only

Notes:

CDW Date	Subject	Decision
2011-05	Ammonia	• Secretariat to make links between the ammonia document and the nitrate/nitrite document • Operational considerations to be removed from the guideline statement • Public consultation to be done at the same time as the nitrate/nitrite document • Members approved the document in principle for public consultation
2013-05	Ammonia	• Members approved final document
2009-05	Bacteriological	• CDW agreed that the HPC and Emerging Pathogens Bacteriological documents should be Guidance documents instead of Guideline Technical Documents.
2010-05	Bacteriological	• Secretariat to set up a working group meeting for June 2010.
2010-11	Bacteriological - E.coli	• Members agreed to go forward with enzyme-based methods are 'recommended' and see what feedback comes back. • Members approved the E.coli document for public consultation.
2012-02	Bacteriological - e.coli & total coliforms	• Members approved by consensus e.coli and total coliforms documents with discussed changes on a conference call, Feb 14th, 2012
2011-05	Bacteriological - Emerging	• Members approved the document in principle for consultation with minor adjustments to text to be made by Secretariat.
2010-05	Bacteriological - HPC	• Members approved document for a two month public consultation.
2011-11	Bacteriological - HPC	• Members approved document with discussed changes
2010-11	Bacteriological - Total coliforms	• Members approved the document for public consultation in principle. The Secretariat to make changes and circulate the document for final approval.
2012-10	Bacteriological - WBP	• Members approved document in principle, awaiting confirmation from Quebec. The approval from Qc was received one month after the meeting by email (Nov 2012).
2013-11	Benzo(a)pyrene	• Members approved the document for consultation with the modified purpose of consultation section. Secretariat to include context in the purpose of consultation section of the document, noting that the lack of information on Canadian laboratory capacity and methods in this area is a gap.
2014-05	Benzo(a)pyrene	• Members approved the document in principle with proposed changes for public consultation.
2013-11	Boil Water Advisories	• Members approved the document, amended as discussed, for consultation. Secretariat to work with C Robert on wording changes.
2014-10	Boil Water Advisories	Members approved the document in principle for publication.
2014-10	Bromate	Members approved the document in principle for public consultation.
2010-05	Carbon Tetrachloride	• Members agreed to approve the document for publication.
2013-05	CDW Administration	• Members agreed to contribute to the cost of providing light refreshments at meetings.
2014-05	CDW Administration	• Secretariat to maintain the collaboration centre on CNPHI for CDW use • Members approved the use of carbamazepine data by CCME.
2012-05	CDW collaborating centre	• Members agreed to try using CNPHI as a tool for CDW communication, especially as an archive and a place for approved documents. Alternates and CHE reps will have access, as will working group members who are not CDW members (to appropriate sections only). • Secretariat to continue to send the latest versions of the documents by email.
2010-11	CDW Stuff	• Members agreed that the conference is a venue for presentations. The committee is a working committee with business to cover. • Members agreed that for the time being, presentations from outside groups will be considered on a case-by-case basis and that there is a need to deal with questions from lobby
2014-10	Chromium	Members approved the document in principle for public consultation.
2011-11	Cyanobacterial Toxins	• Members agreed to rolling revision of the guideline technical document • Secretariat to draft letter to jurisdictions alerting them to the need to review the guideline and that in the meantime, the recommendation is to test for total microcystins
2011-05	DBPs publication	• Members agreed on need to develop a plan of action to address false or misleading clains regarding Guidelines
2009-05	DCM	• CDW agreed with proposed approach.
2010-11	DCM	• Members approved the guideline with a MAC of 0.05 mg/L.
2012-05	Dichloroethane 1,2-	• Members approved the document for a two month consultation. • Members agreed that no impact paragraphs are needed since the proposed guideline value is unchanged.
2013-11	Dichloroethane 1,2-	• Members approved the guideline for publication.
2009-11	Dichloromethane	•Members approved the document for public consultation.
2010-05	Election	• Members elected J. MacDonald as Chair and C. Robert as Vice-Chair.
2014-05	Election of Chair and Vice-Chair	• Members elected S.Ferris as Chair and C.Robert as Vice-Chair.
2013-11	Enterococcus	• Members asked Secretariat to pursue option 2 (develop more formal guidance on the use of
2015-05	*Enterococcus*	Members approved moving forward with a guideline technical document for *enterococcus*.
2010-11	Fluoride	• Members approved the document.
2009-05	Future meetings	• Fall 2009: Ottawa, November 4-6 ; Spring 2010: Ottawa, May 5-7 ; Fall 2010: Saskatoon, October (exact date to be determined)
2009-11	Future meetings	•S.Deshpande volunteered to attend expert workshop on risk assessment for drinking water
2010-05	Future meetings	• 2010 Fall - Saskatoon, Nov 3,4,5 (National Conference Oct 30 - Nov 2) • 2011 Spring - Ottawa, May 4,5,6 • 2011 Fall - Halifax • 2012 Spring - Ottawa

2012-05	Future meetings	Next meeting in Kelowna - October 2012 May 2013 - Ottawa November 2013 - Edmonton
2013-11	Future meetings	• April 30 - May 2, 2014 Ottawa • Oct 30 – 31, 2014 Ottawa (after National Conference) – members requested to start the meeting in the afternoon on the 29th from 2 to 6 pm.
2014-05	Future meetings	Spring 2015: May 6-8, 2015 in Ottawa
2014-10	Future meetings	Spring 2015: May 6-8, 2015 in Ottawa, Fall 2015: November 4-6, 2015 in Ottawa
2015-05	Future meetings	Fall 2015: November 4-6, 2015 in Ottawa; Spring 2016: May 4-6, 2016 in Ottawa with possible workshop
2012-05	Guideline booklet	• Members agreed the guideline booklet should be published as a companion to the summary table. • Members agreed that the title of the summary table should match what is referenced in provincial and territorial legislation and regulations. Members to provide the Secretariat with specific wording
2015-05	Hydraulic fracturing	Hydraulic fracturing to remain as a standing item on the agenda.
2015-05	Lead	Members approved the document in principle for public consultation, subject to the above noted changes being made.
2009-11	MCPA	•Members approved the document for final publication.
2015-05	Microcystins	Members approved the document for public consultation in principle, subject to the above noted changes.
2014-10	Minutes	Members approved changing the name of the "notes" to "minutes". Members agreed with the Technical Secretariat to no longer prepare the summarized version of the notes/minutes.
2009-05	Monitoring Framework	• G Somers, S Ferris, K Philip and possibly D Reid agreed to validate the decision matrix approach.
2010-05	Monitoring Framework	• Members to provide comments on the monitoring framework by May 31. P Brooks to provide comments after June 1. • Conference call to be set up for the 3rd week in June, a week apart from the turbidity call. • S. Deshpande to take P. Brooks place on the working group.
2009-05	National Drinking Water Conference	• CDW agreed to change the time and location of the next conference.
2009-05	National Drinking Water Conference	• CDW agreed on the following dates and locations for future conferences: 2010 (fall): Saskatoon, SK ; 2012 (fall): Kelowna, BC 2014 (fall): St. John's, NL 2016 (fall): Winnipeg, MB
2010-05	National Drinking Water Conference	• The next National Drinking Water Conference is Oct 30 to Nov 2, 2010. • Members agreed to proceed with WaterNet publication of the conference papers.
2013-05	National Drinking Water Conference	• Members agreed to change location of next conference to Ottawa
2009-05	NDMA	• CDW agreed with a guideline level of 40 ng/L and no ALARA statement.
2009-05	NDMA	• CDW agreed on the need for quarterly sampling and location to be included in the document prior to consultation. Secretariat to add information.
2009-05	NDMA	• CDW approved the document in principle for public consultation.
2010-11	NDMA	• Members approved the document in principle, with the understanding that members will see Appendix 2 before it is posted.
2011-05	Nitrate / Nitrite	• Members approved the document for public consultation in principle, subject to the communications process to be developped Secretariat to follow up about the levels in soy-based infant formula • Secretariat to make links between the nitrate/nitrite document and the ammonia document • Secretariat to look into the need to monitor for both nitrate and nitrite in the distribution system (section 3.1 of the document) • Members agreed that information about bottle fed infants needs to be up front in the document. • Secretariat to look into additional information on limitations for using ion exchange at residential scale • Members approved the document for public consultation in principle, subject to the communications process to be developped
2011-07	Nitrate / Nitrite	• Members approved document in principle for public consultation with discussed changes on a conference call, July 12
2011-09	Nitrate / Nitrite	• Members approved document for public consultation with discussed changes on a conference call, Sept 21st
2012-05	Nitrate / Nitrite	• Members approved the document in principle for consultation. • Members agreed to remove ALARA from the guideline statement and from the rationale, and to add a sentence to the effect that for nitrate "it is recommended that levels be kept as low as reasonably practicable" in the Application of the Guideline section.
2013-05	Nitrate / Nitrite	• Members approved final document pending minor changes
2009-11	Other Bureau Projects	•Secretariat to post document as soon as it's ready (summer 2010).
2009-05	Other Chemical / Radiological	• CDW agreed it is okay for them to share emergency guidance values with each other but not to share them widely or publish them

2012-10	Other Chemical / Radiological	• Members agreed the Technical Secretariat should develop the benzo(a)pyrene guideline technical document (even if lower on priority list)
2014-10	Other Chemical / Radiological	The members approved the following parameters for the priority list: strontium, chloramines, 1,4-dioxane, barium and cadmium.
2013-01	Overarching microbiological document	• Conference call Jan 15th: Members approved the document in principle with discussed changes
2014-10	Pentachlorophenol	Members approved withdrawing the guideline and removing it from the priority list.
2014-05	pH	• Members approved the document in principle with proposed changes for public consultation.
2015-05	pH	Members approved the document in principle for publication, subject to the above noted changes.
2010-05	Priority List	• (B)TEX to be listed as one document/one priority. • Members agreed on the following priority list: 1. Atrazine and metabolites 2. (B)TEX 3. Uranium 4. Copper 5. TOC 6. Microcystin 7. Pentachlorophenol 8. Cadmium 9. Benzo(a)pyrene 10. Boron 11. Dichlorophenol; 2,4- 12. Chloramines 13. Colour 14. Dioxane 1,4- 15. Barium 16. Acrylamide 17. Cyanide 18. Tetrachlorophenol; 2,3,4,6 19. Trichlorophenol; 2,4,6 20. Cyanogen chloride 21. Dimethoate 22. Zinc 23. Malathion 24. Dichloroethylene; 1,1- 25. Total Dissolved Solids (TDS)
2011-05	Priority List	• Members declined to put sodium higher on the priority list
2014-05	Priority list	• Members approved the priority list.
2014-10	Priority List	Members approved waiting for the IRIS assessment before beginning work on arsenic.
2015-05	Priority List	Members agreed switching the priority of aluminum and cadmium.
2009-05	Protozoa	• CDW agreed that the document will not recommend routine monitoring for protozoa.
2009-11	Protozoa	•Members to discuss the revised document in a conference call, with a revised document approved by email by mid-December 2009.
2011-11	Protozoa	• Members approved the document by concensus
2014-10	Regulatory Frameworks	Sub-committee to scope the discussion for a special meeting in May 2015 to compare regulatory frameworks. D. Reid to chair the process.
2014-05	Safe Drinking Water for First Nations Act	• Safe Drinking Water for First Nations Act is to be kept as a standing agenda item for CDW meetings.
2012-10	Selenium	• Members agreed that the guideline should be for total selenium • Members approved the document for public consultation, with the changes discussed.
2013-11	Selenium	• Members approved the document in principle if MAC value remains as proposed. Secretariat and Quebec to discuss concerns about the document ASAP and report back to members.
2009-05	Status / Priority List	• Secretariat to review option of a footnote in the guideline summary table that would indicate substances that may not need to be monitored if covered by treatment product specifications by next meeting.
2011-11	Summary table	• Members agreed that the new summary table should replace the summary table currently on the Health Canada website, with a publication deadline of March 2012 • Members agreed to not include the summary table within the guideline booklet, but rather a summary of guideline development considerations • Members agreed that the summary table would be updated each year, and dated for version control • Members agreed that the information in the table replaces the paragraph version in the guideline booklet and that the guideline booklet will include a link to the summary table.
2012-10	Tetrachloroethylene	• Members approved approach taken to develop the guideline.
2013-06	Tetrachloroethylene	• Conference call June 18th: Members approved the document for consultation in principle with some changes
2014-10	Tetrachloroethylene	Members approved the document in principle for publication.
2012-10	TEX	• Members agreed the Technical Secretariat should proceed with developing the document as a Guideline Technical Document rather than a Guidance Document
2013-06	TEX	• Conference call June 18th: Members approved the document for consultation in principle with some changes
2014-05	TEX	• Members approved the final document.
2015-05	Total coliforms	Members approved moving forward with a guideline technical document for total coliforms with a MAC.
2014-10	Trihalomethanes	Members approved the amended document in principle.
2009-05	Turbidity	• CDW approved the general approach for developing the guideline
2009-11	Turbidity	•Secretariat to broaden the guideline statement to capture GUDI and secure systems.
2010-05	Turbidity	• Secretariat to make links to turbidity in the distribution system more prominent, provide guidance for supplies with no filtration. Members agreed the document has to cover filtration considerations and a more broad consideration of turbidity. • Members to send the secretariat their comments by May 17th. A conference call will be held June 15th to discuss and approve document for public consultation.
2010-06	Turbidity	• Members approved the document for public consultation on a conference call.
2012-05	Turbidity	• Members agreed to use the wording "health-based treatment limits" rather than MAC since turbidity is not measured as a concentration. Secretariat to revise document accordingly.

2012-09	Turbidity	• Members approved by consensus the document on turbidity with discussed changes for final posting on a conference call, September 18th, 2012
2009-05	Uranium	• CDW approved text to be published as addendum for uranium document.
2009-05	Uranium	• CDW approved text also included in appendix of radiological document.
2009-05	Uranium	• Uranium to be added to priority chemicals for review by consultant on analytical methods and treatment technology
2011-11	Vinyl chloride	• Members agreed with including ALARA in the guideline statement • Secretariat to add consideration about age of pipes in distribution system to the document and add monitoring section • Members approved the document in principle. C.Robert and J.MacDonald to confirm with their jurisdictions that they can approve the document. Note: approvals from Quebec and Nova Scotia were confirmed by emails following the meeting Nov 14th and 29th respectively.
2013-01	Vinyl chloride	• Conference call Jan 15th: A few changes were suggested to the document; members need to see the document again before approval
2013-02	Vinyl chloride	• Conference call Feb 14th: The final document on vinyl chloride is now approved by CDW, with suggested changes
2009-05	Viruses	• Secretariat to work with CDW to write clearer definitions for categories or levels of water degradation. Secretariat to shift text related to the QMRA model to the appendix. Secretariat to verify terminology related to virus "units" throughout the document for consistency, as appropriate. Secretariat to send CDW revised document and discuss changes via teleconference.
2009-05	Viruses	• CDW agreed to not put forward cost implication paragraphs related to implementing the guideline.
2010-11	Viruses	• Secretariat to send revised document with highlighted changes to members. • Members to review the changes in the document by email.

CDW meeting May 2015 - action items

Item	Action Item	Status/comment
2-C CDW Status/ROD/Checklist	Secretariat to circulate the appendix for the boil water advisory guideline	Done
2-D Priority list	Secretariat to send the data request to members for exposure levels of requested pesticides and other chemicals.	Done
4-A Lead	Members to submit impact statements.	TBD
4-B Manganese	D. Reid to forward epigenic references to A. Vezina.	Done
4-D Pesticides	Secretariat to follow-up with PMRA regarding how formulations are considered.	Done
4-F pH	C. Robert to forward pH references to A. Vezina	Done
4-H Microcystins	Secretariat to prepare a letter for issuance to members by June 15th.	Done
	G. O'Toole to update CHE.	Done
4-J PFOS, PFOA	H. Khan noted that one site in Newfoundland has contamination and discussions are ongoing with Transport Canada. A number of technical reports have been prepared that he will forward to A. Vezina for consideration	Done
4-K Other chemical/radiological	A. Vezina to follow up regarding the sharing of arsenic speciation data.	On-going
5-A National Drinking Water Conference	S. McFadyen to prepare financial details for an October 2016 conference with NSERC Chairs (Option A).	On-going
5-B Hydraulic fracturing	Dr. A-M. Tugulea to forward reference on hydraulic fracturing to A. Vezina for circulation to members.	Done
5-D Iodo-THM formation	C. Robert to share iodo-THMs information.	On-going
5-E Scope of regulators' meeting	Sub-committee to re-convene and consider feedback.	On-going
7 Members' Reports	D. Fishwick to send British Columbia's distribution system guideline to A. Vezina for circulation to members.	Done
	G. Somers to send Prince Edward Island's operator training information to A. Vezina for circulation to members.	On-going
	C. Robert to share disinfection by-product monitoring results with the Secretariat.	On-going
	C. Robert to send Québec's guidance document on how to design small drinking water systems to A. Vezina for circulation to members.	Done

2- Agenda/Meeting

2-D CDW Priority List / Old guidelines

Reference/Action:

- Oral presentation on priority list and path forward for older guidelines
- Status: Below is the top 20 priorities, as discussed and approved at the April-May 2014 meeting, with latest changes as discussed at the October 2014 and the May 2015 meeting:
  1. Arsenic - (delayed until IRIS assessment completed)
  2. Trihalomethanes - total (THMs)
  3. Strontium
  4. Chloramines (DBP)
  5. Dioxane, 1,4-
  6. Haloacetic acids (HAAs)
  7. Barium
  8. Cadmium
  9. Aluminum
  10. Boron
  11. Acrylamide
  12. ~~Pentachlorophenol~~ (withdrawn)
  13. Trichloroethylene
  14. Iron
  15. Zinc
  16. Formaldehyde
  17. Hydrocarbons, F2, F3, F4
  18. Odour (AO)
  19. Perchlorate
  20. Asbestos
- At the May 2015 meeting, members agreed switching the priority of aluminum and cadmium.
- The Technical Secretariat is now proposing an approach to update or withdraw older guidelines
- CDW to discuss

Notes:

3- Parameters - Microbiological

3-A Protozoa

Reference/Action:

- Oral presentation on the draft guideline technical document on protozoa in drinking water
- To be sent prior to meeting: Draft Guideline Technical Document on Protozoa
- Status: The draft document on protozoa has gone through internal and external peer-review processes. The comments from these reviews were integrated, and the document will be presented at the meeting for approval by CDW for a 2 month public consultation period.
- For CDW discussion/approval

Notes:

3- Parameters - Microbiological

3-B Viruses

Reference/Action:

- Oral presentation on the draft guideline technical document on viruses in drinking water
- Status: The guideline technical document on viruses was last updated in 2011. The work on the next update of the technical document was initiated at the end of 2014. The document is being drafted and will go through internal and external peer-review processes. Once the comments from these reviews are integrated, the document is expected to be presented at the May 2016 meeting for approval by CDW for a 2 month public consultation period.
- For information only

Notes:

3- Parameters - Microbiological

3-C Other microbiological

Reference/Action:

- Verbal update on other microbiological documents and review of other work in the area of microbiology (QMRA, *enterococcus*, etc).
- For information only

Notes:

4- Parameters - Chemical

4-A Manganese

Reference/Action:

- Oral presentation on the draft guideline technical document on manganese in drinking water
- Attached: Draft Guideline Technical Document on manganese
- Status: The draft document on manganese has gone through internal and external peer-review processes. The comments from these reviews were integrated, and the document is presented at the meeting for approval by CDW for a 2 month public consultation period.
- For CDW discussion/approval

Notes:

Manganese in Drinking Water

Document for Public Comment

Prepared by the Federal-Provincial-Territorial Committee on Drinking Water

Consultation period ends
Month, 201?

Manganese in Drinking Water
Document for Public Consultation
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November, 2015

Manganese in Drinking Water

Purpose of consultation

The Federal-Provincial-Territorial Committee on Drinking Water (CDW) has assessed the available information on manganese with the intent of updating the current drinking water guideline and guideline technical document on manganese in drinking water. The purpose of this consultation is to solicit comments on the proposed guideline, on the approach used for its development and on the potential economic costs of implementing it, as well as to determine the availability of additional exposure data.

The existing guideline on manganese, last updated in 1987, established an aesthetic objective (AO) of 0.05 mg/L (50 µg/L), based on treatment limitations as well as taste and staining of laundry and plumbing fixtures. This expanded and updated document proposes both a maximum acceptable concentration and an aesthetic objective for total manganese in drinking water. The proposed MAC of 0.1 mg/L (100 µg/L) is based on neurological effects observed in rodents, which are consistent wih the effects observed in children. The proposed AO of 0.02 mg/L (20 µg/L) would minimize the occurrence of discoloured water complaints and improve consumer confidence in drinking water quality. The document provides updated data and information related to exposure to manganese in Canada and to analytical methods and treatment technologies available at the municipal and residential scales.

The CDW has requested that this document be made available to the public and open for comment. Comments are appreciated, with accompanying rationale, where required. Comments can be sent to the CDW Secretariat via email at water_eau@hc-sc.gc.ca. If this is not feasible, comments may be sent by mail to the CDW Secretariat, Water and Air Quality Bureau, Health Canada, 3rd Floor, 269 Laurier Avenue West, A.L. 4903D, Ottawa, Ontario K1A 0K9. All comments must be received before XXX, 2016.

Comments received as part of this consultation will be shared with the appropriate CDW member, along with the name and affiliation of their author. Authors who do not want their name and affiliation shared with their CDW member should provide a statement to this effect along with their comments.

It should be noted that this guideline technical document on manganese in drinking water will be revised following evaluation of comments received, and a drinking water guideline will be established, if required. This document should be considered as a draft for comment only.

November 2015

Manganese

Part I. Overview and Application

1.0 Proposed guideline

A maximum acceptable concentration (MAC) of 0.1 mg/L (100 µg/L) is proposed for total manganese in drinking water. An aesthetic objective (AO) of 0.02 mg/L (20 µg/L) is also proposed for total manganese in drinking water.

2.0 Executive summary

Manganese occurs naturally in the environment and is widely distributed in air, water and soil. It is not found in the elemental form in the environment, but can exist in 11 different oxidation states. Manganese may be present in water in the environment from natural sources (rock and soil weathering) or as a result of human activities (such as mining, industrial discharges and landfill leaching). Manganese is used in various industries, including in the steel industry, in the manufacture of various products (e.g., fireworks, dry-cell batteries, fertilizers, fungicides and cosmetics and paints). In its permanganate form, it is also used as an oxidizing agent in the treatment of drinking water.

This guideline technical document reviews and assesses all identified health risks associated with manganese in drinking water. It incorporates new studies and approaches and takes into consideration the availability of appropriate treatment technology. Based on this review, the proposed drinking water guideline for manganese is a maximum acceptable concentration (MAC) of 0.1 mg/L (100 µg/L), based on infants, the most sensitive population.

During its fall 2015 meeting, the Federal-Provincial-Territorial Committee on Drinking Water reviewed the guideline technical document on manganese and gave approval for this document to undergo public consultation.

2.1 Health effects

Manganese is an essential element for humans. Deficiency is considered unlikely in Canada, as adequate amounts are obtained from food. A non-cancer endpoint was chosen for this assessment as available studies are not adequate to support a link between manganese and cancer. Some studies in humans suggest an association between manganese in drinking water and neurological effects in children, however they can only be used to support the choice of the key health effect. The effects observed in children are consistent with the neurological effects reported in the key animal studies used to establish the proposed MAC.

2.2 Aesthetic considerations

Concerns regarding the presence of manganese in drinking water are often related to consumer complaints regarding discoloured water. The proposed AO of 0.02 mg/L (20 µg/L) would minimize the occurrence of discoloured water complaints and improve consumer confidence in drinking water quality.

2.3 Exposure

Manganese occurs naturally and is widely distributed in the environment. Canadians can be exposed to manganese through its presence in air, food, consumer products, soil and drinking water, with food being the main source of exposure. However, the bioavailability of manganese is higher from water than from food, as the forms found in water are more readily absorbed than those found in food. Levels of manganese in fresh water in Canada are usually below 100 µg/L, with some spikes reaching into the milligrams per litre range. Higher levels can occur in acidic groundwater and with industrial discharges. Manganese is generally more prevalent in ground waters than in surface waters. Intake of manganese from drinking water is not expected through either skin contact or inhalation.

2.4 Analysis and treatment

There are several analytical methods available for the analysis of total manganese in drinking water at levels well below the proposed MAC and AO. Total manganese includes both the dissolved and suspended forms of manganese in a water sample.

There are various methods available to decrease levels of manganese in drinking water to below the proposed MAC. The choice of an appropriate method will depend on the form of manganese present in the source water. As manganese can easily convert between the soluble and particulate forms, it can be challenging to control in treatment plants and distribution systems. Low levels of manganese in the source water may accumulate in the distribution system and periodically lead to high levels of manganese at the tap. There are several treatment technologies that can be effective for manganese removal at the residential scale; however there are currently no treatment units certified specifically for that purpose.

Most well operated and optimized treatment plants can achieve manganese concentrations of 0.015 mg/L or less in the treated water, which would minimize the accumulation of manganese and its potential release in the distributed water. This would help prevent both consumer complaints related to discoloured water and higher manganese concentrations at consumer's taps (which could be above the proposed MAC).

3.0 Application of the guideline

Note: Specific guidance related to the implementation of drinking water guidelines should be obtained from the appropriate drinking water authority in the affected jurisdiction.

3.1 Monitoring

Water sources should be characterized to determine if manganese is present. This should include sampling during periods when manganese is mostly likely to be elevated in surface waters such as during thermal stratification in the summer and lake turnover in the fall. While manganese concentrations in groundwater are less likely to fluctuate between seasons, large variations have been observed between wells located in close proximity to each other. Therefore, all wells in a well field should be characterized. In source waters where manganese is present at concentrations equal to or greater than 0.02 mg/L, monitoring of surface water should be conducted quarterly with weekly monitoring during summer/fall in lakes and reservoirs subject to stratification and/or large fluctuations in manganese concentrations. Groundwater sources should be monitored semi-annually. Authorities may consider reduced monitoring when it has been demonstrated that manganese concentrations are consistently below the AO.

Utilities that treat their water to remove manganese need to conduct frequent monitoring of raw and treated water in order to make necessary process adjustments and to ensure that treatment processes are effectively removing manganese concentrations below the MAC and the AO. The frequency of monitoring of finished water will depend on historical knowledge of manganese fluctuations in the raw water and the type of treatment processes in place. For example, surface water treatment plants where manganese concentrations fluctuate and oxidation and filtration is used for treatment may need to monitor daily. Monitoring within the treatment plant, at key treatment steps, may be needed if a utility is having difficulty controlling treated water manganese concentrations.

Since manganese can accumulate and release in distributions systems, monitoring within the distribution system and at consumer's taps should also be conducted for systems where manganese is or was historically present in the source water. Since manganese releases tend to be sporadic events, it is difficult to establish a practical routine monitoring programme that could effectively detect manganese in tap water due to manganese release within the distribution system. However the risk factors associated with both distribution system manganese accumulation and release could be used as indictors of when (event-based) and where to monitor for manganese releases. Event-based monitoring may be needed during conditions where risk of release is increased such as following any hydraulic disturbances (e.g., main breaks or hydrant flushing) to the system or changes in water chemistry (e.g., changes to pH, temperature, source water type or uncontrolled source water blending, chlorine residual, or uncontrolled disinfectant blending). Distribution system sampling locations would ideally be located where there are both increased risk factors for manganese accumulation (e.g., proximity to water treatment plant, pipe materials, biofilm) and event-based release risk factors. Monitoring should also be conducted during any discoloured water event, although the absence of discoloured water should not be interpreted as the absence of a manganese release. Monitoring for manganese should be done in conjunction with other metals that can co-occur in the distribution system and have been shown to release with manganese (e.g., iron, arsenic, lead). Utilities that undertake preventive measures with stable hydraulic, physical and water quality conditions and have baseline data indicating that manganese does not occur in the system may conduct less frequent monitoring.

Appropriate filtration should be conducted on all samples collected to determine the particulate and dissolved manganese components. Utilities that are directly oxidizing manganese using potassium permanganate, chlorine dioxide or ozone should also consider quantifying the colloidal manganese fraction of selected samples within the treatment train. This is important in order to determine what type of treatment is needed and if treatment processes are effective.

Homeowners with private wells are also encouraged to have their water tested for manganese once a year to ensure that the concentration in their water supply is below the MAC. In addition, homeowners with private wells using point-of-entry or point-of- use treatment devices should conduct routine testing on both the water entering the treatment device and the treated water to verify that the treatment device is effective.

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Manganese (CAS Registry No. 7439-96-5) is a group VIIb transition metal that often naturally co-exists with iron in geologic deposits and soils, and corrodes under atmospheric conditions. Manganese has a boiling point of 1,962°C and a melting point of 1,244°C. It has a vapor pressure of 1 mm Hg at 1292°C (summarized in U.S. EPA, 2004; ATSDR, 2012). Manganese exists in both organic and inorganic forms, which have different physico-chemical characteristics. Manganese is an essential element for many organisms including humans, and is present in many foods (IOM, 2001).

Manganese occurs naturally in the environment (widely distributed in air, water, soil) and constitutes 0.1% of the Earth's crust; however, it is not found in the elemental form (Barceloux, 1999; Kohl and Medlar, 2006; WHO, 2011). The concentration in various media varies widely depending on the environmental conditions and proximity to anthropogenic sources such as ferroalloy industry facilities (U.S. EPA, 2004). Manganese can have various oxidation states, (the most common being +2, +4, and +7), and can form a large variety of complexes by combining with other elements such as oxygen, sulphur and chlorine, manganese carbonates and manganese silicates (Stokes et al., 1988; ATSDR, 2012). The most abundant minerals found in soil are pyrolusite (manganese dioxide), rhodochrosite (manganese carbonate ($MnCO_3$), and rhodonite (manganese silicate) (Stokes et al., 1988; IPCS, 1999; Kohl and Medlar, 2006). Mn(IV) oxide is the most abundant form found in manganese ores (Kohl and Medlar, 2006). Only a dozen of some of the 300 minerals containing manganese are considered significant geologic ore deposits to support manganese mining (International Manganese Institute, 2014).

Studies have been conducted examining the visual and taste thresholds of manganese in drinking water (Cohen et al., 1960; Sain et al., 2014). Sain et al. (2014) tested the visual and taste thresholds for dissolved Mn(II) and particulate Mn(IV) using one-in-five, one-in-three, and triangle tests for concentrations between 0.005 - 506 mg/L. Results indicated that the population best estimate taste threshold of Mn(II) from manganese sulfate was 101 mg/L although this was likely influenced by both the sulfate and Mn(II) taste contributions. Logistic regression of the data indicated that the 50% population taste threshold for Mn(II) was 75.4 mg/L. Taste threshold testing for Mn(IV) was limited due to discolouration of the water, however, it was reported that 0.05 mg/L of Mn(IV) could not be distinguished from distilled water. The visual threshold testing found that dissolved Mn(II) is colourless and remains visually undetectable at concentrations as high as 506 mg/L. In contrast, particulate Mn(IV) was visually detectable by 100% of participants at a concentration of 0.005 mg/L. The authors concluded that a manganese concentration of 0.01-0.02 mg/L is an appropriate limit to protect against the discolouration of water. This is supported by numerous studies of drinking water systems that have reported that consumer complaints about discoloured water and/or staining of laundry occur at manganese concentrations above 0.02 mg/L (Sly et al., 1990; Casale et al., 2002; Kohl and Medlar, 2006). Based on this information it has been suggested that drinking water guidelines for manganese established at 0.05 mg/L should be lowered to 0.02 mg/L to minimize the occurrence of discoloured water complaints and improve consumer confidence in drinking water quality (Dietrich and Burlingame, 2015).

Surface and ground water sources of manganese can be natural (from rock and soil weathering) and anthropogenic (from industrial discharges, mining activities and landfill leaching) (Stokes et al., 1988; Kohl and Medlar, 2006; Ljung and Vahter, 2007). Physico-chemical properties of the local environment (e.g., organic carbon content, cation exchange

capacity, pH, eH, mineral and particulate content) influence the manganese speciation and aqueous solubility, which in turn influences the concentration in ground and surface waters (Stokes et al., 1988; Kohl and Medlar, 2006). In surface water, manganese occurs in particulate, colloidal, organic and dissolved forms. Most inorganic manganese salts are soluble to some extent in water. Manganese carbonate has lower solubility (0.065 g/L) than the halide salt, but is the major contributor to the dissolved manganese found in water (IPCS, 1999; Luo and Millero, 2003). More soluble forms include manganese chloride ($MnCl_2$), potassium permanganate ($KMnO_4$) and manganese sulphate ($MnSO_4$), which have solubilities of 72.3. 6.38 and 52 g/L, respectively (as summarized in CRC, 1983). In water, the most common oxidation states are Mn(II), Mn(IV) and Mn(VII) (Stokes et al., 1988; ATSDR, 2012; Rumsby et al., 2014). Mn(III), Mn(V) and Mn(VI) are not stable in neutral solutions. Acidic media, lower reducing environments and the presence of nitrates, sulphates and chlorides favor the reduction of Mn(III) and Mn(IV) mineral compounds to the more stable and soluble Mn(II) form and the formation of manganese sulfate and manganese chloride (Stokes et al., 1988; WHO, 2004; Kohl and Medlar, 2006; ATSDR, 2012). In alkaline (pH>8-9) and oxidizing conditions (in the presence of chlorine, ozone, etc.), conversion of Mn(II) to Mn(IV) will occur, with manganese precipitating and forming insoluble minerals of Mn(IV) compounds (WHO, 2004). Hence, Mn(IV) is insoluble, but can be found in the particulate state of water (Kohl and Medlar, 2006). The oxidation-reduction cycle can be perpetrated abiotically or biotically (IPCS, 1999; WHO, 2004).

The concentration of manganese in soil varies, and is more prevalent in metamorphic and sedimentary rock (Stokes et al., 1988). The form of manganese compounds in the soil depends mainly on the soil and water pH and reduction potential; however, soil mineralogy, oxidative microbial activity and organic matter content are also important related factors (WHO, 2004, 2011). For example, the formation of soluble manganese is favored by an acidic pH and reducing conditions, such as caused by acid rain and during decomposition of organic matter (Khol and Medlar, 2006). The soil retention of manganese results from the cation exchange capacity of the soil, forming insoluble manganese oxides and hydroxides, and from the adsorption to oxides and hydroxides (WHO, 2004).

The main sources of particulate manganese in the atmosphere stem from industrial activities including iron and steel-production plants, power plants, coke ovens, and dust from mining operations. Natural sources of manganese can also increase atmospheric levels through volcanic eruptions, forest fires, ocean spray and soil erosion (Stokes et al., 1988; IPCS, 1999; U.S. EPA, 2004). Manganese particulates released into the atmosphere, such as manganese dioxide (MnO_2) and manganese tetroxide (Mn_3O_4), are small and carried over long distances before deposition onto soil or surface waters.

The reduction-oxidation properties of manganese allow its usage in various industries (Kohl and Medlar, 2006). The steel industry represents the principal use of manganese; mainly to improve mechanical properties of stainless steel and ferromanganese and aluminum alloys (Barceloux, 1999; U.S. EPA, 2004; ATSDR, 2012). Manganese dioxide and chloride are used by industries in dry-cell batteries, fireworks, gasoline, as a contrasting agent in magnetic resonance imaging, agriculture, leathers and textiles (IPCS, 1999; International Manganese Institute, 2014). Manganese sulphate is used in fertilizers and some fungicides. Manganese is also used in cosmetics and paints for its coloring properties. The permanganate ion (MnO_4^-) is used by drinking water treatment plants as an oxidizing agent to remove iron and other contaminants. Use of the gasoline additive methylcyclopentadienyl manganese tricarbonyl declined dramatically in 2004 in Canada due to voluntary measures taken by national petroleum refiners (Walsh, 2007).

5.0 Exposure

Canadians can be exposed to manganese through its presence in air, food, consumer products, soil and drinking water; however, the main source of exposure is through diet (Barceloux, 1999). Manganese is an essential element, being a cofactor for enzymes involved in antioxidant defences, growth, and metabolism, and, as such, has daily recommended intakes set by international organizations (IPCS, 1999; IOM, 2001). Bioavailability is higher for the forms found in water, as they are more readily absorbed than the forms found in food (WHO, 2004).

5.1 Water

Typical levels of manganese in fresh water are in the range of 1 to 200 µg/L, mainly originating from manganese carbonate ($MnCO_3$), either dissolved or in particulate matter. Higher levels can occur in acidic groundwater and with industrial discharges. This is reflected by Canadian data, which indicates that most drinking water contains less than 100 µg/L of Mn, with a few cases where water manganese levels may reach thousands of micrograms per litre. Generally, manganese is more prevalent in groundwater supplies than in surface water supplies because of the increased reducing conditions of the former (WHO, 2011). The National Drinking Water Survey reported manganese concentrations in drinking water in various locations distributed across Canada (Health Canada, 2014a). Treated drinking water points in the distribution systems were sampled and analysed for dissolved manganese in all Provinces and Territories (n = 65). In 2009, 39% of the samples were below the limit of detection (2 µg/L) and 63.2% in 2010. The means were 16.1 µg/L in 2009 and 10.8 µg/L in 2010; and 75% of the measurements were under 11 µg/L in 2009 and under 8 µg/L in 2010. There were only 2 measurements over 100 µg/L in both years (maximum value was 440 µg/L in 2009 and 160.0 µg/L in 2010).

In Alberta, manganese levels were measured between 2003 and 2013 in two water treatment plants that received water from the Elbow and Bow rivers in Calgary, and in four of their distribution systems (North and South ends of Calgary) (Alberta Environment and Sustainable Resource Development, 2014). Dissolved and total manganese in untreated raw water (n=2810) was not detected in 17 samples (less than 1%, detection limit 0.4-0.5 µg/L), the average was 8.7 µg/L, the median was 0.60 µg/L and 31 samples were above 50 µg/L (1%), with a maximum of 434.3 µg/L. In the treatment plant effluents (n=2,175), dissolved and total manganese were not detected in 1,578 samples (72%, detection limit 0.4-0.5 µg/L), the average was 0.61 µg/L, the median was 0.5 µg/L and the maximum was 16.3 µg/L. In the distribution system (n=1925), dissolved and total manganese was not detected in 1169 samples (59%), the average was 0.74 µg/L, the median was 0.5 µg/L and the maximum was 12.6 µg/L.

In British Columbia, the Ministry of Environment reported that manganese was monitored in various locations including both surface and groundwater between 1991 and 2014 (British Columbia Ministry of Health, 2014). Total manganese (chemical extraction) was equal or less than 5 µg/L in 288/3,593 samples (8%), the average manganese was 96.1 µg/L, the median was 8 µg/L and 417 samples were above 200 µg/L (12%). Dissolved manganese was equal or less than 5 µg/L in 4/155 samples (3%), the average manganese was 311 µg/L, the median was 8 µg/L, 20 samples were above 200 µg/L (13%) and 6 samples were above 10,000 µg/L (4%).

In New Brunswick, drinking water manganese was measured in Crown (all were from groundwater wells) and municipal water supply systems (ground and surface water) (New Brunswick Department of Health, 2014). Drinking water on Crown lands had levels of manganese at or below 5 µg/L in 957/1817 samples (53%), the mean was 88 µg/L, the median was 5 µg/L,

310 were above 200 µg/L (17%) and the maximum was 4,000 µg/L. In distribution system of municipal water, manganese levels were at or below 5 µg/L in 1,186/2,115 samples (56%), the mean was 75 µg/L, the median was 5 µg/L, 139 were above 200 µg/L (7%) and the maximum was 2,560 µg/L. In municipal systems with groundwater sources 563/2,081 had levels of manganese at or below 5 µg/L (27%), the mean was 30.6 µg/L, the median was 53 µg/L, 694 were above 200 µg/L (33%) and the maximum was 4,400 µg/L. For municipal systems with surface water sources, 154/490 had levels of manganese at or below 5 µg/L (31%), the mean was 172 µg/L, the median was 28 µg/L, 60 were above 200 µg/L (12%) and the maximum was 3,130 µg/L. Additionally, some information on the content of manganese in private wells (n=10,571) was reported in geo-referenced samples in the New Brunswick Groundwater Chemistry Altas 1994-2007 (New Brunswick Minister of Environment and Local Government, 2008). There were 7,811 samples above 5 µg/L (74%), 4,207 samples above 50 µg/L (40%) and the maximum concentration was 33,600 µg/L. The Sackville treatment plant reported a typical range of 1,500 to 2,500 µg of total Mn/L for raw water, and less than 50 µg/L for finished water concentration leaving the treatment plant.

In Newfoundland and Labrador, levels of manganese in drinking water were reported for samples taken between 2011 and 2014 (Newfoundland and Labrador Department of Environment and Conservation, 2014). All measurements were above the detection limit (10 µg/L). Tap water (n=253) had a mean of 170.9 µg/L, a median of 120 µg/L and the maximum was 980 µg/L. Source water (n=96) had a mean of 224.6 µg/L, median of 115 µg/L and the maximum was 2,400 µg/L.

In Ontario, levels of manganese in drinking water were reported for samples taken between 2009 and 2014 (Ontario Ministry of the Environment and Climate Change, 2014). In distribution systems (measured at treatment plants), manganese levels were at or below 0.1 µg/L in 153/1,330 samples (detection limit of 0.05-0.1), the mean was 4.4 µg/L, the median was 1.5 µg/L, 4 were above 100 µg/L, none above 200 µg/L and the maximum was 187 µg/L. In treated water (measured at the tap), manganese levels were at or below 0.1 µg/L in 222/1,700 samples, the mean was 5.8 µg/L, the median was 1.2 µg/L, 12 were above 100 µg/L, 2 were above 200 µg/L and the maximum was 442 µg/L. In raw water, manganese levels were at or below 0.1 µg/L in 98/2,105 samples, the mean was 23.5 µg/L, the median was 6.8 µg/L, 109 were above 100 µg/L, 51 were above 200 µg/L and the maximum was 838 µg/L.

In Quebec, levels of manganese in treatment plants and distribution system with groundwater sources between 2010 and 2014 were reported (Ministère du Développement durable, de l'Environnement et Lutte contre les changements climatiques, 2014). The average manganese in raw water (n=283) was 86.6 µg/L, the median was 4.3 µg/L, 36 samples (13%) were at or above 200 µg/L and the maximum was 4,100 µg/L (detection limit was 0.2 µg/L). The average manganese in treated water (n=126) was 35.4 µg/L, the median was 2.9 µg/L, 22 samples (17%) were above 50 µg/L, 7 above 200 µg/L and the maximum was 470.0 µg/L. The only manganese measurement in the distribution system was 68 µg/L. A study in Southwest Quebec reported levels between 0.5-71.1 µg/L (mean of 4.11 µg/L) for municipal sources (n=262) (Baldwin et al., 1999). Wells had levels between 0.2-158.9 µg/L (n=16; mean of 2.78 µg/L).

In Saskatchewan, treated drinking water samples were taken in the distribution system (95% of samples) and treatment plants between 2003 and 2014 (n=2239 in 640 sites, detection limit 0.5-10 µg/L) (Saskatchewan Ministry of Environment, 2014). In the distribution system, a mean of 143 µg/L, a median of 10 µg/L and a maximum of 8,440 µg/L were reported for total and dissolved Mn. Treated water had a mean of 229 µg/L, a median of 10 µg/L and a maximum of 3,510 µg/L.

In Yukon, levels of manganese in drinking water was reported for 21 groundwater sources taken in 2012, 2013 and 2014 (detection limit 1-50 µg/L) (Yukon Environmental Health Services, 2014). The mean manganese concentrations were 60.3 µg/L and 13.3 µg/L; and the medians were 20 µg/L and 6 µg/L in raw drinking water (n=33) and in treated drinking water (n=13), respectively. There were 11 samples above 100 µg/L (23.9%, all from raw water) and the maximum was 209 µg/L.

5.2 Food

Food is the main source of exposure to manganese, with grains, nuts and vegetables contributing to most of the intake. Average concentrations of manganese were estimated in various food items in the Canadian Total Diet Study (TDS) (Health Canada, 2009). High manganese concentrations (above 1.0 µg/g) were reported for grains [bread (3.5-19.1 µg/g), white flour (3.5-7.5 µg/g), rice (3.0-4.9 µg/g), cereals (1.0-25.9 µg/g) , popcorn (7.2-10.6 µg/g)], nuts (28.5 µg/g), peanut butter (13.1-16.8 µg/g), organ meats (3.1-4.0 µg/g), some fruits [blueberries (8.3-10.0 µg/g), canned pineapples (12.0-20.4 µg/g), bananas (1.7-4.6 µg/g)], vegetables [0.8-3.0 µg/g for beets, broccoli, cabbage, cauliflower, carrots, celery, lettuce, corn, cucumbers, onions, potatoes and 3.0-7.5 µg/g for spinach], and tea (2.3-5.1 µg/g) and herbs and spices (71.0-123.6 µg/g). Intermediate manganese concentrations (range of 0.5-1.0 µg/g) were reported for cheese (0.05-1.0 µg/g), peppers (0.6-0.8 µg/g), grapes (0.5-0.8 µg/g), and sausages (0.4-1.0 µg/g). Lower manganese concentrations (range of 0.02-0.5 µg/g) were reported for meats [0.02-0.2 µg/g for beef, lamb, chicken, fishes, and veal], mushrooms (0.4-0.6 µg/g), apples (0.2-0.3 µg/g), coffee (0.2-0.3 µg/g), eggs (0.3-0.4 µg/g), and milk (0.01-0.04 µg/g).

The dietary intakes of different constituents for different age–sex groups of the Canadian population were also measured in the TDS (Health Canada, 2009). Manganese average dietary intakes were estimated in the 0-1, 2-3, 4-6, 7-9, 10-12 months old age groupings and for those 1-4, 5-11, 12-19, 20-39, 40-64 and 65+ years old. The average across all age groups of dietary intakes of manganese were estimated at 61.3 µg/kg body weight (bw) per day in 1993 to 1999 (Montreal), 59.0 µg/kg bw per day in 2000 (Ottawa), 51 µg/kg bw per day in 2001 (St John's), 56.0 µg/kg bw per day in 2002 (Vancouver), 52 µg/kg bw per day in 2003 (Montreal), 50 µg/kg bw per day in 2004 (Winnipeg), 44 µg/kg bw per day in 2005 (Toronto), 53 µg/kg bw per day in 2006 (Halifax) and 54.0 µg/kg bw per day in 2007 (Vancouver). These manganese intakes support previous estimates of 2-9 mg/day for adults (higher levels for vegetarians) (Schroeder et al., 1966; Barceloux, 1999; IOM, 2001)

Average breast milk concentrations have been estimated at 3.7 µg/L (2.7-5.4 µg/L; n=11 healthy mothers) during the first month, with the highest levels measured at day 1 (Casey et al., 1985). Levels decreased to 1.9 µg/L at 3 months, post-partum (Casey et al., 1985; IOM, 2001). Based on preliminary data, Health Canada has estimated a median content of 2.2 ng Mn/g in breast milk using the TDS measures (Health Canada, 2014b). Using this estimated median manganese level and assuming an average breast milk intake of 780 mL/day, dietary intake of manganese from breast milk for 0-6 month old infants can be calculated as ~ 0.2 µg/L (Health Canada, 2014b). The WHO has estimated a daily intake of manganese of 2.6-11.1 µg/day for breast fed infants (WHO, 1989).

In the U.S., daily intake from food was estimated at 2.7 and 2.2 mg for men and women, respectively (NRC, 1989). As for 6-11 months infants, the levels were estimated at 1.1 mg/day and at 1.5 mg/day for 2 year old children. In the UK, average adult intake was estimated at 4.9 mg/day, with tea contributing to half of this amount (EVM, 2002).

With regards to manganese in infant formula, a minimum of 5 µg of manganese/100 Kcal (3.33 µg/100 mL of ready to feed infant formula) is indicated by the Canadian Food and Drug Regulations (Minister of Justice, 2014). The regulations did not set a maximum for manganese in infant formula. The Expert Panel of the Life Science Research Office (LSRO) and the Codex Committee of the WHO and FAO have set guidelines at a minimum of 1 µg manganese/100 kcal and a maximum (guidance upper level (GUL) by WHO and FAO) of 100 µg manganese/100 Kcal (67 µg/100 mL) infant formula (liquid or powdered form) intended to be marketed as substitutes for breast milk in order to comply with nutritional requirements (Raiten et al., 1998; WHO, 2011).

5.3 Air

Ambient air generally has low levels of manganese, consistent with the low vapour pressure of the manganese compounds (Stokes et al., 1988). Low levels have also been measured in particulate matter (PM) in Canada. In Canada, ambient air manganese is monitored in atmospheric aerosols (fine/coarse) through the National Air Pollution Surveillance (NAPS) Network. In 2013, levels of manganese were measured in the range 0.050-51.4 ng/m^3 for $PM_{2.5}$ (vast majority of samples < 10 ng/m^3) and 1-43 ng/m^3 (0.001-0.043 µg/m^3) for PM_{10} (vast majority of samples < 0.010 µg/m^3) (Environment Canada, 2014). This is similar that what had been measured between 2003 and 2005, with manganese levels in the range of 0.002-0.025 µg/m^3 (Health Canada 2010). The levels were between 0.06 and 0.22 µg/m^3 in some areas of cities with major manganese-emitting industries (2003 and 2005). Levels of manganese ($PM_{2.5}$ and PM_{10}) have dropped between the late 1980s and early 2000s by 13-77% (Health Canada, 2010).

Studies investigating population exposure in Canadian and U.S. cities (Toronto, Riverside, and Indianapolis) were also conducted in Toronto in 1995 and 1996, years of widespread use of MMT in gasoline (Wallace and Slonecker, 1997). A median of 0.015 µg/m^3 and 0.024 µg/m^3 were measured for personal (general population) and fixed monitoring sites, respectively (limit of detection 2-9 ng/m^3). In the U.S, median of personal exposure was measured at 0.003 µg/ m^3 in Indianapolis (where MMT was not added to gasoline) and 0.020-0.049 µg/ m^3, in Riverside, California, respectively. Levels of 1-2 ng/ m^3 were estimated as background concentrations in non-contaminated environments in Canada and the U.S.

5.4 Consumer products

Manganese is available as a nutritional supplement in Canada (Health Canada, 2007a). The Health Canada recommended doses in natural health products are between 0.13 and 9 mg/day for adults (none for less than 19 years old) from multiple sources including manganese chloride, citrate and oxide.

5.5 Soil

Manganese is naturally found in soil in concentrations estimated between 40 and 900 mg/kg. Depending on rock type, it can be found in concentrations outside of this range (higher in iron ores, mafic and sedimentary rocks, lower in sandstones) (Barceloux, 1999; IPCS, 1999; Michaelke et al., 2007).Children can ingest manganese in soil through hand-to-mouth behavior (IPCS, 1999).

The mean background (not influenced by anthropogenic activity) manganese concentration for different soil profiles of five major geological areas (n=173) of Canada was 520 mg/kg, with a range of 100 to 1 200 mg/kg in a comprehensive survey at the national and regional levels (McKeague and Wolynetz, 1980).

5.6 Biomarker concentrations in the Canadian Population

Statistics Canada, Health Canada and the Public Health Agency of Canada launched Cycle 1 of the cross-sectional Canadian Health Measures Survey to collect health data and biological specimens in approximately 5600 Canadians aged 6–79 years distributed among five age groups (6–11, 12–19, 20–39, 40–59 and 60–79 years) at 15 sites between 2007 and 2009 (Health Canada, 2010). Cycle 2 of the Survey, conducted between 2009 and 2011with a similar protocol, included Canadians aged 3–79 years old. For all ages, the geometric mean whole blood manganese concentration was 9.2 µg/L (95% confidence interval [CI] = 9.0–9.5 µg/L; n=5309) in Cycle 1 and 9.8 µg/L (95% CI = 9.5–10.0 µg/L; n=5575) in Cycle 2. Mean whole blood manganese concentration was in 11.0 µg/L (95% CI = 11.0-12.0 µg/L) in 3-5 year olds (cycle 1 only; cycle 2 not reported). Age groups older than 6 years were ranged from 8.8-10 µg/L in cycle 1 and 9.4-11 µg/L in cycle 2. Mean whole blood manganese concentrations from all age groups ranged from 8.6-9.5 µg/L in cycle 1, and 9-10 µg/L in cycle 2 for males, and 9.2-11 µg/L in cycle 1, and 9.5-11 µg/L in cycle 2 for females. The highest blood manganese levels were reported in the 6-11 yrs. age groups (10-12µg/L). The geometric mean urinary manganese concentration was 0.081 µg/L (95% CI = 0.072–0.092 µg/L; n =5431), for the total Canadian population aged 6–79 years in Cycle 1 (not reported for Cycle 2 since most measurements were under the limit of detection). Whole blood manganese concentrations ranged from 6.3 µg/L (10th percentile) to 15.0 µg/L (95th percentile). No data were provided for children less than 3 years of age.

The Health Canada MIREC study (n=1415-1938) reported geometric means in 1st trimester (8.8 µg/L 95% CI = 8.7-8.9 µg/L, maximum of 29.1 µg/L) and in 3rd trimester of mother's blood (12.0 µg/L 95% CI = 12.0-12.4 µg/L, maximum of 33.5 µg/L), in cord blood (30.9 µg/L 95% CI = 30.9-32.0 µg/L, maximum of 98.9 µg/L), and in meconium (4.5 µg/L 95% CI = 4.3-4.7 µg/L, maximum of 40.0 µg/L) (Health Canada, 2015).

Manganese geometric means of 20.4 µg/L, 0.36 µg/g, and 0.10 µg/g (5th and 95th percentiles of 11.1-40.4, 0.16-0.87, and 0.06-0.16 µg/L) were measured in mother's blood, hair, and placenta, respectively, in a French cohort study (n=247 pregnant women and their offspring) (Takser et al., 2003). Manganese geometric means of 38.5 and 0.75 µg/L (5th and 95th percentiles of 19.1-71.2, 0.22-4.25 µg/L) were measured in cord and newborn blood, respectively. Levels in blood at follow-up at six years were very similar to the levels at birth.

In Quebec, a cross-sectional survey collected data on trace metals in men and women 18–65 years of age residing in the Quebec city area in 2001 (n=500) (Leblanc et al., 2004). Levels of manganese in whole blood (geometric mean 169.8 nmol/L (95% CI = 164.9–174.8 nmol/L); n=427) and serum (geometric mean 12.0 nmol/L (95% CI = 11.8–12.3 nmol/L); n=403) were reported. Another study in Southwest Quebec looked at manganese exposure including blood levels (n=306, aged 20-69 years old) (Baldwin et al., 1999). The geometric mean blood manganese was 7.1 µg/L (range 2.5-15.9). The geometric mean whole blood manganese concentration in a sample of non-smoking oyster growers (age 33-64 years old; n=61) living in British Columbia was 176.8 nmol/L for males and 217.8 nmol/L for females, and 16.5 nmol/L for males and 12.9 nmol/L for females in serum (Clark et al., 2007). Although the blood manganese concentrations were significantly higher in females compared to males, serum manganese levels were not different between genders.

5.7 Total daily intake/exposure

Estimated intakes from drinking water can vary considerably depending on water manganese concentrations (see section 5.1 on exposure), and an accurate estimation of the exposure of the Canadian population is dependent on multiple factors. In addition, caution is

merited when extrapolating the estimated intakes from various sources to the relative uptake from each source, as additional factors (including bioavailability and manganese form/speciation) play a role in the toxicological significance of the estimated dose.

5.8 Multi-route exposure through drinking water

Based on the physical and chemical properties of elemental manganese, exposure from drinking water through the dermal and inhalation routes is likely negligible (Karim, 2011).

6.0 Analytical methods

The U.S. Environmental Protection Agency (EPA) currently has four recommended analytical methods (Method 200.5 revision 4.2, Method 200.7. revision 4.4, Method 200.8 revision 5.4 and Method 200.9 revision 2.2) for the analysis of total manganese in drinking water (U.S. EPA, 2014). The EPA also recommends several methods (SM 3111B, SM 3113B, and SM 3120B) developed by a voluntary consensus standard organization.

Total manganese is defined as the sum concentration of both the dissolved and suspended (particulate) fractions of a water sample and is analyzed using methods to determine total recoverable manganese. Analysis of total manganese is needed for comparison to the MAC. However, determining the concentration of both the dissolved and particulate fractions is critical for determining the appropriate treatment method and monitoring treatment performance for manganese removal. This is discussed in more detail in sections 6.2 and 7.2.

The method detection limit (MDL) for each of the recommended methods are provided below. It should be noted, however, that MDLs are dependent on the sample matrix, instrumentation, and selected operating conditions and will vary between individual laboratories.

- EPA Method 200.5 Rev. 4.2 uses axially viewed inductively coupled plasma atomic emission spectrometry (ICP-AES) and has a MDL of 0.06 µg/L (U.S. EPA, 2003).
- EPA Method 200.7 Rev.4.4 uses ICP-AES and has an MDL of 1.4 µg/L (U.S. EPA, 1994a).
- EPA Method 200.8 Rev. 5.4 uses inductively coupled plasma mass spectrometry (ICP-MS) and has MDLs of 0.02 µg/L for total recoverable manganese and 0.04 µg/L for direct aqueous injection (U.S. EPA, 1994b).
- EPA Method 200.9 Rev. 2.2 uses stabilized temperature graphite furnace atomic absorption (GFAA) spectrometry and has a MDL of 0.3 µg/L (U.S. EPA, 1994c).
- SM 3111B uses direct air-acetylene atomic absorption spectrometry and has a MDL of 0.01 mg/L (10 µg/L) (APHA et al., 1992, 1995, 2005, 2012).
- SM 3113B uses electrothermal atomic absorption spectrometry and has a MDL of 0.2 µg/L (APHA et al., 1992, 1995, 2005, 2012).
- SM 3120B uses ICP-AES and has a MDL of 2 µg/L (APHA et al., 1992, 1995, 1998, 2005, 2012).
- The online versions of SM 3113B-04, 99 and SM 3120B-99 are also recommended methods.

One additional standardized analytical method is available that is not included in the U.S EPA recommended methods. SM3125 is a well-established method that is acceptable for conducting manganese analyses in drinking water.

- SM 3125B uses ICP-MS and has a MDL of 0.002 µg/L (APHA et al., 1992, 1995, 2005, 2012).

6.1 Methods

EPA Method 200.5 revision 4.2, EPA Method 200.7 revision 4.4 and SM3120B are based on multi-elemental determinations by inductively coupled plasma atomic emission signals (ICP-AES) using sequential or simultaneous instruments. The instruments measure characteristic atomic-line emission spectra by optical spectrometry. Element specific emission spectra are produced by radio-frequency inductively coupled plasma (ICP). The spectra are dispersed by a grating spectrometer and the intensities of the line spectra are monitored at specific wavelengths by a photosensitive device. A variation for EPA Method 200.5 is that it uses axially viewed plasma atomic emission signals for the analysis of all analytes. Matrix effects may occur in EPA 200.5 when total concentrations of calcium, magnesium, and sodium exceed 125 mg/L and silica exceeds 250 mg/L. Interferences may occur in EPA Method 200.7 and SM3120B when total dissolved solids are greater than 0.2% (w/v) or 1500 mg/L, respectively.

In EPA Method 200.8 Rev. 5.4 and SM 3125 B samples are atomized and ionized into a radio-frequency plasma. The ions are extracted from the plasma by a vacuum interface and separated on the basis of their mass-to-charge ratio by a mass spectrometer. Separated ions are detected by an electron multiplier or Faraday detector. Matrix effects may occur in EPA Method 200.8 and SM 3125B when total dissolved solids are greater than 0.2% and 0.5% (w/v), respectively.

Method 200.9 Rev. 2.2 and SM 3113B use stabilized temperature platform graphite furnace atomic absorption spectrometry. The technique includes a series of three heating steps to dry, char (to reduce interferences by other ions) and atomize analytes from the pyrolytic graphite surface. The atomization raises the analytes into an atmosphere of high-purity argon, and light of a specific wavelength is passed through the atomic cloud. The attenuation of the intensity of light is measured. No matrix interferences relevant to manganese were identified in these methods.

SM 3111B is a direct air-acetylene flame atomic absorption method. The sample is aspirated into the flame and atomized. A light beam is directed through the flame, into a monochromator, and onto a detector that measures the amount of light absorbed by the atomized element in the flame. Because each metal has its own characteristic absorption wavelength, a source lamp composed of that element is used.

There is no U.S. EPA practical quantitation level (PQL) for manganese. However, a U.S. EPA (2010) report indicated that the use of PQLs for determining analytical capabilities can be problematic as different methods have been used for its determination. The report noted that minimum reporting levels (MRLs) may be useful as an alternative to PQLs. The MRL for an analyte is measured using a specific analytical method and is defined as an estimate of the lowest concentration minimum reporting level or LCMRL that is achievable by the analyst with 95% confidence at least 75% of the time (U.S. EPA, 2010). MRLs were not reported for the methods listed above with the exception of EPA Method 200.5 that reported an MRL of 0.2 µg/L. With the exception of EPA Method 3111B, the reported MRLs and/or MDLs of the methods listed above are well below the levels needed for accurate quantitation of manganese below the MAC and AO.

6.2 Sample preservation and preparation

Accurate quantification of dissolved, particulate and total manganese in samples is dependent on the proper sample preservation and preparation steps. SM 3030B provides guidance on filtration and preservation procedures for the determination of dissolved or particulate metals

(APHA et al., 2012). To determine dissolved metals, samples should be filtered at the time of collection using preconditioned plastic filtering devices under either vacuum or pressure. Membrane filters with pore diameter sizes between 0.22 to 0.45 µm are recommended for fractionating dissolved and particulate manganese (Kohl and Medlar, 2006; Brandhuber et al., 2013). The filtrate should be acidified to pH < 2 with concentrated nitric acid. To determine particulate manganese, the filter should be retained and the particulate material on it digested in the laboratory using appropriate methods (APHA et al., 2012).

Currently, EPA methods 200.7, 200.8 and 200.9 and SM 3111B, SM 3113B, SM 3120B and SM 3125B require acid digestion of samples only when the turbidity of the acid-preserved sample is greater than 1 nephelometric turbidity unit (NTU). Digestion for EPA methods is performed by transferring an aliquot of the sample into a solution of nitric acid and hydrochloric acid followed by gentle heating to a temperature of approximately 85°C (i.e., hot digestion) (EPA, 1994,a,b,c). Microwave assisted digestion (SM 3030 K) is recommended for analysis of total recoverable manganese using SM methods that are based on ICP-MS. Although the methods cited above do not require hot acid digestion for total manganese analysis unless turbidity is greater than 1 NTU, research conducted on other metals such as lead and chromium have indicated that this does not accurately quantify the total metal concentration in a sample. For example, analytical requirements under UCMR3 include solubilizing the acid preserved sample by gentle heating using nitric acid, regardless of the sample turbidity or the method used (U.S. EPA, 2012). Similarly, APHA et al. (2012) recommends verifying if adequate recovery of metals has occurred in different sample matrices by comparing digested and undigested results.

In some cases, utilities may want to quantify the fraction of colloidal manganese present within a treatment plant or in the finished water. This could be of particular importance when troubleshooting problems with treatment plant operations. Colloidal manganese can be found in water samples collected following the application of a strong oxidant such as ozone, permanganate or chlorine dioxide, prior to coagulation or in plants were intermediate ozonation is practiced (i.e., biological filtration plants). These colloidal solids are also more likely to be found in soft waters as calcium and magnesium ions help to destabilise and aggregate manganese oxide particles. Colloidal manganese is typically defined as manganese oxide particles that are <0.20 µm and > 30,000 daltons. If colloidal manganese is present it will pass through 0.20 µm filters and it will be incorrectly quantified as dissolved manganese. Therefore, following initial filtering through a 0.20 µm filter, the sample will require additional filtering through a 30,000 molecular weight cut-off (MWCO) filter when quantification of colloidal manganese is needed.

6.3 Colorimetric methods

Colorimetric methods are available for quantifying dissolved manganese in drinking water. These methods are based on a reaction between dissolved manganese and other compounds to produce permanganate which can then be measured colorimetrically. These reactions can be subject to interferences form other metals or organics in solution which can affect the accuracy of the results. Therefore, these methods are best suited to monitoring within treatment plants to assess treatment effectiveness and not for compliance monitoring. The advantage of colorimetric methods is that commercial kits are available and they can be used to obtain a rapid indication of changes to manganese concentrations that can aid process monitoring within a treatment plant (Brandhuber et al., 2013).

SM 3500 Mn B is a colorimetric methods based on persulfate oxidation of dissolved manganese in the presence of silver nitrate. Samples with particulate manganese oxides need to be treated with a series of reducing compounds to dissolve the manganese oxides. Photometric

measurements can be made by preparing standard solutions and comparing the sample absorbance to those of the standards. This method has a minimum detectable concentration of 42 µg/L (APHA et al., 2012). A proprietary colorimetric method that employs ascorbic acid, alkaline cyanide and an indicator solution is also available. This method has a detection range of 0.01 to 0.7 mg/L (Brandhuber et al., 2013).

7.0 Treatment technology and distribution system considerations

7.1 Manganese chemistry and treatment

An understanding of the chemistry and microbiology of manganese in drinking water systems is important when determining the most appropriate treatment system or assessing and optimizing existing systems for manganese removal. As discussed in section 4.0, manganese exists in many oxidation states in water systems. The four most important oxidation states from a drinking water treatment perspective are: 1) Mn(II) a soluble free metal divalent cation that is clear in water; 2) Mn(III) a transitional state which exists as a manganese oxide (Mn_2O_3) that is a dark brown/black solid; 3) Mn(IV) as MnO_2(s) a black solid and; 4) Mn (VII) as MnO_4^- a dissolved permanganate ion that appears purple in water and is added to water as a oxidant during drinking water treatment. A brief overview of manganese chemistry relevant to drinking water treatment is provided below. More detailed information can be found in Sommerfield (1999), Kohl and Medlar (2006), and Brandhuber et al. (2013).

The chemical reactions that control which species of manganese are present in drinking water treatment include oxidation/reduction, precipitation/dissolution, and sorption/desorption reactions. In a drinking water treatment plant all three reactions can occur throughout the treatment process. The species of manganese which are present are controlled by the oxidation/reduction potential and pH of the water along with the presence of other parameters in the water that can combine with manganese to form manganese compounds. Under high pH or strongly oxidizing conditions, dissolved Mn(II) will, at equilibrium, form insoluble oxides, hydroxides or carbonate solids.

Manganese treatment processes are designed to take advantage of the differences in the solubility of manganese species. The solubility of reduced Mn(II) is orders of magnitude greater than the solubility of Mn(IV). Therefore, oxidation of Mn(II) to Mn(IV) results in precipitation of manganese oxide solids. Since these solids can exist in several oxidation states (e.g Mn(III) and Mn(IV)) they are often referred to as MnO_x(s) (Brandhuber et al., 2013). The tendency of manganese to precipitate or dissolve can be controlled by changing the oxidation/reduction and pH conditions in a drinking water treatment plant.

Adsorption/desorption is the third process that controls manganese removal in drinking water treatment plants. MnO_x(s) particulates have an electric charge that varies with pH but in most cases, these particles are negatively charged and have the capability to adsorb Mn(II) ions from solution. Once Mn(II) is adsorbed to MnO_x(s) particles, the surface catalyzes oxidation of the adsorbed Mn(II) to Mn(IV). This increases the rate at which Mn(II) can be oxidized to Mn(IV).

In practice, manganese can convert between the soluble and particulate forms and can be challenging to control in treatment plants and distribution systems (Brandhuber et al., 2013). It is also important to note that MnO_x (s) can exist in both particulate and colloidal forms. The particulate form is comprised of large oxidized solids (>0.20 - 0.45 µm) whereas the colloidal form is comprised of smaller oxidized particles (<0.20 µm and >30,000 daltons). Under certain

conditions, substantial amounts of colloidal manganese can be formed during the direct oxidation of Mn(II) with a strong oxidant such as ozone. Colloidal particles can be difficult to destabilize and coagulant addition needs to be optimized to effectively remove these particles during sedimentation and filtration (Casale et al, 2002; Brandhuber et al., 2013).

7.2 Municipal scale treatment

In order to select the appropriate treatment system for manganese removal or optimize an existing system, it is critical to have a good understanding of the form of manganese (dissolved, colloidal or particulate) present in the source water. When source water needs to be treated for manganese removal, most often dissolved Mn(II) is the predominant species present (i.e., in anoxic groundwater or lake). However, depending on the pH and dissolved oxygen (DO) content of the water a combination of dissolved and particulate manganese can be present. In general, treatment methods used for manganese rely on a combination of processes to remove both dissolved and particulate forms of manganese (e.g oxidation, adsorption and/or filtration). If manganese is present only in colloidal or particulate form (Mn(IV)) it can be removed using common particle removal processes such as conventional filtration or low pressure membrane filtration (microfiltration or ultrafiltration).

Dissolved manganese as Mn(II) can be removed or controlled by source water practices, oxidation/physical separation, adsorption/oxidation, biological filtration, and precipitative softening. One of the most commonly used technologies effective for decreasing manganese concentrations in drinking water is based on directly oxidizing dissolved Mn(II) to form particulate MnO_x(s), which are then removed by a physical removal process such as clarification and granular media filtration or low pressure membrane filtration. These processes typically remove 80 to 99% of manganese to achieve treated water concentrations below 0.04 mg/L. Another common treatment technique for manganese removal is the use of MnO_x(s) coated filter media that adsorbs dissolved Mn(II) and then oxidizes it at the surface when coupled with the presence of an appropriate oxidant such as free chlorine or potassium permanganate. This treatment technology generally achieves higher levels of manganese removal to achieve treated water concentrations below 0.020 mg/L. Biological filtration and softening have also been found to be effective for manganese removal achieving treated water concentrations below 0.03 mg/L (Casale et al., 2002; Kohl and Medlar, 2006; Tobiason et al., 2008; Kohl and Dixon, 2012; Brandhuber et al., 2013). Many of these technologies, in particular MnO_x(s) coated filter media, can be used to effectively remove manganese from drinking water in small systems.

The most effective type of treatment for manganese removal will depend on the type and concentration of manganese in the source water, overall water chemistry, treatment process selected, and other water quality objectives. Utilities should conduct monitoring within treatment plants including periodically determining the different forms of manganese (e.g., dissolved and particulate) to ensure that unit processes are adequately removing manganese. Extensive guidance on the treatment of manganese in drinking water systems can be found in Brandhuber et al. (2013).

Historically, limits for manganese in treated water have been based on aesthetic considerations and treatment achievability (U.S. EPA, 1979). More recently, studies have shown that MnO_x(s) particulates in drinking water cause discolouration of water and are visible to consumers at concentrations as low as 0.005–0.02 mg/L (Sly et al, 1990; Sain et al., 2014). In addition, extensive surveys have found that a manganese concentration of 0.05 mg/L in treated water is not sufficiently low to ensure minimal consumer complaints (Sly et al., 1990; Casale et al., 2002; Kohl and Medlar, 2006). Based on detailed utility surveys, Kohl and Medlar (2006)

reported that the majority of consumers experience episodic difficulties with water discolouration when manganese concentrations are 0.05 mg/L at the tap. Many studies have found that existing treatment plants are capable of achieving a treated water manganese concentration of less than 0.02 mg/L through optimized design and operation of new or existing treatment plants (Kohl and Medlar, 2006; Tobiason et al., 2008; Brandhuber et al., 2013). Kohl and Medlar (2006) reported data from a survey of 189 treatment plants removing manganese from groundwater and surface water sources using a variety of treatment technologies. The geometric mean of the average treated water concentrations from these plants was 0.010 mg/L. Similarly, Casale et al. (2002) reported that approximately 80% of groundwater and 70% of surface water treatment plants (193 treatment plants) achieved treated water concentrations of 0.01 mg/L. These data indicate that utilities can achieve lower treated water concentrations than previously reported and that a manganese concentration below 0.02 mg/L in treated water is achievable for most utilities (Casale et al., 2002; Kohl and Medlar; 2006; Tobiason et al., 2008; Brandhuber et al., 2013).

The implications of the accumulation and release of manganese and co-occurring metals in distribution systems has also been the subject of extensive research in recent years (U.S. EPA, 2006; Friedman et al., 2010; Ginige et al., 2011; Brandhuber et al., 2015). Elevated manganese concentrations at the tap can be associated with the accumulation and release of manganese in the distribution system rather than elevated manganese in the source or treated water (Brandhuber et al., 2015).

Based on the information discussed above, it is recommended that treatment plants establish a treated water goal of ≤0.015 mg/L of total manganese (Brandhuber et al., 2013), which is achievable in most well operated and optimized treatment plants. As the establishement of such a goal will minimize the accumulation of manganese in the distribution system, it will also minimize the subsequent release of manganese in the distributed water, preventing both consumer complaints related to discoloured water and higher manganese concentrations at consumer's taps (which could be above the MAC).

7.2.1 Source water control

In some cases, it may be possible to lower the levels of manganese entering a treatment plant by managing the levels occurring in the source water. Manganese concentrations in groundwater from an individual well tend to be less variable temporally (daily or seasonally) than in surface water (Barbeau et al., 2011). However, large variations in manganese concentrations have been observed between different wells in the same well field located in close proximity. Therefore, utilities with multiple wells can selectively pump different combinations of wells at different flow rates to achieve a lower overall manganese concentration in the water entering the treatment plant (Brandhuber et al., 2013). Another option for controlling manganese concentrations in groundwater is to oxidize dissolved Mn(II) in-situ by raising the redox potential in the aquifer surrounding the wells. This can be achieved by injecting aerated water into the aquifer through recharge wells. This technology is not often used due to concerns with altering the aquifer geochemistry and risk of clogging the extraction wells (Mettler et al., 2001). Despite these concerns, full-scale applications of this technology have been operating successfully in Switzerland and the United States (AWWA, 1984; Mettler et al., 2001).

Aeration techniques can also be used as a control option for lowering manganese levels in surface water. As discussed in section 4.0, reservoirs and lakes can experience a complete loss of dissolved oxygen (DO) in the hypolimnion during thermal stratification. This can result in an increase in the concentration of dissolved Mn(II) in the water column due to release from sediments under anoxic conditions. Hypolimnetic aeration and oxygenation can be used to add

DO to reservoirs while maintaining stratification (Brandhuber et al., 2013). There are several types of aerators that can be used that generate a stream of gas in contact with water to transfer oxygen to the water which is then delivered to the hypolimnion. The amount of oxygen required to adequately aerate a portion or all of the hypoliminion depends on the volume of water, the DO profile in the lake and the oxygen demand of the sediments. Careful control is needed to avoid reservoir destratification which can result in other water quality issues (Kohl and Medlar, 2006). Brandhuber et al. (2013) reported data from a case study of a full-scale hypolimnetic aeration system installed in a reservoir experiencing thermal stratification and resulting in Mn(II) concentrations of 1.7 mg/L at the plant intake. After considering a number of treatment options, the utility decided to install a liquid oxygen system that consisted of two gaseous oxygen diffuser lines placed at the bottom of the reservoir. The system was operated from April to October with oxygen flows adjusted to maintain DO concentrations above 5 mg/L. This minimized the occurrence of dissolved Mn(II) released from the sediment and lowered source water concentrations to a year-round average below 0.05 mg/L (maximum value below 0.2 mg/L).

Variable depth intake is also a control option for surface water treatment plants that have deep reservoirs and a multilevel intake system. These systems can select the level in the reservoir from which to draw water into a plant based on the water quality present at different depths. When minimizing manganese concentrations is the primary objective, treatment plants can monitor the DO and dissolved Mn(II) concentration at each intake and take water with the lowest concentrations (typically from shallower depths once the hypoliminion becomes anoxic in a reservoir). In practice, a variety of water quality considerations are typically taken into consideration when selecting the depth of intake to use since drawing water from shallower depths can result in other water quality concerns such as increased algal cell counts and taste and odour issues (Benskin et al., 2004; Brandhuber et al., 2013).

7.2.2 Chemical oxidation/ physical separation

When the predominant form of manganese in the source water is dissolved Mn(II) then direct oxidation to convert Mn(II) to MnO_x(s) precipitates followed by physical separation can be effective for manganese removal from drinking water. The effectiveness of these processes for manganese removal depends largely on the ability of the oxidant(s) to completely convert manganese from its dissolved state Mn(II) to solid MnO_x(s). Effective oxidation of manganese depends on several factors including pH and Eh, temperature, reaction time, alkalinity, and the total oxidant demand in the water (e.g. presence of iron, sulphide, nitrate, ammonia and organic compounds) (Casale et al., 2002; Brandhuber et al., 2013). Once dissolved Mn(II) has been converted to particulate MnO_x(s) removal can be achieved using coagulation/flocculation, sedimentation or dissolved air flotation and granular media filtration. Low pressure membrane filtration (ultra and microfiltration) can also be used. The effectiveness of physical removal processes is dependent on ensuring that the manganese entering the filter is in the particulate form (Tobiason et al., 2008). In addition, Brandhuber et al. (2013) indicated that a key aspect of effective removal of manganese particles depends on their size and the location in the treatment train in which they are generated. For example, colloidal particles need to be destabilized using coagulation/flocculation prior to filtration.

Oxidation of manganese in water is an autocatalytic three-step reaction process with different reaction kinetics for each step that has important implications for drinking water treatment. The first step is solution-phase oxidation of Mn(II) by the oxidant (relatively slow step), the second step is adsorption of Mn(II) to MnO_x(s) solids (fast step) and the third step is the surface-catalyzed oxidation of the sorbed Mn(II) ion by additional oxidant (moderate step). It

should be noted that the second step is important in filtration processes as well because $MnO_x(s)$ coatings present on filter media rapidly adsorb dissolved Mn(II) which can then be oxidized. This is discussed in greater detail in section 7.2.3.

The chemical oxidants typically used to convert dissolved Mn(II) to $MnO_x(s)$ precipitates include permanganate (MnO_4), chlorine dioxide (ClO_2) and ozone (O_3). Under high pH conditions chlorine and oxygen may also be effective. Studies conducted by Knocke et al. (1990a) and Gregory and Carlson (2003) indicated that the kinetics of the reactions of these oxidants with Mn(II) are sufficiently rapid under most pH, temperature, dissolved organic carbon (DOC) and initial Mn(II) concentrations to be used in drinking water treatment processes. Oxidation using chlorine and oxygen is not effective unless pH is greater than 9 or 9.5, respectively (Knocke et al., 1990a; Brandhuber et al., 2013). Detailed information on the effectiveness of different oxidants for manganese removal in drinking water is available in Knocke et al. (1990a), Casale et al. (2002), Gregory and Carlson (2003), Kohl and Medlar (2006), Tobiason et al. (2008) and Brandhuber et al. (2013).

Brandhuber et al. (2013) reported on the key factors that affect the efficiency of the chemical oxidation of Mn(II) including oxidant selection, dosing, reaction kinetics, reaction time location of oxidant addition, and monitoring. The most important operational factor is to allow sufficient reaction time in the treatment plant for complete and efficient Mn(II) oxidation. Typically for reaction rates to be sufficiently rapid for effective oxidation in a treatment plant, addition of a strong oxidant at an appropriate pH is needed (Brandhuber et al., 2013). In addition, oxidant doses greater than the stoichiometric ratios are needed to meet the oxidant demand of the source water and achieve adequate oxidation of manganese (Kohl and Medlar, 2006). In particular, the presence of iron which often co-occurs with manganese in source water can impact the efficiency of manganese oxidation. Iron is easier to oxidize than manganese at any pH, therefore the oxidant demand from iron must be satisfied before significant manganese oxidation will occur (Brandhuber et al., 2013). Utilities should conduct jar testing to assess which oxidants may be effective with their source water and treatment plant design prior to selecting an oxidant.

When using permanganate, chlorine dioxide and ozone to oxidize Mn(II) colloidal $MnO_x(s)$ with particles sizes below 1 µm can be created (Knocke et al., 1990a; Brandhuber et al., 2013)). This colloidal MnOx(s) formation is seen more often in softer, low hardness waters as the presence of dissolved calcium and magneisum ions help to destabilize and aggregate these colloids. It is generally recommended that these oxidants be added prior to coagulation/flocculation processes so that the colloidal particles can be destabilized and removed through conventional sedimentation and filtration processes (Brandhuber et al., 2013).

Many different combinations of oxidation and physical separation are used for manganese treatment including the use of multiple oxidants, variations in placement of the oxidant addition, and different physical separation methods. Considerations for each oxidant and filtration technology are discussed in the following sections. The capabilities of these technologies for removal of dissolved manganese with examples of full- and pilot-scale treatment plants are also reported below, recognizing that the effectiveness of any treatment process is site specific and varies based on source water quality and the design and operation of each plant.

7.2.2.1 Permanganate

Oxidation of dissolved Mn(II) can be achieved using permanganate (MnO_4^-) supplied in either the sodium ($NaKMnO_4$) or potassium ($KMnO_4$) forms. Historically, $KMnO_4$ was the predominant form of permanganate used for oxidation of Mn(II). However, Brandhuber et al. (2013) noted that an increasing number of utilities are using $NaKMnO_4$ because it can be

purchased as a highly concentrated solution which eliminates the need for equipment at the facility for dissolution of the dry product.

Data reported on the oxidation of Mn(II) using permanganate indicates that it occurs rapidly under a wide range of temperature and pH conditions in water with low DOC (< 3 mg/L) (Knocke et al., 1987 and 1990). The stoichiometric dosage of permanganate required to oxidize Mn(II) to Mn(IV) is 1.9 mg $KMnO_4$ per mg Mn(II), however as with all oxidation reactions, the demand from other parameters found in the source water can increase the overall dosage required. Knocke et al. (1990a) demonstrated that for a pH range of 5.5 to 9.0, oxidation of 0.25 mg/L of Mn(II) by permanganate at 105% of the stoichiometric requirement occurred within 60 seconds (T=25°C, DOC <1 mg/L). Increasing the DOC to 10 mg/L decreased the rate of Mn(II) oxidation to 1-2 minutes (T= 25°C, pH-7.0). Conditions in which oxidation was not effective at lowering final Mn(II) residuals to levels below 0.05 mg/L included a temperature of 5°C and a pH of 5.5. The authors noted that using permanganate to oxidize Mn(II) when significant organic matter is present in the source water may be impractical due to high chemical costs (Knocke et al., 1987). Work conducted by Gregory and Carlson (2003) found that reaction times for oxidation of Mn(II) with permanganate increased with lower initial Mn(II) concentrations. For an initial Mn(II) concentration of 60 µg/L and a 300% stoichiometric dose of $KMnO_4$, 1,200 seconds were required to achieve a residual Mn(II) concentration below 20 µg/L (treated water goal for the study). In comparison, the oxidation rate at 1,000 µg/L was far more rapid and resulted in oxidation of Mn(II) to a concentration below 10 µg/L within less than 200 seconds. The water quality for these tests was pH =7.0, TOC = 3.4 mg/L and T = 9°C.

In practice, dosing of permanganate to oxidize Mn(II) must be precisely optimized to completely oxidize Mn(II) without resulting in any excess permanganate in the treated water. Excess permanganate exiting the drinking water treatment plant can result in pink water. It can also lead to $MnO_x(s)$ precipitation in the distribution resulting in an increase in consumer complaints due to discoloured water. Therefore, careful consideration to the contact time and the permanganate dose is needed in this process. Brandhuber et al. (2013) reported that for most treatment plants, a reaction time of 2 to 4 minutes is sufficient for lower initial Mn(II) concentrations and/or lower pH values (e.g., pH 6-6.5) but that shorter reaction times may often be possible for higher pH conditions.

Many studies have demonstrated the effective removal of dissolved Mn(II) in full-scale treatment plants using oxidation with permanganate followed by physical separation (Carlson et al.,1997; Kohl and Medlar, 2006; Brandhuber et al., 2013). Kohl and Medlar (2006) reported data from seven full-scale treatment plants using $KMnO_4$ addition followed by filtration for manganese removal. In all cases, the plants were capable of achieving greater than 80% removal of manganese to achieve average treated water concentrations less than 0.045 mg/L. Two of the plants using oxidation with $KMnO_4$, followed by conventional mixing, flocculation, settling and granular media filtration (conventional filtration) were able to achieve between 80% and 86% removal of manganese from average influent concentrations of 0.090 and 0.111 mg/L down to average treated water concentrations of 0.019 mg/L to 0.021 mg/L, respectively. Utilities that coupled $KMnO_4$ with additional oxidation achieved higher manganese removals. Two plants using a combination of aeration, $KMnO_4$ and conventional filtration removed 92 and 97% of manganese to achieve average treated water concentrations of 0.019 and 0.045 mg/L. Dissolved air flotation has also been used to remove oxidized manganese. An Australian utility combined pre-treatment with potassium permanganate, followed by polyaluminum chlorohydrate addition, flocculation and dissolved air flotation to successfully remove manganese (Kohl and Medlar, 2006). The concentration of manganese was reduced from 0.08 mg/L in the raw water to less than

0.02 mg/L in the treated water. No operational data were available for the treatment plants discussed above.

Several case studies of techniques for optimizing systems using $KMnO_4$ oxidation followed by conventional filtration have been reported in the literature (Brandhuber et al., 2013). A utility treating a lake water source with a highly variable Mn(II) concentration in the raw water (0.2 to 1.0 mg/L fluctuations hourly) was optimized using oxidation/reduction potential (ORP) measurements to control the permanganate feed in the plant. The plant changed from using flow-controlled chemical addition to using ORP controlled dosing. Using this method treated water manganese concentration are below 0.01 mg/L 90% of the time and below 0.02 mg/L 95% of the time.

The combination of oxidation of Mn(II) using $KMnO_4$ and low pressure membrane filtration for removal of manganese has also been applied in full-scale drinking water treatment plants. For facilities that use oxidant resistant membranes, permanganate is the oxidant of choice. In these cases it is important that the oxidation reactions are completed before the water reaches the membranes as formation of precipitates within the membrane pores can damage the membrane structure. A full-scale potassium permanganate/ultrafiltration plant successfully treated raw water with a manganese concentration of 0.62 mg/L and an iron concentration of 0.4 mg/L to achieve treated water concentrations below the detection limit (not provided) (AWWA,2005). The plant operates at a net flux of 25 gfd and consists of $KMnO_4$ addition followed by static mixing, an oxidation chamber, and three parallel immersed membrane tanks. A reclaim tank receives the reject water goes and the supernatant is recycled back to the head of the plant resulting in an overall system recovery of 99%. Kohl and Medlar (2006) also reported high manganese removals for a full-scale drinking water treatment plant using $KMnO_4$ followed by microfiltration. The plant reported achieving 99% removal of manganese from an average influent concentration of 0.811 mg/L down to 0.005 mg/L. Operational data were not available for this treatment plant (AWWA, 2005).

7.2.2.2 Chlorine dioxide

Chlorine dioxide can effectively oxidize dissolved Mn(II) to Mn(IV) although it is best suited for source waters that do not have a high oxidant demand from organic matter (Tobiason et al., 2008). Reaction rates between ClO_2 and dissolved Mn(II) are rapid with typical reaction times of 1-2 minutes or less, depending on the dosage of ClO_2 and the initial dissolved Mn(II) concentration (Brandhuber et al., 2013). Similar to permanganate, a significant decrease in oxidant efficiency was observed at low temperatures (5°C) and low pH (5.5) (Knocke et al., 1990a). The stoichiometric dosage of ClO_2 required for oxidation of Mn(II) is 2.45 mg ClO_2 per mg Mn(II). However, in the presence of Mn(II), chlorine dioxide is not completely reduced to a chloride ion (Cl^-); instead it is reduced only to chlorite (ClO_2^-) (Knocke et al., 1990a). In addition, it should be noted that if chlorine dioxide and chlorite ion are not removed prior to secondary disinfection with chlorine, they will react with free chlorine to form chlorate ion. Once chlorate ion is present in water, it is very persistent and very difficult to remove. In Canada, chlorite and chlorate have health based drinking water guidelines of 1 mg/L. However, to ensure that the chlorite and chlorate guidelines can be met, it is recommended that treatment plants using chlorine dioxide as a primary disinfectant not exceed a feed dose of 1.2 mg/L (Health Canada, 2008).

Knocke et al. (1987) demonstrated that a dosage of 1-1.5 mg/L effectively oxidized initial Mn(II) concentrations of approximately 0.25 mg/L over a wide pH range when DOC was below 2.5 mg/L. In contrast, water with DOC between 8-10 mg/L required more than 3 mg/L of ClO_2.

Gregory and Carlson (2003) compared oxidation of Mn(II) with chlorine dioxide, potassium permanganate and ozone at lower initial Mn(II) concentrations (60 µg/L) and found that chlorine dioxide was the most effective for achieving treated water concentrations < 10 µg/L. At a relative stoichiometric ClO_2 dose of 200%, oxidation of 60 µg/L down to less than 10 µg/L occurred within 300 seconds in water with T=9°C, pH=7.0, and TOC= 3.4 mg/L. This was reduced to less than 75 seconds when the initial Mn(II) concentration was 200 µg/L.

Given that chlorine dioxide dosing needs to be controlled to below 1.2 mg/L, several authors have noted that the application of only chlorine dioxide for Mn(II) oxidation is limited to waters with low DOC and relatively low dissolved Mn(II) levels that require oxidation for treatment. In some cases the addition of permanganate in conjunction with chlorine dioxide may be effective for higher DOC waters (Knocke et al., 1987; Casale et al., 2002; Brandhuber et al., 2013). An additional consideration is that on-site generation of chlorine dioxide is required due to its high degree of reactivity.

Despite these limitations, several full-scale treatment plants have reported using chlorine dioxide followed by physical separation for manganese removal. Kohl and Medlar (2006) reported data from several plants using chlorine dioxide followed by conventional filtration that were capable of achieving between 81% and 95% removal of manganese to achieve average treated water concentrations as low as 0.001 mg/L. In a case study reported by Brandhuber et al. (2013) a full-scale treatment plant that was experiencing coloured water complaints successfully switched from using potassium permanganate to chlorine dioxide for oxidation of raw water concentrations of Mn(II) between 0.07 and 0.2 mg/L. The utility found that ClO_2 was more effective at controlling Mn(II) concentrations to below 0.02 mg/L. Similarly, studies to determine the most effective oxidant for Mn(II) removal found that ClO_2 was more effective than potassium permanganate and ozone for achieving low levels of Mn(II). Chlorine dioxide doses ranging from 0.44 to 1.5 mg/L effectively oxidized Mn(II) to 0.005 mg/L without creating unacceptable levels of chlorite (Carlson and Gregory, 2003).

The combination of oxidation using chlorine dioxide and microfiltration is also effective at removing manganese from drinking water. Tobiason et al. (2008) reported that a pilot-scale system using 0.5 mg/L of chlorine dioxide as the pre-filter oxidant and microfiltration was capable of reducing an influent manganese concentration of 0.094 mg/L down to 0.001 mg/L.

7.2.2.3 Ozone

Ozone is a strong oxidant that can be effective for Mn(II) oxidation although it is considered less effective than other oxidants for achieving levels of manganese below 0.02 mg/L in drinking water (Brandhuber et al., 2013). Typically oxidation using ozone in drinking water treatment processes occurs with molecular O_3 and the uncharged hydroxyl radical OH. In the case of oxidation of dissolved Mn(II), studies have shown that it is molecular O_3 that reacts directly with Mn(II) and hydroxyl radicals are relatively ineffective (Nowell and Hoigne, 1987). The stoichiometric requirement for Mn(II) oxidation is 0.87 mg O_3 per mg Mn(II) (Knocke et al., 1990a). The actual dosage needed is usually 2 to 5 times higher depending on the alkalinity and DOC of the source water. The presence of DOC in source water significantly inhibits oxidation of Mn(II) by ozone due to the competitive oxidant demand exerted by the DOC (Knocke et al., 1990a). This effect can be minimized by increasing the alkalinity which promotes direct oxidation of Mn(II) by O_3 due to less hydroxyl radical formation (Paillard et al., 1989). The kinetics of Mn(II) oxidation by ozone are similar to those observed with permanganate and chlorine dioxide under similar pH and temperature conditions, although the manganese residual levels tend to be higher. Knocke et al. (1990a) and Carlson and Gregory (2003) reported that oxidation of Mn(II)

with ozone occurred rapidly (30-60 seconds) with various ozone doses (0.5-2.0 mg/L) for various pH (5.63-7.0), DOC (1 and 3.4 mg/L) and temperature (9 and 25°C) conditions but low levels of residual manganese (<0.02 mg/L) were not observed in these experiments.

Several authors have noted that optimizing ozone dosing can be challenging due to competitive oxidant demands (Kohl and Medlar, 2006; Tobiason et al., 2008; Brandhuber et al., 2013). Ozone oxidizes not only dissolved Mn(II) but at high enough doses it can also oxidize Mn(III) and Mn(IV) oxide particles to the Mn(VII) oxidation state and produce permanganate which can result in discolouration of the water (pink water). Gregory and Carlson (2003) noted that to achieve effective Mn(II) removal using ozone, the background demand exerted by NOM required the use of ozone dosages that were high enough to result in the production of Mn(VII) and discolouration of the treated water.

Limited pilot-scale studies have been conducted examining the use of ozonation followed by filtration for manganese removal (McKnight et al., 1993; Wilczak et al., 1993). McKnight et al. (1993) conducted pilot-scale testing to determine if ozone could be used to replace chlorine for oxidizing manganese in a conventional filtration plant. The raw water quality at this site had TOC = 6-8 mg/L, pH= 6.5-7.2 and alkalinity 30-40 mg/L as $CaCO_3$. The authors found that high ozone doses were required to oxidize Mn(II) in the raw water and that the oxidized particles formed small pinfloc that was difficult to settle and filter. Ozone was then applied to the settled water. Applying an ozone does of 2.5 mg/L to the settled water followed by filtration achieved 95% removal of dissolved Mn(II) (initial Mn(II) 0.6-1.0 mg/L). Other authors have reported that oxidation of Mn(II) creates colloidal $MnO_x(s)$ particulates which are difficult to remove following settling and filter aids are need to capture the solids at the filtration stage (O'Brien et al., 1996; Tobiason et al., 2008). In addition, chlorine addition prior to filtration is often not practiced if ozonation is being used at this step which eliminates the potential for adsorption/oxidation reactions within the filter. These factors make it difficult for ozone treatment to achieve residual dissolved Mn(II) levels below 0.025 mg/L (Tobiason et al., 2008).

7.2.2.4 Chlorine and oxygen

Direct chemical oxidation of Mn(II) by chlorine and oxygen are generally not used in drinking water treatment plants due to slow reaction kinetics and insufficient contact times unless alkaline pH conditions are present (pH >8- 9) (Kohl and Medlar, 2006; Brandhuber et al., 2013). Knocke et al. (1990a) reported that dosages 4 times greater than the stoichiometric requirements for free chlorine and a minimum contact time of 3 hours was needed to lower an initial Mn(II) concentration of 1.0 mg/L to 0.7 mg/L at pH 7.0 and a temperature of 25°C. When pH was increased to 9.0, Mn(II) was oxidized within one hour to below 0.05 mg/L. Lower temperatures (14°C) and the presence of DOC also increased reaction times significantly. An additional consideration with chlorine is that elevated dissolved Mn(II) concentrations leaving a treatment plant can be oxidized by the free chlorine residual in the distribution system due to longer contact times resulting in the creation of $MnO_x(s)$. This can lead to consumer complaints due to water discolouration (Kohl and Medlar, 2006; Brandhuber et al., 2013). As discussed previously, although chlorine is not effective for direct oxidation of dissolved Mn(II) under typical treatment plant operations, it is an integral component of the effective operation of certain adsorption/oxidation processes discussed is section 7.2.3 (Brandhuber et al., 2013).

DO is capable of oxidizing dissolved Mn(II), however as with chlorine, the kinetics of the reaction are slow unless the pH of the water is above 9.0 to 9.5. These alkaline conditions are not present in most drinking water treatment processes, with the exception of lime or lime-soda ash softening treatment plants.

7.2.3 Adsorption/oxidation

Treatment of dissolved Mn(II) using adsorption and oxidation is based on the presence of MnO_x(s)s MnO_x(s) as coatings on filter media which are capable of adsorbing dissolved Mn(II) in the feed water and retaining it in the filter bed. The oxide surface then acts as a catalyst for oxidation of the adsorbed Mn(II) by oxidants (e.g. chlorine or permanganate) dosed into the water so that more oxides are produced . Several types of filter media are available that have the capability to adsorb dissolved Mn(II). These include traditional manganese greensand, pyrolusite and conventional filter media with MnO_x(s) coatings that are commercially applied by the media supplier. Continuous or intermittent dosing of an oxidant to the raw water prior to contact with the media is required to maintain the MnOx(s) adsorption sites (Knocke et al., 1990b; Tobiason et al., 2008; Islam et al., 2010). The location of this process within a treatment plant can vary. For surface water treatment plants that chlorinate prior to filtration, it is often part of the existing particle removal filtration process. When pre-filter chlorination is not practiced, an adsorptive contactor unit can be placed following filtration (Knocke et al., 2010). For groundwater treatment plants, adsorption/filtration is often a process that is installed specifically for manganese and/or iron removal. A key benefit to having MnO_x(s)-coated media as part of the treatment train is the ability of this process to achieve consistently low (<0.015 mg/L) treated water manganese concentrations (Brandhuber et al., 2013).

7.2.3.1 Manganese greensand:

Traditional manganese greensand is a granular filter medium processed from glauconite sand. Glauconite is synthetically coated with a thin layer of manganese base material (manganous ions) which is then converted to a MnO_x(s) coating by conditioning the greensand in a potassium permanganate or chlorine solution (Knocke et al., 1990b; Sommerfield, 1999). This media has a large adsorptive capacity for removing dissolved Mn(II) (1.5 kg/m^3). Greensand media is typically smaller (effective size 0.30 to 0.35 mm) than silica sand so it is good at capturing small particles. Since the head loss generated is higher than an equivalent bed depth of silica sand, most applications of greensand use pressure filtration (Brandhuber et al., 2013). In addition, greensand filters are best applied in groundwater systems with iron and manganese concentrations below 5 mg/L (Kohl and Medlar, 2006).

There are two standard approaches in which greensand filtration can be used to remove manganese: continuous and intermittent regeneration. Continuous regeneration involves feeding an oxidant (potassium permanganate or chlorine) or a combination of two oxidants into the raw water prior to contact with the greensand media. When potassium permanganate is used as the oxidant, most of the dissolved Mn(II) in the source water will be directly oxidized to MnO_x(s) and the greensand media will function primarily as a physical removal process. If, however, any dissolved Mn(II) reaches the greensand media it can be removed via adsorption onto the MnOx(s) surface coating. In these cases, the adsorptive capacity of the greensand is depleted more slowly since most of the manganese entering the filter is already oxidized. Backwashing to remove the MnO_x particulates is conducted once head loss has reached a specified level (Knocke et al., 1990). An excess of oxidant is required to ensure the MnO_x(s) adsorption sites are regenerated. Utilities should be aware that continuously dosing greensand with potassium permanganate can result in discolouration of the treated water due to excess permanganate present in the process (Brandhuber et al., 2013). Lower doses of potassium permanganate combined with chlorine or chlorine alone can also be used to continuously regenerate greensand media. Maintaining a free chlorine concentration of 0.5 to 1.0 mg/L across the media results in regeneration of MnOx(s) coatings on the media by oxidizing the adsorbed Mn(II). Brandhuber et al. (2013) indicated that the use of

free chlorine is a suitable alternative for regeneration of greensand media due to lower chemical costs, less solids loading in the filter and the elimination of the risk of discolouration of treated water from the presence of excess permanganate. Free chlorine can regenerate the $MnO_x(s)$ surface on the media by oxidizing the adsorbed Mn(II). In cases where Mn(II) concentrations are greater than 1 mg/L in the source water or where the formation of disinfectant by-products (DBPs) needs to be decreased, then potassium permanganate may be the preferred or primary oxidant employed, with reduced levels of free chlorine being applied.

In an intermittent regeneration process, dissolved Mn(II) is removed by greensand media through adsorption onto the $MnO_x(s)$ coating on the greensand media. As the adsorption sites become filled, the media starts to lose its capacity to remove dissolved Mn(II). The media then needs to be taken offline so that an oxidant can be applied to oxidize the adsorbed Mn(II) and create new adsorption sites. This method requires careful monitoring of Mn(II) in the treated water to ensure that the greensand media is taken offline and regenerated prior to significant amount of dissolved Mn(II) passing through the filter and into the finished water.

Khol and Medlar (2006) reported data from four groundwater treatment plants using manganese greensand filtration. These plants achieved manganese removals between 86% and 100% from average influent concentrations ranging from 0.35 mg/L to 0.52 mg/L to average treated water concentrations below 0.020 mg/L.

In addition to granular filter material manufactured from glauconite, several manufacturers also produce anthracite coal and silica sand media with a $MnO_x(s)$ coating applied to it through chemical processing. This media removes Mn(II) by the same mechanisms as greensand media. Recently, the supply of glauconite has been limited and these alternative media are viable options for water treatment plants using adsorption/oxidation treatment technology.

7.2.3.2 $MnO_x(s)$ coatings on conventional filter media:

An important and often overlooked treatment method for Mn(II) removal is the adsorptive uptake of Mn(II) onto $MnO_x(s)$ coatings that have developed within a treatment plant on anthracite coal or silica sand filter media due to the presence of dissolved Mn(II) and free chlorine across the filter bed (Knocke et al., 1988, 1990b). In this process, the adsorbed Mn(II) is subsequently oxidized by the presence of free chlorine across the filter to create new $MnO_x(s)$ adsorption sites (e.g. continuously regenerated). In addition, only partial removal of the $MnO_x(s)$ coating occurs during backwashing, resulting in a net increase in $MnO_x(s)$ adsorption sites over time of operation (Hargette and Knocke, 2001). This process has been referred to as a 'natural greensand effect' by Knocke et al. (1988) or 'induced oxide-coated media effect (IOCME)' by Kohl and Medlar (2006). In many treatment plants this $MnO_x(s)$ coated media process initiates and sustains itself without process engineers or operators being aware that it is occurring (Kohl and Melar, 2006; Brandhuber et al., 2013).

Several research studies have been conducted to better understand the factors that contribute to the effective removal of Mn(II) in treatment plants under $MnO_x(s)$ coated media filtration conditions. The effectiveness of $MnO_x(s)$ coated media filtration is dependent on the number and oxidation state of adsorption sites on the media, pH of the water, and the concentration of free chlorine across the filter (Knocke et al., 1988, 1990b, 1991; Hargette and Knocke, 2001; Tobiason et al., 2008). The key operational conditions for this process to function properly were summarized by Brandhuber et al. (2013). They include a free chlorine concentration in the filtered water of 0.5 to 1.0 mg/L (to ensure effective MnOx(s) coating regeneration) and a filter applied pH of 6.0 or higher, as lower pH levels results in competition for Mn(II) adsorption sites from H^+ ions. In addition, manganese should be in the dissolved Mn(II)

form entering the filter as particulate Mn(IV) will not be adsorbed onto the media. Brandhuber et al. (2013) noted that under these conditions, drinking water treatment plants are routinely able to achieve very low treated water manganese concentrations (<0.015 mg/L) even when pre-filter manganese concentrations are as high as 0.5 mg/L.

Tobiason et al. (2008) conducted research on MnO_x(s) coated anthracite coal and silica sand filter media obtained from full-scale water treatment facilities. Results indicated that MnO_x(s) coating levels were greatest for the media first exposed to free chlorine and Mn(II) as water passes through filter (e.g. top of a dual media filter) regardless of the material type (anthracite and sand). Therefore, Mn(II) uptake occurs in the upper portion of a filter bed. The study also found that while typical free chlorine residuals used in a treatment plant are capable of partially regenerating MnO_x(s) adsorption sites, the manganese removal capacity decreases over time. It was suggested that utilities could occasionally use offline intermittent regeneration of media, using concentrated chlorine or potassium permanganate solutions to improve the adsorptive capacity of media.

One of the main considerations with the use of MnO_x(s) coated media filtration for manganese removal is the potential for the formation of DBPs. Tobiason et al. (2008) demonstrated that use of continuous pre-filter chlorination and MnO_x(s) coated media for manganese control can cause increases of 10 to 50% in levels of distribution system DBPs (THMs and HAAs) in comparison to operation with post-filter chlorination only.

Over the last decade, changes to drinking water regulations for DBPs in many jurisdictions have led many utilities to move the application point of chlorine downstream of filters. This process change eliminates the presence of a free chlorine residual across the filters and therefore, also eliminates the ability to control manganese by MnO_x(s) coated media filtration. Several authors have demonstrated that previously accumulated manganese on MnO_x(s) coated filter media will release and cause elevated manganese concentrations in treated water during the transition to biological filtration (Gabelich et al., 2006; Tobiason et al., 2008; Kohl and Dixon, 2012). Utilities that are considering moving the application point of chlorine to a point following filtration should assess the potential for filter media to release manganese. Manganese release from filter media has been shown to occur in systems with different levels and sources of manganese (e.g., not only in systems with high manganese concentrations in the source water). Examples of these include systems with low but constant levels of manganese in the source water and systems using coagulants (e.g. ferric chloride) with manganese impurities. Kohl and Dixon (2012) conducted pilot testing of a 23 L/min conventional filtration system using filter media taken from a full-scale treatment plant with a well-established uniform MnO_x(s) coating on the filter media. When the filters were operated without chlorine, manganese began leaching from the filters resulting in increases of up to 0.03 mg/L in the total manganese concentration of the filtered water for up to 30 days. Similarly, Gabelich et al. (2006) reported manganese leaching from full-scale filter media within hours of removing chlorine from the filters (e.g converting to biological filtration). The source of manganese was determined to originate from impurities in the ferric chloride coagulant used in the plant combined with the presence of free chlorine across the filters, resulting in an accumulation of MnO_x(s) on the filter media. The utility reported an increase of 70-110 µg/L of total manganese leaving the plant following removal of chlorine across the filters. More detailed testing demonstrated that dissolution of manganese from filter media is a complex process in which three chemical forms of manganese interchange in the upper meter of filter media. Coagulant selection and solution pH were found to be important factors affecting the mobility of manganese in the filter media.

In cases where there is a need to limit the amount of pre-filter chlorine to control the formation of DBPs, post-filtration MnO_x(s) media contactors can be a suitable manganese treatment (Tobiason et al., 2008; Knocke et al., 2010; Bierlein et al., 2015). Knocke et al. (2010) demonstrated that a MnO_x(s) coated media adsorptive contactor effectively removed dissolved Mn(II) over a wide range of solution pH values (6.3 to 8.0), free chlorine levels (> 1.0 mg/L), initial Mn(II) concentrations (0.03 to 0.3 mg/L) and hydraulic loading rates (up to 24 gpm/ft^2).

As noted above, the effective removal of manganese using MnO_x(s) coated media filtration in full-scale plants has been demonstrated in a number of studies (Charlton et al., 2002; Kohl et al., 2002; Herzner et al., 2003; Angara et al., 2004; Kohl and Medlar, 2006, Tobiason et al., 2007, 2008). In a survey of several plants relying on MnO_x(s) coated media filtration, the average treated water concentration of all of the plants was 0.007 mg/L. The percentage removal in these plants ranged from 98% to 99% with average treated water concentrations for each plant ranging from 0.001 mg/L to 0.014 mg/L (Kohl and Medlar, 2006). Jeffcoat et al. (2007) reported that moving the location of the pre-chlorine addition from the rapid mix basin to the filter influent (creating MnO_x(s) coated filter media) in a full-scale conventional treatment plant was an effective method for removing manganese. Influent manganese concentrations of approximately 0.05 mg/L were lowered to less than 0.01 mg/L using this process.

Tobiason et al. (2008) and Brandhuber et al. (2013) reported data from a number of case studies of utilities using MnO_x(s) coated media filtration for control of dissolved Mn(II). Tobiason et al. (2008) demonstrated that a 25 MGD plant using alum coagulation, flocculation, settling, dual media filtration and disinfection with free chlorine was able to decrease pre-filter chlorine levels without compromising Mn(II) removal. The pre-filter chlorine dose was decreased from 2.8 to 1.6 mg/L, resulting in a decrease in the post-filtration chlorine residual from 0.9 to 0.2 mg/L. Treated water Mn(II) concentrations remained below 0.020 mg/L throughout this change despite raw water concentrations from 0.1 to 0.7 mg/L.

7.2.3.3 Pyrolusite

Manganese can be removed from solution by adsorption on a packed bed of granular pyrolusite, the mineral form of MnO_2(s) (e.g. no coating required). Pyrolusite filters for drinking water treatment are typically a blend of sand and pyrolusite with the ratio of sand to pyrolusite varying depending on the concentration of manganese in the source water. The addition of chlorine to the source water prior to the filter for continuous regeneration of the pyrolusite media is typical. However, intermittent regeneration using chlorinated backwash water can also be effective. An advantage to using pyrolusite filter media is that higher filtration rates are possible than with greensand processes resulting in filter sizes and construction costs that are lower (Sommerfield, 1999, Casale et al., 2002). However, pyrolusite media has a very high specific gravity (>4.0), resulting in a need for substantially higher hydraulic loading rates during backwashing operations in order to fluidize the media bed.

Limited information is available on the effectiveness of pyrolusite for manganese removal. Data reported by Kohl and Medlar (2006) indicates that pyrolusite was effective at removing between 81 and 99% of manganese at three groundwater treatment plants. These plants achieved average treated water manganese concentrations between 0.001 mg/L and 0.024 mg/L.

An alternative use of pyrolusite for dissolved Mn(II) control was reported by Kenari and Barbeau (2014) who utilized a fluidized-bed reactor as the means of contacting the water with the pyrolusite media. Test results showed nearly 100% removal of dissolved Mn(II) (initial manganese concentrations up to 0.3 mg/L) using contact times with the media that were one minute or less. Free chlorine was used as the oxidant of choice for regenerating the pyrolusite

media surface within the fluidized bed. Hydraulic loading rates to the bed between 24 to 63 m/hr produced highly effective dissolved Mn(II) removal (pH between 6.2-7.8).

7.2.4 Biological filtration

Removal of manganese using biological filtration relies on the ability of naturally occurring manganese oxidizing bacteria (MOB) present in biofilms on filter media to adsorb and oxidize dissolved Mn(II) to form particulate Mn(IV), which can then be removed by backwashing. Many different strains of bacteria have been identified in the literature as having the capability of oxidizing Mn(II) including, but not limited, to *Leptothrix*, *Sphaerotilus*, *Crenothrix*, and *Metallogenium* (Mouchet, 1992). Research has indicated that the mechanisms of Mn(II) removal by MOB include intercellular oxidation by enzymatic action, adsorption at the surface of the cell membrane and extracellular oxidation by catalytic action of excreted polymers. Adsorption to $MnO_x(s)$ solids that accumulate in the filter during the oxidation process also contributes significantly to Mn(II) removal in biofiltration (Casale et al., 2002; Burger et al., 2008a, Sahabi et al., 2009; Kohl and Dixon, 2012; Brandhuber et al., 2013; Bruins et al., 2015).

There are several biological and physicochemical factors that influence the performance of biological filters for manganese removal. Biological factors include the presence and diversity of MOB in the source water, the ability of MOB to form an active biofilm under the operating conditions of the filter, acclimation period of the MOB population, and maintaining biological activity after backwashing or other stresses to the filter. Acclimation periods for MOB range from 14 to 100 days with shorter periods observed following seeding of filters and when the temperature is between 20 and 30°C (Mouchet et al., 1992; Holst, 2004).

The important physicochemical factors are pH, redox potential, initial Mn(II) concentration and filter loading rates (Kohl and Dixon, 2012). The operating conditions required to establish an adequate MOB population in filters include maintaining aerobic conditions with a minimum dissolved oxygen (DO) level of 5 mg/L, a redox potential of 300 to 400 mV, and pH equal to or greater than 6.3 (Mouchet al., 1992; Burger et al., 2008a; Hoyland et al., 2014). The presence of ammonia, nitrite, and sulphide in the source water negatively impacts the ability of MOB to oxidize manganese. It has also been noted that groundwater is typically better suited to biofiltration for manganese removal since it has relatively stable influent manganese levels, temperature and pH. In contrast surface waters can have large fluctuations in manganese levels and temperature and it is uncertain if MOB remains viable in a biofilter under these conditions for extended periods of time (Brandhuber et al., 2013).

Many full-scale biofiltration treatment plants that have been successful at removing manganese from groundwater have been reported in the literature (Mouchet et al., 1992; Li et al., 2005; Burger et al., 2008b; Kohl and Dixon, 2012). Kohl and Dixon (2012) reported data from 8 treatment plants in Canada, Europe and China using downflow mono-medium sand biofilters. These treatment plants were capable of greater than 93% removal of manganese to achieve treated water concentrations below the method detection limit of 0.03 mg/L. Several of the plants discussed above are located in New Brunswick and were reported in Burger et al. (2008b). The treatment train for these plants consist of water pumped from an aquifer into a downflow filter with 1,325 L/min design capacity and a filter unit with an outer diameter of 2.1 meters, a filter bed depth or 1.8 m and a surface area of 3.4 m^2. Compressed air is pumped into the filters to ensure a high ORP is achieved. The filters are backwashed at a rate of 20 m/hr at a frequency of approximately every 300 hours of operation. After backwashing the filters are ripened for 5 minutes before being returned to service. Influent concentrations of manganese ranged from 0.86

to 1.39 mg/L and >99% removal of manganese was achieved (<0.03 mg/L in the effluent) in these plants. The pH of the source waters ranged from 6.46 to 7.63 and temperature was 9 to 10°C.

To date the majority of manganese biofiltration plants have been installed for treatment of groundwater sources. Recently research has focussed on the feasibility of biofiltration for manganese removal from surface water supplies (Kohl and Dixon, 2012; Granger et al., 2014; Hoyland et al., 2104). Bench-scale studies were conducted by Hoyland et al. (2014) to evaluate the potential for removal of both NOM and Mn(II) by biofiltration under conditions representative of surface water treatment plants using coagulation and ozonation prior to filtration. The study demonstrated that MOB can achieve greater than 98% removal of Mn(II) in a biofilter with pH as low as 6.3. Stress tests further supported that well acclimated MOB (50 days) were successfully able to remove Mn(II) over a range of influent concentrations (0.1-0.2 mg/L), hydraulic loading rates ($1.3 \times 10^{-3} - 2.72 \times 10^{-3}$ m/s), and temperatures (7 - 22°C) for a period of 1-2 days. Kohl and Dixon (2012) reported data for manganese removal in a 454 ML/d surface water treatment plant employing intermediate ozonation and 14 dual-media filters with 180 cm of GAC over 25 cm of sand. Ozone was applied after sedimentation before filtration at a dose of 1.5 to 2.0 mg/L and the pH entering the filters was 7.2 to 7.6. The filter influent total manganese concentrations ranged from 0.032 to 0.089 mg/L. The treated water manganese concentration was less than 0.002 mg/L (MDL) in all samples demonstrating manganese removals greater than 94% were achieved. In contrast, much lower removals were reported for a 190 ML/d intermediate ozonation treatment plant using 6 feet deep granular activated carbon (GAC) filters. The filter influent total manganese concentration ranged from 0.018 to 0.071 mg/L. On average the filters removed 40% of the total manganese but large variations (21 to 76%) were observed on different sampling dates. The authors did not investigate the cause of the difference in performance between the two treatment plants.

As discussed in section 7.2.3.2, an important consideration for utilities that are considering transitioning from $MnO_x(s)$ coated media filtration to biological filtration is the potential for release of previously accumulated manganese on the filter media once the free chlorine residual across the filters is terminated (Gabelich et al., 2006; Kohl and Dixon, 2012). It is recommended that utilities intending to convert an existing $MnO_x(s)$ coated media filter consider removing the media and cleaning or replacing it prior to converting to biological filtration (Kohl and Dixon, 2012).

7.2.5 Softening and ion exchange

Treatment plants that use lime or soda ash softening can also achieve manganese removal by raising the pH of the water (e.g. greater than 9.5 – 10) above the solubility of various manganese hydroxide and carbonate solid phases. Likewise, the elevated pH present in lime or lime/soda ash softening will greatly increase the rate at which dissolved Mn(II) is oxidized in the presence of DO. Where DO is present, formation of oxidized $MnO_x(s)$ solids will occur. Raising the pH of the source water to achieve dissolved Mn(II) removal is not a cost effective treatment approach by itself; rather this treatment method is typically used only if softening of the source water is also required. Many lime or soda ash softening facilities achieve highly effective manganese removal (and iron removal) as a by-product of the chemical softening reactions. Furthermore, the plant personnel often do not proactively operate the treatment system for achieving manganese removal. In some cases, manganese removal occurs in softening treatment plants without the operator's knowledge particularly when manganese is not being routinely monitoring in source and treated water. A full-scale lime softening treatment plant reported

lowering the average manganese concentration in the source water from 0.520 mg/L down to an average treated water concentration of 0.001 mg/L (Kohl and Medlar, 2006).

Dissolved Mn(II) can also be removed through cation exchange in zeolite softening processes. As with other cation exchange processes, backwashing the zeolite, typically with a brine solution, removes the manganese (as well as iron, calcium and magnesium) accumulated on the resin. One concern associated with zeolite softening as a means of dissolved Mn(II) removal is the presence of oxygen or another oxidant. Such conditions can result in oxidation of the exchanged Mn(II) to MnO_x(s) on the zeolite surface, which in turn can decrease the overall cation exchange capacity of the zeolite resin over time (Sommerfield, 1999).

7.2.6 Sequestration

Sequestration is a control measure to limit the aesthetic water quality problems associated with oxidation of dissolved Mn(II) to form MnO_x (s) particles within the distribution system. In general, sequestration is considered a temporary control measure for manganese because the sequestrant's effect is time limited (Kohl and Medlar, 2006). Since sequestration does not remove manganese from the water, it does not limit exposure to manganese from drinking water. As such, only water supplies with manganese levels below the MAC in the source or treated water should consider it as a control option for reducing the potential for discoloured water but there is a need to maintain a continuous dose over the long term. In most cases, the most appropriate method for reducing dissolved Mn(II) concentrations at the tap is installation or optimization of manganese treatment systems to maintain concentrations well below the MAC and AO to limit the amount of manganese accumulation in the distribution system. Very small groundwater systems with low levels of dissolved Mn(II) in the source water and limited resources may find the use of a sequestrant to control coloured water events to be the most practical option (AWWA, 1993). However, careful consideration needs to be given to the potential for the accumulation and subsequent release of manganese in the distribution system.

During chemical sequestration, a chemical agent is used to bind to dissolved manganese in to create a solution phase complex in which manganese is not available for oxidation or precipitation. The addition of polyphosphates alone or in conjunction with chlorine is the most commonly reported methods used to sequester manganese (Sommerfield, 1999; Kohl and Medlar, 2006). The proper dosage of sequestering chemicals must be determined based on water quality characteristics and the manufacturer's recommendations. Establishing the correct chemistry is often difficult due to changing water quality (i.e., variability of concentrations of manganese and other cations) and conditions in the distribution system (i.e., varying detention times and temperatures) (Kohl and Medlar, 2006). In addition, hydrolization of polyphosphates occurs over time and can result in the release of previously sequestered dissolved Mn(II). The rate of hydrolization increases at either low or high pH and increases with water temperature (Brandhuber et al., 2013). When sequestration is used as a control measure, routine sampling in the distribution system to measure total manganese concentrations is needed to ensure that the concentration remains below the MAC.

7.2.7 Other considerations

In addition to manganese present in source water, chemical addition and treatment plant processes can contribute to the amount of manganese that a treatment plant needs to manage. The three main sources of manganese from treatment plant operations are: 1) presence of manganese impurities in coagulants (principally ferric-based coagulants) used for particle destabilization; 2) resolubilization of Mn(II) from reduction of MnO_x(s) solids stored in sedimentation basins as a

result of anoxic conditions in the basin; 3) presence of dissolved manganese in recycle streams from solids processing operations (Tobiason et al., 2008). Kohl and Medlar (2006) summarized the literature that indicates the potential for contamination of treated drinking water by ferric salts that may contain manganese. Some studies demonstrate that in cases where a treatment plant uses enhanced coagulation, manganese contamination of the ferric chloride can result in soluble manganese concentrations up to 0.5 mg/L. Typical levels of manganese attributable to coagulant addition in surface water treatment plants range from 0.025 to 0.055 mg/L. Release from solids in sedimentation basins typically ranges from 0.01 to 0.10 mg/L with variations observed seasonally and manganese in residuals recycle streams can range from 0.01 to 1 mg/L (Tobiason et al., 2008). Thus, while the total flow from residual processing side streams can be relatively small in comparison to the influent flow to the treatment plant the total mass loading of dissolved Mn(II) from such side streams can be quite significant. Careful sampling of dissolved Mn(II) concentrations in these residuals processing side streams is strongly recommended. Likewise, treatment of such side streams for dissolved Mn(II) removal should be considered. Brandhuber et al. (2013) reported a case study where one utility constructed a full-scale, MnO_x(s) -coated media filter for treating their liquid side stream from the residuals processing facility prior to discharge of that side stream into the plant's terminal reservoir (which served as the source water to the facility). The dissolved Mn(II) concentration in the untreated side stream waters ranged from 0.02 mg/L to values in excess of 1 mg/L. Passage of the side stream waters through the bed of MnO_x(s)-coated media yielded an average removal of greater than 90% dissolved Mn(II). Over time, the utility was able to demonstrate that treatment of this residuals processing side stream prior to release to their terminal reservoir resulted in a substantial decrease in the dissolved Mn(II) concentrations entering the treatment facility. This resulted in fewer operational challenges in addressing manganese issues, while also generating cost savings due to the reduced need for oxidant chemicals (e.g., permanganate) for treating the source water.

7.3 Distribution system

Manganese concentrations above 0.02 mg/L can cause complaints about discoloured water, plumbing fixture and laundry staining and general dissatisfaction with the water quality (Sommerfield, 1999; Casale et al., 2002; Kohl and Medlar, 2006; Tobiason et al., 2008). In some cases manganese problems at the tap are not associated with high manganese concentrations in the source water. Rather, they are the result of the release of accumulated manganese in the distribution system from low but constant manganese present in the source or treated water. These manganese deposits can periodically release as a result of physical or hydraulic disturbances or unstable water chemistry and enter the distribution system water resulting in discoloured water complaints.

In addition to the aesthetic concerns, manganese can act as an effective scavenger and sink for undesirable metals and inhibit the formation of stable Pb(IV) scale in lead pipe (Schock et al., 2014) creating other potential health risks due to possible release of co-occurring inorganic contaminants (Schock and Holm, 2003; Shock, 2005). An extensive review of the literature conducted by Kohl and Medlar (2006) indicated that manganese can be deposited in distribution systems even when the concentration leaving the treatment plant is as low as 0.02 mg/L. Therefore, a treated water goal of $\leq$0.015 mg/L of manganese in treated water is recommended (Brandhuber et al., 2013).

Utilities should ensure that manganese treatment and control measures include consideration of the deposition and possible release of manganese in the distribution system. In

many cases, minimizing the manganese concentrations to as low possible before distribution is the most effective strategy.

7.3.1 Manganese accumulation and release in distribution systems

Manganese deposition can occur as a physical process, as a result of particle settling (U.S. EPA, 2006), through physical-chemical sorption (Friedman et al., 2010) and through biological accumulation (Sly et al., 1990; Cerrato et al., 2010; Ginige et al., 2011). Manganese has been shown to accumulate in loose deposits of distribution pipe materials including iron (Zacheus et al., 2001; Cerrato et al., 2006; Peng and Korshin, 2011), polyethylene (Zacheus et al., 2001), polyvinyl chloride (Cerrato et al., 2006) and lead (Schock et al., 2014) pipes. Cerrato et al. (2006) found that manganese accumulated to a lesser extent in iron pipes (3.48% by weight) compared to PVC pipes (6% by weight). Cerrato et al. (2006) found that in the iron pipes, manganese was associated with tubercle deposits; whereas manganese accumulated in PVC pipes, resulted in easily removed/released surface deposits. Manganese concentration in distributed water decreases as distance from the water treatment plant increases (Kohl and Medlar, 2006). Barbeau et al. (2011) observed that manganese decreased as water age increased, with a 37% decrease in manganese concentration after a residence time of 24h. Notably, in Brandhuber et al. (2015) estimates were made for manganese stored on distribution system pipes based on data collected in Friedman et al. (2010). Deposited manganese ranged from 0.1 mg/ft^2 to 10, 000 mg/ft^2, with an estimated median of 210 mg/ft^2, equivalent to approximately 3.8 lbs Mn/mile (based on 6 inch diameter pipe) or 7.7 lbs Mn/mile (based on a 12 inch diameter pipe). Brandhuber et al. (2015) also noted that only 1.5% of the manganese deposit would need to be released to exceed the U.S. EPA Health Advisory values of 1 mg Mn/L for both 1 day and 10 days. Peng and Korshin (2011) found that manganese was significantly associated with the organic and mobile fractions of the corrosion scale, and the majority of the manganese was found to be in the dissolved fraction. The authors also found that 9% of manganese was in the exchangeable fraction which is prone to displacement by competing ions, thus making manganese deposits susceptible to changes in water quality.

Physical disturbances can also cause release of scale deposits. Del Toral et al. (2003) observed that the highest lead releases were associated with disturbed lead service line pipes as compared to undisturbed lead service line pipes. Disturbances included events such as meter installation/replacement, autometer reader installation, leak repair, external service shut-off valve repair/replacement and significant street excavation (Del Toral et al., 2003).

Manganese can also accumulate in distribution system biofilms (Ginige et al., 2011; Cerrato et al., 2010; Sly et al., 1990). Both manganese oxidizing (Cerrato et al., 2010; Sly et al., 1990) and manganese reducing (Cerrato et al., 2010) bacteria have been identified. The entrapped manganese accumulated in drinking water biofilms has been shown to be susceptible to release during biofilm inactivation (Ginige et al., 2011). In bench-scale experiments by Ginige et al. (2011), biofilm reactors fed with either low (0.02 mg/L) or high (0.04 mg/L) influent levels of manganese were subjected to a 14 day biofilm inactivation treatment with 3 mg/L chlorine. In both the high and low level reactors, the biofilm ATP concentration decreased approximately 10-fold within a 2 day time frame. During inactivation, turbidity and manganese increased in both reactors. In the low influent reactor, manganese release peaked on day 4 at 0.07 mg/L and returned to baseline levels of 0.01 mg/L by day 8. In the high reactor, manganese release peaked on day 4 at 0.08 mg/L from 0.06 mg/L, and effluent manganese levels gradually decreased to 0.03 mg/L by day 12. The authors suggested that exopolymeric substances and the metal oxide/hydroxide layer could play a role in the detachment timing for manganese from biofilms.

7.3.2 Implications of manganese accumulation for other distribution system concerns

The presence of manganese in distribution systems also has implications for other metals of concern. Manganese accumulation on lead pipes can obstruct the formation of the more stable Pb (IV) corrosion scale, increasing risk of lead release through more readily soluble scales (Schock et al., 2014). $MnO_x(s)$ have also been shown to be effective scavengers for a variety of heavy metals, including lead (Dong et al., 2003) and arsenic (Ouvrard et al., 2002). In Freidman et al. (2010) barium, lead, nickel, vanadium, arsenic, radium, chromium and uranium were shown to be associated with $MnO_x(s)$ deposits in distribution system pipe materials. Manganese deposits represent potential sinks for the accumulation and subsequent release of these metals. Schock et al. (2014) found that in a distribution system where manganese was controlled through a unidirectional flushing program, lead levels were also reduced as lead accumulation in the scale was decreased in the absence of manganese.

Additionally, a link between the presence of particles in the distribution system and increased organic matter was observed (Vreeburg, 2010). In a study where additional treatment removed all particles (>0.1µm) entering the distribution system, levels of organic matter was found to be six times less than in the conventional distribution system where particles were present. Vreeburg (2010) suggested that the particles could offer increased surface area for biological regrowth.

7.3.4 Manganese management in distribution systems

In a review article on discolouration in distribution systems by Vreeburg and Boxall (2007) two pathways for managing discolouration risk in distribution systems were noted: 1) adoption of a cleaning threshold to prevent the accumulation of material and 2) limiting or preventing particles from entering or being generated in the distribution system. Similarly, Brandhuber et al. (2015) recommended a manganese management approach that minimized the amount of manganese entering the distribution system; minimized the manganese stored in the distribution system through best practices for main cleaning; minimized physical/hydraulic disturbances; and maintained stable water chemistry.

High velocity networks can be used as a self-cleaning method to minimize the accumulation of sediments (Vreeburg, 2010). Particles that accumulate during periods of low water demand can be resuspended by using sufficiently high water velocity thus preventing long-term accumulation issues. The practicality of high velocity networks may be limited as they require compatible distribution system designs (branched vs. looped).

The practice of pigging pipes can also be used to remove sediments but caution must be used when employing pigging as it is not appropriate for all pipe and water quality types (FCM, 2003). For example, the pigging of unlined cast iron pipes was associated with greater iron and downstream lead particle release when compared to cast iron pipes that were lined and pigged and those that were untouched (i.e., unlined and not pigged) (Camara et al., 2013).

Unidirectional flushing is considered a best practice for managing particles in a distribution system (FCM, 2003; Brandhuber et al., 2015). In practice, Zacheus et al. (2001) found that before flushing manganese comprised 3.7% (by weight) of old soft deposits in distribution system pipes; whereas one year after flushing manganese comprised only 0.58% (by weight). Similarly, Barbeau et al. (2005) found that loose deposits from both cement lined ductile iron and unlined grey cast iron distribution system pipes were composed of 5.9% (by weight) manganese. One year following flushing, the manganese content was decreased to 0.35%. In a field study by Carrière et al. (2005), unidirectional flushing was found to be an effective method for the removal of loose distribution system deposits in some cases. The authors also cautioned

that unidirectional flushing should be applied on site specific basis. Vreeburg (2010) also recommended the "clear water front" approach which requires that the upstream water used to flush pipes comes from pipes with no re-suspendable material to prevent the introduction of sediment into the flushed pipe. In extreme cases, pipe replacement could be used as a last resort option for managing accumulated manganese in distribution systems (Brandhuber et al., 2015).

Maintaining stable water quality conditions is an important factor in minimizing release of accumulated manganese in the distribution system. Friedman et al. (2010) identified several key water quality conditions that should be controlled in order to maintain water stability for deposited inorganics including pH, ORP, corrosion control measures as well as avoiding the uncontrolled blending of surface water and ground water, and the uncontrolled blending of chlorinated and chloraminated water.

Managing manganese accumulation and release may be a significant challenge for utilities, as even utilities meeting the aesthetic objective could have historical reserves of legacy manganese stored on distribution system pipes. Identifying high risk areas in the distribution system will require an understanding of factors affecting risk of accumulation (e.g., presence of manganese in source/treated water, proximity to water treatment plant, pipe materials, biofilm) as well as risk of release (e.g., unstable water quality conditions, hydraulic/physical disturbances). Distribution system areas where there is high risk for both accumulation and release may be the ideal locations for increased event based monitoring.

7.4 Residential scale treatment

In cases where manganese removal is desired at the household level, for example when a household obtains its drinking water from a private well, a residential drinking water treatment device may be an option for reducing manganese concentrations in drinking water. Before a treatment device is installed, the water should be tested to determine general water chemistry and verify the presence and concentrations of manganese in the source water. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Treatment devices lose their removal capacity through usage and time and need to be maintained and/or replaced. Consumers should verify the expected longevity of the components in their treatment device according to the manufacturer's recommendations and service it when required.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. NSF/ANSI Standard 42: Drinking Water Treatment Units-Aesthetic Effects includes reduction requirements for manganese. For a device to be certified for manganese reduction under Standard 42 it must be capable of achieving the reduction of 1-2 mg/L of dissolved manganese (Mn(II)) down to a maximum treated water concentration of 0.05 mg/L (NSF/ANSI, 2014a).

Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 2014):

- CSA Group (www.csagroup.org);
- NSF International (www.nsf.org);

- Water Quality Association (www.wqa.org);
- UL LLC (www.ul.com);
- Bureau de Normalisation du Québec (www.bnq.qc.ca/fr/); and
- International Association of Plumbing & Mechanical Officials (www.iapmo.org).

An up-to-date list of accredited certification organizations can be obtained from the SCC (www.scc.ca).

Although there are currently no treatment units certified specifically for manganese reduction, there are several treatment technologies that can be effective for manganese removal at the residential-scale. Traditionally manganese treatment systems have been installed at the point-of-entry (POE) into the home to reduce the potential for discoloured water and staining of laundry (i.e., aesthetic concerns). These systems are typically designed and constructed for residential use by drinking water system providers or dealers. Treatment technologies that can be used at the point-of-entry to reduce the likelihood of discoloured water and staining within the home are ion exchange (i.e., water softener) and greensand filtration. Drinking water treatment devices are also available to reduce manganese concentrations at point-of-use (POU) devices in a home (e.g., kitchen tap) or as pour-through filters (e.g, pitcher type of filter). Treatment technologies for manganese removal that are appropriate for residential treatment are reverse osmosis, ion exchange (including water softeners and other cation exchange systems), and oxidizing filters (e.g., greensand filters).

Health Canada strongly recommends that any chemicals and components used in these treatment systems be certified to NSF/ANSI Standard 60 – Drinking Water Treatment Chemicals Health Effects (NSF/ANSI, 2014b), NSF/ANSI Standard 61 – Drinking Water System Components Health Effects (NSF/ANSI, 2014c) and NSF/ANSI Standard 372 – Drinking Water System Components Lead Content (NSF/ANSI, 2011). Reverse osmosis systems are covered in NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems (NSF/ANSI, 2014d) and water softeners are covered under NSF/ANSI Standard 44: Cation exchange water softeners (NSF/ANSI, 2014e).

Selection of the most effective treatment system for a household will depend on a variety of factors including the concentration and form (dissolved or particulate) of manganese and other parameters such as hardness, iron, alkalinity, sulphide, ammonia and dissolved organic carbon that are present in the source water.

Reverse osmosis (RO) drinking water treatment systems have been shown to be the most effective and reliable POU treatment technology to reduce manganese concentrations in drinking water in households with a water supply containing elevated manganese concentrations (Barbeau et al., 2011; Brodeur and Barbeau, 2015; Health Canada, 2015). Barbeau et al. (2011) found that eight reverse osmosis systems installed in homes supplied by well water achieved close to 100% removal of manganese even in the presence of high manganese concentrations (> 1 mg/L). In a more detailed report prepared using the same data, Brodeur and Barbeau (2015) reported that POU reverse osmosis systems were capable of achieving treated water concentrations below 1.0 µg/L when manganese in the well water ranged between 141 and 3.9 µg/L (86-100% removal). Similarly, in laboratory testing conducted on three POU reverse osmosis systems, greater than 86% removal was achieved by all units to achieve treated water concentrations below 6 µg/L (Health Canada, 2015). Well owners should be aware that reverse osmosis is intended for POU installation only. This is because water treated by a reverse osmosis system may be corrosive to internal plumbing components. These systems also require larger quantities of influent water to obtain the required volume of drinking water and are generally not practical for point-of-entry

(POE) installation. In addition, it may be necessary to pre-treat the influent water to reduce fouling and extend the service life of the membrane.

There are also POU devices available that use cation exchange media which are effective for manganese removal. Carrière et al. (2011) found that pour-through filters composed of cation exchange (and GAC) media were effective at reducing an influent (incoming) manganese concentration of 1 mg/L by greater than 60% at 100% of their estimated treated water capacity. These filters were also often capable of up to 100% removal during the early operation of the filters. Cation exchange devices designed for under-the-sink installation were also found to be effective for dissolved manganese removal (up to 100%) but in some cases their effectiveness decreased after only 50% of their estimated treated water capacity. It is also important to note that the treated water concentrations increased when these units were operated beyond their estimated capacities. Since most cation exchange media used in drinking water treatment devices have a lower affinity for manganese than calcium, magnesium and other metals such as iron, manganese ions will be displaced off of the resin more easily. This results in a lower operating capacity for manganese removal as well as the potential for increased manganese in the treated water (Carrière et al., 2011). Therefore, careful operation and monitoring of these systems is necessary.

Conventional water softeners that treat water entering the home also use ion exchange technology and have the potential to removal low levels of manganese. If particulate manganese is present in the source water, it may damage the resin and reduce the effectiveness of these systems. As discussed above, manganese removal efficiencies can be variable using ion exchange due to the selectivity of the resin towards cations that cause hardness (calcium and magnesium). Therefore, manganese removal using water softeners will be less effective when source water with high hardness or iron is being treated. Brodeur and Barbeau (2015) and Barbeau et al. (2011) observed a large range in the removal efficiencies (-48% - 99%) of ion exchange systems operating in residences treating groundwater. Despite the large ranges in manganese removals observed in this study, overall the systems were found to be effective. Seventy-five percent of the systems achieved 99% removal of manganese (influent concentrations up to 211 µg/L) to achieve treated water concentrations below 19 µg/L.

POE oxidizing filters such as greensand filters can be used for POE residential scale manganese removal. These systems consist of a filter media treated with potassium permanganate to form a coating that adsorbs and then oxidizes dissolved manganese. These filters are often referred to as manganese greensand filters. Greensand filters require significant maintenance including frequent regeneration with an oxidant and regular backwashing to remove oxidized manganese particles. The preferred oxidant is chlorine although potassium permanganate can also be effective. Deficient operation and maintenance of greensand filters has been associated with an increase in manganese concentrations in the tap water in homes treating well water for manganese (Barbeau et al., 2011). Brodeur and Barbeau (2015) reported data for three green filters installed in residences for manganese removal. None of the systems were capable of removing manganese below 100 µg/L. In addition, it was observed that two of the systems were releasing manganese from the filters resulting in an increase in the treated water concentration of between 17 and 199%. For these reasons, homeowners need to give careful consideration to the selection and operation of these types of treatment systems for manganese removal.In addition, it is important to routinely monitor the manganese concentration in the water treated by greensand filtration to ensure that the system is effectively removing manganese and that release of manganese from the filters is not occurring.

Depending on the concentration of manganese in the source water and the type of treatment selected, households with a private well may want to treat water at the POE to reduce

the likelihood of water discolouration and staining of laundry in addition to treating at the POU to ensure that levels are reliably below the MAC in the home's drinking water.

8.0 Kinetics and metabolism

The following section summarizes the data presented in several recent reviews (Aschner et al., 2005; Dorman et al., 2006; Health Canada, 2010) as well as more recently published papers. The reader is referred to these documents for more detailed information.

8.1 Absorption

Manganese is an essential nutrient that is subject to homeostatic control through both regulation of its absorption across the gastrointestinal (GI) tract and its hepatobiliary excretion (the so-called "first-pass effect") following ingestion. In contrast, inhaled manganese occurring as a result of occupational exposures can bypass this homeostatic control on intestinal uptake and first-pass distribution to the liver, and be transported via the olfactory system or respiratory tract to the brain (Aschner et al., 2005; Roth, 2006). Thus, absorption of manganese via inhalation differs significantly from absorption through drinking water ingestion.

Dietary ingestion represents the largest source of oral exposure to manganese in humans. In addition to homeostatic control on uptake, absorption is influenced by the bioavailability and/or bioaccessibility of manganese in the GI tract, its chemical form, the amount of manganese ingested, iron status, as well as gender and age. A smaller fraction of the manganese content from food and water is typically absorbed through the GI tract in adults compared to infants (Davidsson et al., 1988; Johnson et al., 1991; Finley et al., 1994; Institute of Medicine, 2000; Health Canada, 2010). Oral studies in animals generally yield similar absorption results (Pollack et al., 1965; Davis et al., 1993; Finley et al., 1997; Zheng et al., 2000). Absorption of ingested manganese is higher in the neonatal period, and manganese is thought to be more bioavailable (Dorothy Klimis-Zacas, 1993). Neonates have been reported to have a higher retention of manganese, with formula-fed infants retaining approximately 20% of the oral intake (Aschner and Aschner, 2005).

A review of 13 published studies that used a wide variety of exposure scenarios in humans (without consideration of fasted state) found no statistically significant difference in the bioavailability (defined in the review as the fraction that enters into the systemic circulation, i.e., excluding the part excreted in the bile after the first-pass effect in the liver) of manganese when ingested in water compared to in food (food: water ratio was 0.7). (Ruoff et al, 1995, cited in US EPA 2002). For food, the GI bioavailability was similar whether manganese was intrinsically present in the foods or extrinsically added to the diet. However, upon re-evaluating the data for fasted individuals, the bioavailability of manganese in water was roughly 2-fold higher than in food (food: water ratio was 0.5) (Ruoff, 1995). Overall, these data suggest that the GI bioavailability of manganese in humans may partially depend on the interactions between manganese and materials (e.g., fiber, protein and other inorganic substances) present in the gut rather than on the bioavailability in each ingested media. Net manganese absorption from the diet was shown to be influenced by the presence of other trace minerals, cellulose, pectin, phytate or ascorbic acid, and other dietary constituents (Aschner et al., 2005) as well as the bioaccessibility of manganese in solid matrices (i.e., the proportion of manganese in a solid matrix that is potentially biologically available for absorption). Bioaccessibility was estimated at 55% - 95% in a variety of animal-based food (Lei et al., 2013) and at 12% – 41% in 20 urban soils (Sialelli et al., 2010). In adult male rats, bioavailability was also reported in be similar following 61 days of equivalent manganese exposures in diet and drinking water (Foster et al., 2015). However, it

should be noted that adaptive changes to control manganese levels (including reduced gastrointestinal absorption and increased excretion) which occur in adults following elevated exposure to manganese are not established in infants, who lack these homeostatic controls (Aschner et al., 2005; Foster et al, 2015).

The chemical form (i.e. species) and valence state of manganese affects its absorption. Soluble manganese (e.g.., manganese chloride) is more readily absorbed (Roels et al., 1997), as is the complex-associated trivalent oxidation state of manganese found in human milk. This trivalent form binds to lactoferrin and is regulated across the GI tract via lactoferrin receptors in the brush border membranes of epithelial cells throughout the length of the small intestine. Infant formula contains the divalent oxidation state which does not bind to lactoferrin and therefore intestinal uptake cannot be regulated by lactoferrin receptors (Erikson et al., 2007b). In healthy adults, elevated dietary manganese levels were reported to be accompanied by a decrease in percent absorption, and enhanced hepatic metabolism and biliary and pancreatic elimination of manganese (Finley et al., 2003; Aschner et al., 2005).

In both humans and animals, low iron status has been shown to increase manganese absorption, independent of body stores of manganese (Mena et al., 1969; Chandra and Shukla, 1976; Shukla et al., 1976; Finley and Davis, 1999; Arnich et al., 2004). Absorption of both iron and manganese across the gut uses the same transport system, resulting in competition between manganese and non-heme iron at the level of the divalent metal transporter 1 (DMT-1, also known as DCT-1 or nramp-2) (Davis et al., 1992a) with expression of DMT-1 (mRNA levels) being strongly increased in the duodenum in response to iron depletion (Gunshin et al., 2001).

Gastrointestinal absorption of manganese is also influenced by individual factors such as gender and age. In humans, GI absorption of manganese was found to be higher in females than in males (Finley et al., 1994); this is possibly related to the lower iron status in and increased iron need in women. Increased absorption and retention have been observed in neonates and infants in both humans (up to an undetermined age) and rodents (up to 17-18 days age) (Gruden, 1977; Keen et al., 1986; Dörner et al., 1989; Kostial et al., 1989; Zlotkin et al., 1995; Aschner et al., 2005). Infants can absorb up to 40% of ingested manganese (compared to 3% absorption estimated in adults making them particularly susceptible to effects resulting from elevated manganese exposure (Neal and Guilarte, 2013). The enhanced biliary retention of manganese in neonates can be explained by the immaturity of the hepatobiliary system (reduced excretion) (Miller et al., 1975; Cotzias et al., 1976) and by increased GI absorption (Cahill et al., 1980). Increased absorption at very young ages may also be a compensatory mechanism due to the increased metabolic needs of infants in comparison with adults, since manganese is required for adequate bone mineralization, as well as for connective tissue synthesis (Santamaria, 2008). Interindividual variability in manganese retention appears to be large: in human adults administered a dose of radiolabeled manganese in an infant formula. the he mean absorption was 5.9±4.8%, and the range was 0.8 - 16%, i.e., a 20-fold difference; retention measured on day 10 (0.6 - 9.2%) also indicated substantial differences between individuals (Davidsson et al., 1989a).

The dermal absorption of manganese is not well understood but is expected to be extremely limited(Aschner et al., 2005). No experimental data was identified regarding dermal absorption of manganese.

8.2 Distribution

Information regarding the distribution of manganese has been summarized in detail in reviews (Aschner et al., 2005; 2007) and a Health Canada (2010) report.

8.2.1 Tissue distribution

Manganese is distributed throughout the body via systemic circulation. Within the blood, manganese is present in plasma, where Mn(II) is bound to albumin, red blood cells, where it is mainly bound to hemoglobin (Gibbons et al., 1976; Saric, 1986; Davidsson et al., 1989b), and white blood cells.

The distribution of manganese depends on its chemical form (valence and solubility). In a dietary study,levels of manganese in liver and kidney were significantly higher in male mice exposed to manganese acetate or manganese carbonate than in mice exposed to manganese chloride or manganese dioxide (Komura and Sakamoto, 1991).

Manganese concentrations in most human tissues range between 0.1 and 1 µg/g wet weight, but higher values have been reported in the liver, olfactory bulb, kidney and some regions of the brain in presumed normal adult subjects (Aschner et al., 2005). The highest concentrations of manganese tend to be reported in tissues with high mitochondria content, such as liver, pancreas, kidneys, pituitary gland and intestines; the lowest concentrations are reported in muscles, bones and fat (Merian et al., 2004; Health Canada, 2010). Bones represent the largest tissue store of manganese and account for 25-40% of total body burden because of bonemass not concentration (Aschner et al., 2005; Roth, 2006). Pregnancy was found to be associated with elevated levels of manganese in the liver of rats (Jarvinen and Ahlström, 1975).

In human milk, manganese concentrations are generally less than 30 µg/L, although values attaining 60 µg/L have been reported (Health Canada, 2010). Measured concentrations of manganesein milk were found to decrease from birth over seven days postpartum (Arnaud and Favier, 1995).. Ratios of manganese concentrations in whole blood vs. breast-milk were estimated in women with occupational and/or environmental exposure to metals in a region of India highly affected by steel industry, and in (control) women living 100 km away (Sharma and Pervez, 2005). The average ratios varied from 2.8 to 4.1 in exposed women, and from 1.7 to 2.5 in control women. Within both exposed groups, manganese concentrations in blood and milk were correlated. A study that investigated maternal exposure to elevated levels of manganese and other metals in drinking water in Bangladesh reported elevated manganese concentrations in urine, though no correlation between elevated manganese levels in drinking water and breast milk or blood was foundLjung et al., 2009).

Fetuses, neonates and pups are exposed to (maternal) manganese since it crosses the placental barrier and is found in milk. Oral exposure of rat dams to manganese chloride in drinking water (2 000 ppm) during gestation (272 mg Mn/kg bw per day) as well as during lactation (480 mg Mn/kg bw per day) was shown to increase the manganese total body burden (measured by atomic absorption spectometry) in neonates and 11-day-old pups by 6-8 fold; this increase was independent of age and exposure duration (asimilar increase was reported when exposure occured during gestation only, suckling only or both gestation and suckling) (Kostial et al., 2005). Increased manganese concentrations were also reported in the forebrain and hindbrain of newborn rats after *in utero* exposure (Kontur and Fechter, 1985).

8.2.2 Distribution within the brain

The brain readily uptakes manganese from the circulation, and levels may increase in the brain as a result of elevated exposures. The half-life of manganese in the brain was estimated to be 51-74 days in the rat, 53 days in the macaque monkey and 53 days in humans (Cotzias et al., 1968; Newland et al., 1987; Takeda et al., 1995).

Recent reviews regarding the uptake of manganese into the brain led to the conclusion that manganese can enter the brain via several pathways, including the blood through capillary

endothelial cells of the blood-brain barrier (BBB), from the blood through the cerebral spinal fluid (CSF) via the choroid plexuses and, when exposure occurs by inhalation, from the nasal mucosa to the brain olfactory bulb via olfactory neural connections, though the latter is believed to be important only in cases of elevated nasal respiratory exposure (Aschner et al., 2005; Crossgrove and Yokel, 2005; Bock et al., 2008). However, it is not clear whether a particular one of these pathways predominates, in cases of severe manganism or cases of subtle neurological impairment in humans, or what the predominant molecular mechanism(s) of transport are in any of these pathways (Aschner et al., 2005).

In animals, increased concentrations of manganese in the brain following acute or chronic oral exposure have been reported in numerous studies (Holbrook et al., 1975; Rehnberg et al., 1982; Kristensson et al., 1986; Newland et al., 1989; Chan et al., 1992; Davis et al., 1992b; Malecki et al., 1996; Lai et al., 1999). For instance, in rats exposed to manganese through drinking water (10 mg $MnCl_2 \cdot 4H_2O$/mL) for five days, manganese concentrations were increased in some regions of the brain, with the highest concentration in the striatum and lowest concentration in the cerebral cortex. After ten days the highest concentrations were in the pons and medulla and the lowest concentration in the hypothalamus., variation in manganese content across brain regions was more pronounced in neonates than in weanling and adult rats (Chan et al., 1992). In the mature (PND120) female offspring of Wistar rats exposed through gestation, lactation and from weaning onwards by direct exposure to manganese in drinking water (280, 2 800 or 5 600 mg Mn/L), dose-dependent increases in manganese concentration were observed in all brain regions (midbrain, pons and medulla, cerebellum, cerebral cortex and, more prominently in hypothalamus, striatum and hippocampus) except in the cerebral cortex and hippocampus of rats treated with the lowest dose (Lai et al., 1999).

A difference in manganese brain distribution between neonatal and adult rats exposed to the same oral doses of manganese chloride (25 or 50 mg/kg bw per day) was reported in a study by Dorman et al. (2000). An increase in manganese concentration was observed only in the striatum and cerebellum in adult rats of the highest dose group, whereas neonatal exposure resulted in increased striatal, hippocampal, hindbrain, and cortical concentrations of manganese in all groups exposed. These results suggest that neonates may be at greater risk for neurotoxicity resulting from high oral exposures to manganese than adults.

Manganese-induced neurotoxicity is asociated with elevated brain levels of manganese that occur following elevated exposure, with the striatum (caudate nucleus and putamen), globus pallidus, subthalamic nuclei (collectively the basal ganglia) and frontal cortical areas appearing particularly susceptible (Dobson et al., 2004). The human caudate/putamen and globus pallidus have been identified as primary neurotoxicity targets following exposure to manganese (Pal et al., 1999; Aschner et al., 2005).

8.2.3 Cellular uptake and efflux

Both Mn(II) and Mn(III) can cross the BBB (Aschner et al., 1999), with Mn(II) utilizing a number of different divalent cation transporters, while transferin-associated Mn(III) is taken up via the transferin receptor (Health Canada, 2010). Uptake of non-protein bound Mn(II) appeared to be much more rapid than uptake of Mn(III)-transferrin (Tf) complex; Mn(II) would thus be the predominant species entering the brain from plasma, while the Mn(III)-Tf complex uptake may play a lesser role in brain manganese uptake (Yokel et al., 2006). Little is known about transport mechanisms of manganese into the brain during the developmental period. DMT-1 and TfR are present in the developing brain, as shown by the expression of DMT-1 and TfR proteins in

Sprague-Dawley rat pups as early as PND5 with concentrations that increase through PND15 in all regions examined (cortex, hippocampus, striatum) (Siddappa et al., 2002; Garcia et al., 2006).

Recently, the SLC30A10 cell-surface transporter has been shown to play an important role in manganese efflux from the brain (Leyva-Illades et al., 2014). The transporter has been demonstrated to reduce cellular levels of Mn, and mutations this transporter lead to manganese toxicity. A number of other transporters also help to maintain manganese homeostasis within the cell (Chen et al., 2015).

8.3 Metabolism

In its elemental form manganese does not undergo metabolism and is absorbed and excreted unchanged. Manganese is usually ingested in the form of ionized salts and can change valence states during or after absorption. Although the divalent form of manganese is predominant in biological systems, manganese can be present in the trivalent form in most enzymes; bound to transferrin (Tf); in human milk, bound to lactoferrin (Aschner et al., 2005).

In the liver and circulation, a proportion of divalent manganese is oxidized to the trivalent form and stabilized to protein ligands such as Tf (Aschner et al., 2005). Tf binds Mn(III) (or Fe(III)), and not Mn(II) (Aisen et al., 1969; Critchfield and Keen, 1992; Ueda et al., 1993). Oxidation of Mn(II) to Mn(III) may also occur intracellularly via reaction with free radical species such as the superoxide anion (Archibald and Tyree, 1987). While ceruloplasmin in circulating plasma has been suggested to catalyze oxidation of Mn(II) to Mn(III), leading to a shift in manganese binding in vitro from α2-macroglobulin to Tf (Gibbons et al., 1976), recent studies in ceruloplasmin knock-out mice have shown clearly that ceruloplasmin is not necessary for plasma manganese oxidation and loading onto plasma Tf (Jurasa and Smith, 2009). In addition, it is possible that small amounts of Mn(II) may be spontaneously oxidized to form small amounts of Mn (III) which, even in trace amounts, can lead to the formation of reactive free radicals (HaMai et al., 2001). While studies have suggested that the majority of manganese in mammalian cells exists as Mn(II) (Reaney et al, 2002), accurate detection of manganese valence state *in* vivo is limited by a number of technological challenges.

Data suggest that the valence state of manganese is an important determinant for manganese retention and toxicity (Yokel et al., 2006). Mn(II)-α2-macroglobulin was cleared more rapidly from cows than Mn(III)-Tf (Gibbons et al., 1976). *In vitro* studies revealed a higher potential of cytotoxicity and neurotoxicity for Mn(III) than for Mn(II), presumably due to the higher reduction potential of Mn(III), and its ability to induce oxidative stress (Ali et al., 1985; Archibald and Tyree, 1987; Chen et al., 2001; Reaney et al., 2002; Reaney and Smith, 2005). In rats administered the same doses of Mn(II) or Mn(III) intraperitoneally, brain and blood concentrations were higher in the rats treated with Mn(III) (Reaney et al., 2006).

8.4 Excretion

Manganese is largely removed from the blood by the liver and then excreted through the bile into the intestine (Miller et al., 1967). From the intestine, a large fraction of the biliary manganese is then excreted via feces, while a small fraction is reabsorbed (Schroeder et al., 1966; Davis et al., 1993).

Whole-body clearance half-time is approximately 4 days for the rapid phase and 39 days for the slow phase, during which about two-thirds of the elimination occurs (WHO, 1981). Whole-body retention half-times have been estimated to be 13 to 37 days in humans who ingested tracer levels of radioactive manganese (as manganese chloride) (Mena et al., 1969; Sandstrom et al., 1986; Davidsson et al., 1989a). Half lives in the brain have been reported to range from 50-

220 days in rats and non-human primates (Takeda et al., 1995; Health Canada, 2010). Although absorption by the brain is mediated by facilitated transport, efflux from the brain has been proposed to occur at a slower rate through diffusion, thus allowing a potential for accumulation over time (Yokel and Crossgrove, 2004).

Direct transport across the intestinal wall from serum can contribute to excretion in the feces (Bertinchamps et al., 1965; Garcia-Aranda et al., 1984). Small amounts of manganese are excreted in urine, sweat, milk, hair and nails (Merian et al., 2004; Health Canada, 2010). The concentration of manganese in urine is generally low (Alessio et al., 1989; Minoia et al., 1990; Park et al., 2003) and urinary excretion is considered to be a poor biomarker of body burden from oral and inhalation exposure (Andersen et al., 1999). Hair has also been used as a biomarker of environmental manganese exposure and body burdern in a number of studies, though proper cleaning is required to ensure removal of exogenous manganese contamination so as to examine only metabolically incorporated manganese (Eastman et al., 2013).

Infants, and especially neonates have a reduced capacity for biliary excretion compared to adults (Cotzias et al., 1976). As a result, neonates and young children will acquire a higher body burden of manganese from a given exposure compared to adults, which along with the important neurodevelopmental processes occuring in neonates, renders them particularly susceptible to manganese-induced toxicity (Neal and Guilarte, 2013).

8.5 PBPK models

Physiologically-based pharmacokinetic (PBPK) models for manganese have been developed for rats (Teeguarden et al., 2007a; 2007b; 2007c; Na et al., 2008; Nong et al., 2008; 2009; Yoon et al., 2009 a; 2009b), monkeys (Nong et al., 2009; Schroeter et al., 2011; 2012) and humans (Schroeter et al., 2011; Yoon et al., 2011). The PBPK models published from 2008 include both the oral and inhalation routes. Injection routes (i.p., s.c. and i.v.) were also included in human and monkey models (Schroeter et al., 2011) to allow the evaluation of experimental data obtained with radiolabeled manganese (^{54}Mn). Lactational transfer in rats (Yoon et al., 2009a), as well as fetal dose and disposition of manganese in rats (Yoon et al., 2009b) and humans (Yoon et al., 2011) (mother and fetus) can be estimated. A PBPK model was also developed for transport of inhaled manganese from the olfactory mucosa to the striatum in rats (Leavens et al., 2007). An overview of these models is available in Taylor et al. (2012).

The most recent models for monkeys and humans (Schroeter et al., 2011; 2012) allow estimation of manganese concentrations in target brain tissue (globus pallidus). These models can estimate manganese tissue concentrations following exposure through ingestion, inhalation and injection (i.v., i.p., s.c.). Briefly, they include compartments for liver, lung, nasal cavity, bone, blood, olfactory bulb[1], cerebellum[2], globus pallidus[2], pituitary gland[2], and remaining body tissues. The models include saturable manganese tissue-binding capacities, preferential fluxes of manganese in specific (brain) tissues and homeostatic control processes (i.e. reduced intestinal absorption and induced biliary secretion at elevated levels of exposure).

Both the human and the monkey models were validated against available manganese tracer data. The monkey model validation included fecal excretion (after s.c. injection or inhalation), whole-body retention (after i.p. injection, i.v. injection or oral exposure) and brain tissue concentrations (following inhalation exposure). The human model was able to capture the

[1] Selected because it receives direct transport from olfactory epithelium during manganese inhalation

[2] Cerebellum, globus pallidus and pituitary gland were selected because they accumulate manganese to varying degrees during inhalation exposure

dose-dependent characteristics of manganese disposition (whole-body retention, plasma retention) across multiple exposure routes. The authors suggest that use of the models to estimate exposure concentrations that would result in increased tissue concentrations could be used in a risk assessment based on dosimetry (Shroeter et al., 2011). Although the model can be used to estimate manganese concentrations in brain tissue, such simulations have not been validated in humans.

9.0 Health effects in humans

Numerous epidemiological studies have investigated the effect of manganese exposure on human health. High exposure to Mn, possibly occurring in occupational settings, can cause a clinical neurological disease referred to as manganism, which is characterized by generalized cognitive and motor disturbances, including bradykinesia, widespread rigidity, gait disturbances, falling, dystonia, difficulty walking backwards, and speech difficulties. In addition, many studies have shown that lower exposures to Mn, particularly by inhalation, can result in deficits in neurofunctional outcomes such as impaired fine motor skills, eye hand coordination and reaction time. Moreover, some recent epidemiology studies have suggested an association between exposure to manganese in drinking water and neurological effects in children (Bouchard et al., 2011; Khan et al., 2011; Roehls et al., 2012; Oulhote et al., 2014).

9.1 Essentiality

Manganese is considered to be an essential element by Health Canada and other international agencies (NRC, 1989; IOM, 2001; Expert Group on Vitamins and Minerals, 2002; National Institutes of Health, 2011; WHO, 2011). Manganese is an essential cofactor for some enzymes (pyruvate carboxylase, Mn-superoxide dismutase) (NRC, 1989; IOM, 2001). In addition, manganese can serve as a cofactor to activate enzymes (decarboxylases, hydrolases, kinases, etc.), that are also activated by other similar divalent cations, and not be altered by manganese deficiency (EVM, 2002). The enzymes requiring manganese have multiple functions including antioxidant defence, bone formation, and the metabolism of carbohydrates, cholesterol, and proteins, in addition to utilization of other nutrients including the vitamins biotin and ascorbic acid (Saudin et al., 1988; IOM, 2001).

Mn deficiency is extremely rare and symptoms are not well defined (Dupont and Tanaka, 1985; IOM, 2001). In animals, bone and cartilage malformations, impaired growth, reproductive functions, neurologic disturbances and metabolism of glucose, carbohydrates (diabetic-like symptoms) and lipids are observed (EVM, 2002). In humans, skin anomalies such as erythematous rash, slow growth of nails, reduced bone density, hair depigmentation, hypocholesterolemia are observed with diets that have very low levels of manganese (approximately 0.01-0.34 mg/day).

The IOM established Dietary Reference intakes for manganese, which were adopted by the Health Products and Food Branch of Health Canada. No Estimated Average Requirement (EAR) was established because of the lack of sufficient data on dose and response. Adequate Intake levels (AI) were calculated based on dietary data from average population intakes among healthy individuals. The established AIs are 0.003 mg/day for infants 0 to 6 months, 0.6 mg/day for 6 to 12 months, 1.2 mg/day for children 1-3 years old, 1.5 mg/day for children 4-8 years old, 2.3 mg/day for adult males, 1.8 mg/day for adult females, 2.0 mg per day for pregnant females and 2.6 mg/day for breastfeeding females, based on median intake data from the Food and Drug

Administration Total Diet Study for children, adolescents and adults; and on human milk concentrations for infants (IOM 2001; Health Canada 2007b).

Tolerable Upper Intake Levels (UL) were set at 2-6 mg/day for children 1-18 years old, 11 mg/day for adults and 9-11 mg/day for pregnant and lactating women (IOM 2001). No UL was determined for infants, since toxicity data are insufficient, and it is not clear at what age infants can develop mechanisms to maintain manganese homeostasis (IOM, 2001). The American Academy of Pediatrics' fifth edition of the 'Pediatric Nutrition Handbook' and the American Society for Parenteral and Enteral Nutrition report both recommend 1 µg Mn/kg bw per dayay for parenterally-fed neonates (3-10 kg), though retention of intravenously administered manganese is close to 100% (compared with 8% from breast milk ingestion) (Committee on Nutrition, 2003; Mirtallo et al., 2004; Aschner and Aschner, 2005).

The UL for adults is based on the absence of observed effects in healthy adults consuming a Western-type diet containing up to 10.9 mg manganese/day (NOAEL of 11 mg/day indicated in the Greger review study (1999)), and in a study with manganese-rich, vegetarian diet, possibly containing 13 to 20 mg/day of manganese (Schroeder et al., 1966). A LOAEL of 15 mg/day was identified in Davis and Greger (1992). An increase in lymphocyte manganese-dependent superoxide dismutase activity was observed after 90 days of supplementation at this dose. No dietary study that assessed the neurological effects of manganese in humans at the UL level was found.

The European Commission's Scientific Committee on Food set a maximum manganese concentration of 100 µg/100 kcal for infant formula (SCF 2003). The derivation of this value is not clearly explained, but the commission identified manganese's neurotoxicity as a topic of growing concern.

Manganese deficiency is not expected in Canada, as food is the main source of intake, and the Canadian TDS (Health Canada, 2009) shows that the population is meeting the AIs established by the IOM Natural health products (i.e., via supplementation with manganese) can also contribute significantly to the daily intake, up to 9 mg/day in Canada.

9.2 Acute toxicity

Accidental ingestion of low doses of potassium permanganate (about 1.8 mg Mn/kg bw/day) for 4 weeks in a 66 year-old man was associated with muscle weaknesses and neurological disturbances, such as impaired mental capacity (Holzgraefe et al., 1986). However, it is unclear whether the effects were caused by manganese because of the exposure to other substances. Another case study reported a 50-year-old man being lethargic, vomiting, and suffering diffused abdominal pain, profuse diarrhea, liver failure, acute renal injury, acute respiratory distress, myocardial dysfunction, and shock with lactic acidosis after ingesting hydrated manganese sulfate (three table spoons daily, total duration unknown). Death occurred within 72 h. It should be noted that the man was on a protein-free diet and consuming several herbal teas during a liver cleansing diet (Sanchez et al., 2012).

9.3 Epidemiology

Studies with chronic exposure to air-borne manganese have been repeatedly associated with adverse neurological effects (Health Canada, 2010). Cohort, cross-sectional and case-report studies have been conducted on the effects of high air-borne manganese exposures in welders and workers plus populations living in the surroundings of ferroalloy plants (Roels et al., 1992; Lucchini et al., 1999; Mergler et al., 1999; Bowler et al., 2006; Bouchard et al., 2007b; Lees-Haley et al., 2007; Myers et al., 2009; Riojas-Rodríguez et al., 2010; Criswell et al., 2011;

Menezes-Filho et al., 2011; Meyer-Baron et al., 2013; Michalke and Fernsebner, 2014; Yoon and Ahn, 2015).

The relationship between occupational exposure to manganese and subclinical neuropsychological tests are equivocal, but some alterations in visual reaction time, eye-hand coordination, motor performance tests or hand steadiness have generally been found. Manganism was observed in the most highly exposed groups, with symptoms such as bradykinesia, speech difficulties, gait disturbances, widespread rigidity, dystonia, propensity to fall backward, and a characteristic way of walking on the toes with the spine erected and elbows flexed. It is not clear whether the effects associated with exposure via inhalation can be induced via the oral route. Extrapolation across routes is difficult because of the toxicokinetic differences observed across routes of exposure and oxidation states (Aschner et al., 2005; Roels et al., 2012).

Many cross-sectional epidemiology studies have observed associations between higher exposure to manganese and neurological outcomes in infants and children, such as behavioral disinhibition, lower scores in tests of executive function, reading, and digit agility tests (Kawamura et al., 1941; Kondakis et al., 1989; He et al., 1994; Woolf et al., 2002; Wright et al., 2006; Ericson et al., 2007; Wasserman et al, 2011; Khan et al., 2012; Bhang et al., 2013; Chen et al., 2014; Yu et al., 2014; Haynes et al., 2015).

A recent cross-sectional epidemiology study conducted in Quebec investigated the association of manganese in the drinking water supply with intellectual impairment of school-aged children (Bouchard et al., 2011). This study included 362 children between the ages of 6-13 years who lived in communities supplied by groundwater containing manganese at various levels (range from 1 µg/L – 2700 µg/L, with a median of 34 µg/L), as measured in home tap water (MnW). The authors measured the concentration of manganese in the children's hair (MnH), in addition to their performance on the Wechsler Abbreviated Scale of Intelligence (IQ). A 6.2 point difference in IQ scores was reported between children in the lowest (median level of 1 µg/L) and highest (median level of 216 µg/L) quintiles of exposure to MnW. Higher MnW was associated with lower full scale and performance IQ scores after adjusting for covariates (i.e., maternal education and nonverbal intelligence, family income, home stimulation score, and family structure). Higher MnH was associated with lower full scale IQ score, after adjusting for the same covariates. MnH increased with water consumption of manganese, but not with the dietary manganese (semi quantitative food frequency questionnaire), suggesting a difference in bioavailability between the forms of manganese in water versus food.

In a second publication from this group, an inverse relationship was also reported between neuro-behavioural functions (memory, attention, motor function, hyperactivity) and manganese exposure in the same children (n=375) (Oulhote et al., 2014). The authors reported an inverse association between standardized (log10-transformed) MnW or MnH and memory, attention or motor function, after adjusting for confounders (i.e., child's sex, age, maternal education, nonverbal maternal intelligence, family income, maternal depression, and water lead concentrations). For hair Mn, one standard deviation (SD) increase in log10 MnH was associated with a 24% decrease in the standard deviation of memory scores (95% CI: –36, –12%) and a 25% decrease in attention SD scores (95% CI: –41, –9%), after adjusting for confounders. No significant association was observed between MnH and motor function. For water Mn, one SD increase in log10 MnW (corresponding range not provided by the authors) was associated with a 14% decrease in memory function SD scores (95% CI: –24, –4%), and a weak negative association with motor function (decrease of 11% in SD scores, 95% CI: –21, –0.4%). Steeper decline in memory and motor function were reported at water manganese concentrations above

100 and 180 µg/L, respectively. The association between MnW and hyperactivity or attention was not significant.

Although the non-metal contaminants in drinking water were not assessed, these studies did consider several covariates (e.g., lead and arsenic) in the drinking water, socio-economic status, and maternal factors that may confound the association between manganese and cognitive abilities. However, the risk of bias in these studies cannot be discarded. Few details on eligibility criteria of subjects and characteristics of lost-to-follow-ups were provided. Misclassification of the exposure was possible for different reasons: MnW was only measured once, residing in one's current home for three months was sufficient for inclusion (previous exposures to manganese not considered), hair as a biomarker can bias exposure, there were no information on diet or soil concentration included, and no information was provided on the timing and duration of exposure levels during critical periods of development. Blinding of the investigators to the exposure levels of participants was not discussed. Finally, the confidence intervals were large and borderline significance was reported for many effects observed.

Children aged 7-9 years (n=404) were enrolled in the cross-sectional Communities Actively Researching Exposure Study in Ohio from October 2008 to March 2013 (Haynes et al., 2015). Covariates such as blood and hair manganese levels, as well as the outcome variables (cognitive development via the WISC-IV) were measured during the first visit. Both high blood (> 11.2 µg/L) and high hair (> 747 ng/g) manganese concentrations were significantly associated with lower full scale IQ scores compared with the control groups (blood: 8.2-11.2 µg/L; hair: 207-747 ng/g), after adjusting for confounders (most important being: creatinine, blood lead, community, gender, and parent's IQ and education). The authors only looked at the association between the predictors and the outcomes, and did not interpret their results in terms of risk. The measured associations can be biased since the information on participants and exposure was poorly detailed. For example, the authors excluded participants with missing data for any model covariates and those with higher manganese levels, which could bias the observed relationship (e.g., if participants with missing data had low manganese and low IQ, or high manganese and high IQ, then excluding these would bias the results away from the null in both scenarios, artificially inflating the effects). The characteristics of the excluded participants were not presented, so it is unknown how well the included subjects represent the population. Exposure was subjected to misclassification; since previous exposures and variations over time were poorly assessed (hair and blood are limited bioindicators, there were no estimate of the manganese total intake or the contribution from drinking water, and only one measurement of the manganese bioindicators and of the other covariates levels was taken). There was also a risk of confounding; since the baseline characteristics were not stratified according to exposure groups (cannot assess differences other than manganese at baseline) and the statistical models were not built in a way to ensure inclusion of all important confounders (changes in the outcome variable should be the basis for covariates selection, and not in the exposure variable). Moreover, manganese was correlated with other included covariates, lowering the confidence in the model. Also, participants could be classified in different quartiles of exposure depending on the bioindicator chosen as the main predictor variable (hair or blood Mn). There was also a risk of chance finding and it would have been useful to provide the significance (p-values) of the multivariable models since the results were imprecise (large 95% CI almost including the null).

Several cross-sectional studies conducted in Bangladesh reported associations between manganese levels in drinking water and cognitive performance in school-aged children. Wasserman et al. (2011) investigated the association of manganese and arsenic exposure with intellectual function in 304 children aged 8-11 years old using adapted subtests from the Weschler

Intelligence Scale for Children IV. The authors classified children based on whether well water manganese concentrations were above or below 500 µg/L, and above or below 10 µg/L for As. After adjustments were made (maternal education and intelligence, house type, family ownership of a television, and child height and head circumference), increasing blood manganese concentration (MnB) was associated with a reduction in working memory and perpetual reasoning scores. Weaknesses of this study include the fact that the study was originally designed for another objective and other contaminants of drinking water could be responsible for the observed effects. Also, no account for other sources of manganese was made, and there were no attempts to verify an association between MnW and MnB. Also, the neurological outcomes were measured with an adapted scale which was not validated or standardized. In addition, the lack of quantitation of the exposure quartiles used in the study does not allow for use of the data in a quantitative risk assessment. Finally, only standard errors of the regression coefficients were presented.

The limitations of the Wasserman et al. (2011) study also apply to an earlier publication by the same authors(Wasserman et al., 2006) study, In the earlier study there was a dose-related reduction in full-scale, performance, and verbal raw scores after adjustment for confounders (same as in the 2011 study). In contrast with the 2011 study (where the association with MnB was significant), only the association with MnW was significant in the 2006 study.

Khan et al. (2012) examined the associations between manganese and arsenic exposure from drinking water and academic achievement of 840 children in Bangladesh. Intellectual function was evaluated in language and mathematics. A significant association between MnW > 400 µg/L and decreased mathematics test scores was observed after adjustment for confounders (i.e., arsenic, school-grade, maternal education, paternal education, head circumference, and within-teacher correlations in rating the children). In a previous study of the same author with a similar protocol, increasing MnW was associated with classroom negative behaviors after adjustment for confounders (i.e., arsenic, sex, BMI, maternal education, and arm circumference) (Khan et al., 2011). The conclusions of these two studies may be qualified by the lack of account of other possible exposure to other neurotoxic substances (e.g. incomplete arsenic and lead adjustments for exposure), the lack of a thorough characterization of the exposure (and consideration of other sources of manganese such as air and dust), the high variability of the results (wide 95% CI), and the risk of teacher's bias.

The association between cord blood manganese levels and psychomotor sub-scales was assessed in a cohort study of socially advantaged individuals (n=247 pregnant women and their offspring) in Paris (Takser et al., 2003). The children were assessed during three psychological examinations (at 9 months, 3 years, and 6 years of age). Attention, non-verbal memory, and hand skills were negatively associated with exposure, after adjustment for confounders (child's gender, mother's educational level). However, there were no relationships between birth exposure to manganese and the general psychomotor indices, Brunet–Lézine developmental quotient at 9 months or McCarthy general cognitive index (GCI) at 3 and 6 years. The contribution of manganese exposure from drinking water was not clear. The authors did not mention a method to factor the intra-individual correlation (repeated measures on the same individual through time) into the statistical analysis increasing the risk of type I error. Although the authors indicated all regression models were adjusted for maternal and cord blood lead levels, different set of covariates were used and it was not clear which ones were chosen for each model.

A longitudinal multicentre cohort study in Shanghai, China investigated the effects of prenatal exposure to manganese at environmental levels through examination of umbilical serum concentrations of manganese (MnUmbi) and administration of Neonatal Behavioural

Neurological Assessments (NBNA) (Yu et al., 2014). The authors examined 933 mother-newborn pairs by measuring MnUmbi and evaluating corresponding newborns using the NBNA test to assess the behavioural development of newborns (reflexes, functional abilities and behavioral status). Being in the highest quartile of MnUmbi was associated with lower NBNA score (statistical significance of the regression coefficient) after adjusting for confounders (parents' age, education, incomes, occupation, and smoking status, gestational age, gender, birth weight, lead, and mercury) . However, the low rate of participation (70% of recruited subjects) could have induced selection bias. Maternal serum during pregnancy was not analyzed to assess a possible relationship with intrauterine development. There were no long-term follow-up for impact on childhood development. No adjustment for important confounders (other exposure sources, environmental risk factors, metals exposure) was conducted. Moreover, residual confounding is likely since there were large differences in socio-economic status between exposure groups. The authors did not explain the clinical significance of the changes (importance of a 1.1 decrease in the regression coefficient), and it was not clear why the relationship was described as non-linear since there was no clear dose-response effect. The included covariates were likely to be collinear (e.g. maternal education and occupation), but the authors did not present a rationale for including these together in the model.

The association between environmental contaminants exposure and neurodevelopment at 2 years old was investigated with the Taiwan Birth Panel Study (n = 230 pairs of non-smoking mothers and their children) (Lin et al., 2013). In utero exposure to manganese levels above the 75th percentile (i.e., 59.3 µg/L) in the umbilical cord blood was associated with lower cognitive and language quotients of the Comprehensive Developmental Inventory for Infants and Toddlers compared with levels below the 75th percentile (statistical significance of the regression coefficient), after adjusting for maternal age, sex, smoking, home support and stimulation, and arsenic and mercury levels in cord blood. Global, motor, social, and self-help quotients were not associated with the model. No rationale was provided for including less than 50% of the selected participants, which differed from the general population by having mothers with higher levels of education, umbilical cord blood with greater levels of mercury and lead, and higher birth weight. Moreover, only one measurement of the contaminants (lead, mercury, manganese, arsenic) was done. Finally, the study focussed on co-exposure effects, and the authors did not indicate whether they adjusted for lead in the manganese model.

Case studies in two children (6- and 10-year old girls) drinking well water containing high levels of manganese (up to 2.4 mg/L in both cases) were reported by Sahni et al. (2007 and; Brna et al. (2011). High serum levels of manganese and neurological symptoms such as pica, behavioral changes, speech difficulties, lack of coordination, difficulty walking, and social withdrawal were observed in both girls. The rest of the family members were asymptomatic in each situation. The authors have suggested that a metabolic disorder involving divalent metals could have been associated with the development of the symptoms.

A case study of a 10 year-old Massachusetts boy who had been drinking turbid well water for 5 years containing manganese at a concentration of 1210 µg/L was reported by Woolf et al. (2002). The child had normal cognition, neurology, fine motor skills, balance, classroom performance, magnetic resonance imaging, and IQ. However, her performance as reflected in her ranking in the general memory index (17th percentile), verbal memory (19th percentile), visual memory (14th percentile), and learning index (19th percentile) were below average. His teachers noticed a lack of focus in the classroom. Causality is uncertain, since the water contained high levels of iron (1570 µg/L) plus toxic wastes had been an issue of concern by residents in their

highly industrialized neighborhood. Only one water sample was collected at the end of the 5-year exposure.

Some cross-sectional studies (Zota et al., 2009; Chen et al., 2014; Eum et al., 2014; Guan et al., 2014) and one cohort study (Yu et al., 2013) investigated the association between manganese exposure and body weight at birth. A minority of these observed an association between manganese and reduced body weight (those conducted in Asia with a cross-sectional design). Each of the studies with a positive association suffered from several limitations, such as designs not allowing determination of temporality (direction of effect), selection bias, and lack of adjustments for important covariates that limits establishing the causality of manganese for the observed health effects.

On the other hand, other studies did not observe an association between high environmental exposure to manganese and neurological outcomes (Vieregge et al., 1995; Torrente et al., 2005a; Hernandez-Bonilla et al., 2011). The exploratory study by Torrente et al. (2005a) found no correlation between the concentration of different elements in hair (average manganese 0.18-0.26 µg/g) and the cognitive status of children 12-14 years old (n ± 100) living close to industrial areas in Catalonia, Spain. Also, the cross-sectional study by Vieregge et al. (1995) found no difference in neurological impairment item values or in Parkinson disease scores between two cohorts of adults above 40 years old (homogenous in terms of age (mean of 57 years old), gender, nutrition, and drugs) exposed to different levels of manganese in well drinking water for at least 10 years in rural Germany (n of group A with manganese < 50 µg/L = 74; n of group B with manganese > 300 µg/L = 41). Blood manganese levels were not statistically different between the two groups. The cross-sectional study by Hernandez-Bonilla et al. (2011) found no significant difference in neuromotor outcomes between children 7-11 years old residing in rural communities with high or low manganese biomarkers of exposure (blood: 9.7 vs 8.2 µg/L; hair: 12 vs 0.57 µg/g), after adjusting for covariates (blood Pb, Hg, sex, age, maternal education), except for a weak association between finger tapping tests and manganese in blood only. The results generally showed a lack of association and were not interpreted in terms of risk by the authors. The marginal association with finger tapping ability is not conclusive since the authors did not adjust for other covariates (smoking by the parents, differences in nutrition, and there were 13 overweight children in the low exposure group compared with 1 in the high exposure group, possibly indicative of other socio-economical factors) and past exposures was not assessed. Conclusions based on these three studies showing no effects are limited because of their cross-sectional design, the possibility that only healthy individuals stayed in areas with higher concentration of the element (sick survivor effect), the possibility of other sources of exposure or unaccounted variations in the past, and the absence of adjustment for major covariates (e.g., nutrition status).

Although manganese is essential to human health, case reports, cross-sectional and cohort studies support an association between exposure to manganese in drinking water at elevated levels with neuropsychological issues in infants and children, such as changes in behavior, lower IQ, speech and memory difficulties, lack of coordination and movement control. Cross-sectional and case report studies reported associations between neuropsychological outcomes and high drinking water levels of manganese (hundreds of µg/L); while cohort studies reported these associations with prenatal manganese levels as reflected in cord blood manganese. Most studies did not allow determination of temporality (i.e., effect coming after the cause) of the association. The risk for spurious associations was estimated to be high, and exposure measurements were generally poor and relied on a single measurement of a single sample. A better understanding of the manganese

neurotoxicity mode of action would allow the identification of specific neurological biomarkers of effect and help measure early signs of toxicity.

Manganism has been observed following inhalation of manganese in occupational settings; however, it is not clear whether this effect can be extrapolated to the oral exposure route because major toxicokinetic differences exist between inhalation versus oral intake and developmental versus adult sensitivity. More reliable exposure measurements that identify a clear toxicological point of departure for the neurological effects are needed in order to conduct a dose-response analysis for the endpoints monitored. It should be noted, however, that the epidemiology studies qualitatively support neurotoxicity as a potential critical endpoint.

10.0 Health effects on experimental animals

Manganese is readily taken up into the central nervous system (CNS), although uptake into a wide range of other tissues including the lungs, kidneys and testes has also been reported. A number of studies in animal models have demonstrated the CNS to be the most susceptible target of toxicity resulting from oral exposure to manganese, followed by reproductive systems. The following sections describe toxicological information based on oral exposure to soluble manganese salts.

It should be noted that animal studies using manganese salts often do not clearly indicate whether the reported dose is reflective of manganese or a manganese complex (e.g. $MnCl_2$, $MnCl_2 \cdot 4H_2O$). Health Canada has therefore reported the dose as worded by the authors of the study. Where possible, authors of studies considered possibly key to the assessment have been contacted to confirm the dosing has been correctly interpreted. In general, the reported dosing in the majority of studies has been found to refer to elemental Mn.

10.1 Acute toxicity

The acute oral lethality of manganese varies with chemical species as well as with the route of exposure (gavage vs dietary ingestion). Manganese compounds appeared to exhibit lower acute toxicity when provided in feed than when provided by gavage (Finley and Johnson, 1996; U.S. EPA, 2003; Health Canada, 2010). The median oral lethal doses (LD_{50} values) ranged from approximately 250 mg Mn/kg bw (as manganese chloride) to 1 082 mg Mn/kg bw (as manganese acetate) in adult rats exposed by gavage (Hazaradze, 1961; Smyth et al., 1969; Kostial et al., 1989; WHO, 2011). In contrast, repeated exposure to a similar dose of manganese (50,000 ppm) as manganese sulfate in feed resulted in no death in rats exposed for 14 days (NTP, 1993).

Following a single exposure of rats to aqueous $MnCl_2$ (50 mg/kg $MnCl_2 \cdot H_2O$) by gavage, a number of neurological effects were reported, including a significant and reversible decrease in total activity, along with delayed acquisition of an avoidance reaction in response to unconditioned and conditioned stimuli, an increased latent period of conditioned reflex activity, and a temporary worsening of the learning process (Shukakidze et al., 2003).

10.2 Short-term and chronic exposure

10.2.1 Neurotoxicity

A number of studies have identified neurotoxicity as a particularly sensitive endpoint following exposure to manganese. Neurotoxic effects resulting from exposure to manganese can be categorized as affecting behavioural endpoints (including information related to altered reflex, motor activity, learning, memory, or sensory alterations), structural endpoints (including gliosis and neuroinflammation, in addition to neurostructural alterations), and neurochemical endpoints

(altered neurotransmitter systems). Neurotoxic effects resulting from exposure to manganese both during development and in adulthood are presented in this section.

10.2.1.1Neurobehavioral endpoints in neonates and juveniles

Neurobehavioral effects were reported in rats and mice (pups or neonates) following exposure during gestation, lactation and/or after weaning through direct exposure (diet, drinking water or gavage). Similarly, neurbehavioural effects have also been reported in non-human primates exposed to manganese through formula.

A transient increase of locomotor activity was observed in mice exposed to manganese on PND2-PND24 through lactation (dams exposed to 5 mg Mn/mL (equivalent to 5 000 ppm Mn) in drinking water) and on PND25-PND180 (3 µg/mL or 3 ppm manganese in drinking water). The actual dose of exposure (in mg/kg bw to the dams) was not provided, and exposure to the pups during lactation is unknown. Locomotor activity (measured at 30-day intervals) was increased at PND60 and PND90 only, and not on PND 30, 120, 150 or 180 (Chandra et al., 1979a). The effect of manganese on motion at higher doses was observed in a three generation study in mice: abnormal motion was reported in the gait of 2 neonates of the 3rd generation litter exposed to 25 mg Mn/kg bw per day (Ishizuka et al., 1991). Similarly, increased spontaneous motor activity was observed in neonatal rats exposed orally (*per os*) to an aqueous solution of manganese chloride at the highest dose tested (50 mg $MnCl_2$/kg bw per day) for 50 days (PND1 to PND49) (Brenneman et al., 1999). Effects were not reported at the 25 mg $MnCl_2$/kg bw per day dose level.

Alterations in open field activity (assessment of behaviour and locomotion) were reported in male mice exposed during the juvenile period only or during both the juvenile (PND20 to PND34) and adult periods (PNW12 to PNW20) to 10 or 30 mg Mn/kg bw per day as manganese chloride in saline for 2 weeks via gavage. It was found that developing mice were more sensitive to the effects of Mn, and that early exposure increased susceptibility to manganese exposure when the treated animas were adults. No effects were observed in female mice (Moreno et al., 2009b). A NOAEL of 250 µg Mn/day was reported following administration in a 10% sucrose solution by micropipette (LOAEL: 750 µg Mn/day) for neurobehavioral effects (negative geotaxis task and traveled scores of rats challenged with cocaine) Rats were exposed for 21 days (PND1 to PND21; Reichel et al., 2006).

Manganese exposure is associated with various sensory effects in young animals. Effect on orientation was assessed by the air righting reflex in rats after *in utero* and lactational exposure (from GD10 to PND21, via maternal dietary exposure to 32, 160, or 800 ppm $MnCl_2 \cdot 4H_2O$. Male offspring exposed to a maternal dose $\geq$ 160 ppm and female offspring exposed to 800 ppm exhibited significant decrease in air righting indices (Ohishi et al., 2012).

Decreased olfactory discrimination was reported in rats exposed orally to 500 µg Mn per day as $MnCl_2$ in a 10% sucrose solution from PND1 to PND20, and trends toward decreased memory and learning ability were observed, as evidenced by burrowing detour and passive avoidance tests (Tran et al., 2002a; Tran et al., 2002b). In neonatal rats orally exposed (PND1 to PND21) to 25 or 50 mg $MnCl_2$/kg bw per day given as $MnCl_2.4H_2O$ via micropipette for 21 days, an increased pulse-elicited acoustic startle response amplitude was observed (Dorman et al., 2000) (it is presumed that the actual dose reported by the authors refers to Mn).

The neurobehavioral effects resulting from an excess of manganese in soy formula were assessed in infant rhesus monkeys fed a commercial cow's milk-based formula (Cow; 50 µg Mn/L), a commercial soy protein-based formula (Soy; 300 µg Mn/L) or a soy formula with added manganese (Soy+Mn; 1 000 µg Mn/L) for 4 months following birth (Golub et al., 2005). Corresponding doses reported by the authors were 0.018, 0.106, and 0.323 mg Mn/kg bw per day,

respectively (as noted in an *erratum;* Golub, 2012). An extensive behavioral test battery (motor, cognitive and social domains, as well as specific tests related to the dopamine system)[3] was administered over an 18-month period (approximately equivalent to 6 years of age in children). It is important to note that besides differing in manganese content, the cow's milk-based and soy-based formulas differ in several nutritional dimensions related to protein, carbohydrate and fat composition, and other components that could contribute to differences in behavioral responses reported (Golub et al., 2005). Thus, the Cow group does not represent an appropriate control to assess the effect of manganese in the Soy and Soy+Mn groups for quantitative risk assessment purposes. The effect of manganese would be best assessed by comparing the Soy+Mn group to the Soy group, however statistical analysis to compare these two groups was not provided. Nevertheless, changes in activity/sleep patterns and in social interactions (less play behavior and more affiliative clinging in social dyadic interactions) were reported in monkeys of the Soy and Soy+Mn groups when compared to the Cow group. The Soy and Soy+Mn groups also exhibited shorter wake cycles and shorter period of daytime inactivity than the Cow group, with no apparent differences between the Soy and the Soy+Mn groups (statistical analysis not available). All three groups did not differ significantly in dopamine and serotonin metabolite concentrations (HVA and 5HIAA) in the cerebrospinal fluid (CSF), stereotypy and continous performance tests. This study may indicate a sensitivity of social behavior and DA systems to early dietary manganese exposure, however it should be noted that nutritional differences between Cow and Soy formula could contribute to differences in behavioral responses. Overall, results indicated no group differences in the more highly structured testing situations[4] used to assess specific cognitive functions including learning, memory and attention. However, poor engagement of the infants with the formal tests of cognitive function was seen at the ages tested, and additional testing at more mature ages may provide further insight (Golub et al., 2005, *erratum* Golub, 2012).

The effect of postnatal exposure to manganese on both nonassociative and associative behaviours was also investigated in neonatal rats given oral supplements of manganese (750 µg/day) on PND1-21 in a study by (McDougall et al., 2008) (see also the Neurochemical Endpoint Section for results on the presynaptic dopamine function). The effects of postnatal manganese exposure on nigrostriatal functioning were evaluated by assessing rotorod performance and amphetamine-induced stereotypy in adulthood. Manganese had no impact on the rotorod performance however manganese-exposed rats exhibited substantially more amphetamine-induced stereotypy than vehicle controls. In terms of associative processes, manganese exposure did not alter performance on any aspect of the cocaine-induced conditioned place preference (CPP) task (preference, extinction, or reinstatement testing), nor did manganese affect progressive ratio responding (sucrose-reinforced operant responding, a measure of motivation). However, acquisition of a fixed ratio task was impaired, suggesting a deficit in procedural learning.

Other behavioural effects reported in neonate rats were observed at higher oral exposures (estimated at 8.8 mg Mn/kg bw per day (from 500 µg/d) and above), and include decreased

[3] Including: motor development, dyadic social interaction, automated activity monitoring, iron absorption studies, CSF sampling (for CSF catecholamine analysis), WGTA tests (object discrimination learning, object discrimination reversal, delayed nonmatch to sample training, delayed nonmatch to sample test, position learning and reversal, post-session temperament score, reward delay) and CANTAB tests (fixed interval (FI) training, dopamine drug challenge, continuous performance test (CPT), stereotypy observations).

[4] Delayed nonmatch to sample (DNST), object discrimination, position discrimination and reversal and continuous performance test.

olfactory discrimination (Tran et al., 2002a). In addition, impaired neurobehavioral endpoints reflecting increased anxiety and alterations of other emotional behavior, decreased learning and memory ability, increased signs of hypo/hyperactivity and altered motor activity (Kristensson et al., 1986; Pappas et al., 1997; Brenneman et al., 1999; Liu et al., 2006; McDougall et al., 2008; Kern et al., 2010; Kern and Smith, 2011; Molina et al., 2011; Nowak et al., 2011;Peneder et al., 2011; Betharia and Maher, 2012; Ohishi et al., 2012; Beaudin et al., 2013) were reported at levels ≥25 mg/kg bw per day.

A detailed investigation of the neurodevelopmental effects of manganese exposure in rats was provided by Kern et al., 2010, who exposed neonatal Sprague-Dawley rats to oral doses of 25 or 50 mg Mn/kg bw per day in sucrose solution via micropipette for 21 days following birth. The study conducted a battery of neurological tests (open arena, elevated plus maze, and 8-arm radial maze) on the rats (n=15-20 males/treatment) to assess the effects of oral exposure to manganese during a period that corresponds to the development of dopaminergic pathways in regions of the brain that are important in the regulation of executive function behaviours (involving attention, learning, and memory). In addition to the behavioural tests, levels of dopamine receptor and transporter proteins were measured in the brain (described in the 'neurochemical endpoints' of this section). Though a NOAEL could not be identified, a LOAEL of 25 mg Mn/kg bw per day can be established for this study, based on increased stereotypic behavior on a greater number of session days during the 8-arm radial maze test (shift in goal-oriented behavior, indicating impaired spatial memory) and a reduced level of D1-like receptors in the dorsal striatum. At the higher tested dose (50 mg Mn/kg bw per day), the authors also observed altered locomotor activity and behaviour disinhibition in the open area test on post-natal day (PND) 23, altered learning and increased number of errors in the radial maze on PND23, and impaired learning/memory (delay/failure to reach the learning criterion and increased number of learning errors in the 8-arm radial test) over PND33-46. Manganese exposure (up to 50 mg Mn/kg bw per day) had no apparent impact on fear and anxiety (as measured by elevated plus maze performance) (Kern et al., 2010).

In a subsequent study aimed to document whether early exposure to manganese results in neurobehavioral and neurochemical effects lasting into adulthood, rats exposed orally to the same doses of manganese as in the previous study, also for 21 days post-natally without further exposure, were examined later in life. It was reported that neonatal exposure to manganese lead to altered dopamine receptor levels and astrogliosis (as measured by Glial Fibrillary Acidic Protein (GFAP)) in adulthood. Although behavioural disinhibition or altered locomotor activity was not observed in adults, an evaluation of behavioral performance (as measured by activity in the center zone of the open arena) in the absence (PND97) and presence (PND98) of a d-amphetamine challenge revealed that exposed animals exhibited an enhanced locomotor response to the d-amphetamine challenge (Kern and Smith, 2011). Collectively, these results suggest that early exposure to manganese can result in lasting effects on the dopaminergic system.

The same neonatal model and dosing regimen was used by Beaudin et al. (2013) to further explore the chronic effects of manganese exposure on sensori-motor development. The study compared the effects of early life and lifelong exposure to manganese on fine sensorimotor function in male Long-Evans rats. The staircase test was used to objectively measure effects that are relevant to motor outcomes studied in pediatric research. The authors exposed the animals (n=11/group) orally to 25 mg Mn/kg bw per day or 50 mg Mn/kg bw per day for either a short post-natal period of 21 days or a life-long period (through adulthood). Testing conducted in adulthood showed a deficit in performance (staircase test, taking and eating pellets) at the 25 mg Mn/kg bw per day dose level, and performance was worse in rats exposed to this dose daily over a

lifetime than those only exposed for a brief period of 21 days postnatally. These findings support findings in epidemiological work reporting a deficit in fine sensorimotor function in children following exposure to manganese (Beaudin et al., 2013; Zoni and Lucchini, 2013).

10.2.1.2 Neurobehavioural endpoints reported in adults

Neurobehavioral alterations following oral exposure to manganese in adulthood were reported in a number of studies. Rats exposed to manganese via drinking water (1 mg $MnCl_2$•$4H_2O$/mL) exhibited signs of hyperactivity and hypoactivity such as increased/reduced spontaneous motor activity, altered response to D-amphetamine test, shorter distance traveled, and decreased open field activity (Nachtman et al., 1986).

In mature female albino rats treated by gavage with manganese chloride (0.357 and 0.714 mg Mn/kg bw per day, in distilled water) for 15 or 30 days, increases in manganese and cholesterol levels in the brain (hippocampus, cerebellum and cortex) were accompanied by learning impairment (after one training period on day 29, treated rats needed 3.7 times more time to reach the exit of a T-maze compcared to controls). The delay in exposed rats was completely corrected by co-administration of mevinolin (an inhibitor of cholesterol biosynthesis) with manganese or by withdrawal of manganese (Öner and Sentürk, 1995; Sentürk and Öner, 1996).

The acquisition of conditioned and unconditioned avoidance reactions and the dynamics of learning and memory impairments were studied in adult rats exposed to manganese before or after training for a multipath maze. Rats were exposed to manganese chloride at doses of 20 or 50 mg $MnCl_2$.$4H_2O$/kg in food for 30 days. Testing was performed immediatelyafter training or 90 days after training. Animals exposed at the higher dose level showed increased aggressivity, frequently fell from the platform in the maze, and were unable to perform the maze tests. Irreversible impariment of the learning process was reported following exposure to manganese, however manganese did not significantly alter the animals' ability to reproduce a previously aquired behaviour (completion of passage through the maze) (Shukakidze et al., 2003).

Young male adult Wistar rats (16/dose) were exposed to manganese chloride by gavage (14.84 or 59.36 mg $MnCl_2$•$4H_2O$/kg bw per day, 5 days/week, in distilled water) for 10 weeks, followed by a 12 week recovery period. Statistically significant decreased short- and long-term spatial memory performance in the eight-arm radial maze test and in the spontaneous locomotor activity in the open field activity test were observed at both doses. At post-treatment week 7, locomotor activity returned to normal. Decreased number of acoustic startle responses and their associated prepulse inhibition were also observed as well as increased latency of sensory evoked potentials and decreased of their duration for both doses following 10 weeks of treatment which persisted in the high dose group only into recovery period. Increased glial fibrillary acidic protein immunoreative (GFAP-IR) density was observed at both doses in the dentate gyrus of the hippocampus but not in the stratum radiatum or the stratum oriens (Vezer *et al.* 2005). In an earlier study that examined the effect of manganese on locomotor activity, rats chronically exposed to manganese via drinking water (1 mg $MnCl_2$•$4H_2O$/mL) exhibited signs of hyperactivity and hypoactivity such as increased(from weeks 5-7) /reduced (week 8-on) spontaneous motor activity, altered response to D-amphetamine test (increased response from 14-29 weeks that was gone at weeks 41 and 65), shorter distance traveled, and decreased open field activity (Nachtman et al., 1986).

Impaired spatial learning was reported in pregnant Sprague-Dawley rats during the Morris water maze test following a 43 week exposure to an iron-defficient diet (3 mg Fe/kg) that was supplemented with 100 mg Mn/kgcompared to pregnant rats fed control diets (35 mg Fe/kg, 10 mg Mn/kg) (Fitsanakis et al., 2009). In this study, exposure to manganese via diet revealed that

iron-deficient status (which occurs more commonly during pregnancy) can increase the effect of manganese on the cognitive system (Fitsanakis et al., 2009).

In male adult rats exposed to 0.1 or 5.0 mg Mn/mL as manganese chloride in drinking water for 8 months, spontaneous motor activity (measured in 60 minute-long weekly session) was increased at both doses during the first month (Bonilla, 1984a). Further exposure for up to six months did not affect this endpoint , but a significant reduction in motor activity compared to controls was observed at 7 and 8 months). Fine sensory motor development in rats exposed from birth for 21 days, and over a lifetime was studied using the staircase test (Beaudin et al., 2013). It was found that exposure to 50 mg Mn/kg bw per day by gavage in in early life alone resulted in altered fine motor control in adults. Further, life-long exposed adults displayed additional widespread impairment in reaching and grasping/retrieval performance (Beaudin et al., 2013).

Signs of muscular weakness and rigidity of the lower limbs were reported in four adult male rhesus monkeys (*Macaca mulatta*) given 25 mg $MnCl_2 \cdot 4H_2O$/kg bw per day orally, corresponding to 6.94 mg Mn/kg bw per day[5]) for 18 months (Gupta et al., 1980).

Impaired neurobehavioral endpoints were reported in pups, juvenile and/or adult rats and mice exposed to oral doses of manganese (estimated to range from 43.7 to 910 mg Mn/kg bw per day, as manganese chloride), for various period of time (ranging from 14 days to 21 weeks) via gavage, diet or drinking water (Gray and Laskey, 1980; Ali et al., 1983; Chandra, 1983; Kristensson et al., 1986; Pappas et al., 1997; Calabresi et al., 2001; Torrente et al., 2005b; Liu et al., 2006; Vezer et al. 2007; Avila et al., 2008; Molina et al., 2011; Nowak et al., 2011; Betharia and Maher, 2012; Fordahl et al., 2012; Shi et al., 2012; Takacs et al., 2012; Krishna et al., 2014). The impaired endpoints observed by researchers included delayed air righting reflex, ataxia, increased learning, memory and locomotor deficits (poorer results in the Morris water maze test, the step-down test), and observation of hypoactivity or hyperactivity, anxiety, negative mood, aggressivity and impulsivity (in the open-field test, the novel object test, the forced swim test, the elevated plus maze test)).

10.2.1.3Structural evaluation of neuronal tissues

Several studies have documented the deleterious effects of manganese exposure on the ultrastructure of brain tissues, such as neuronal degeneration, gliosis (astrogliosis)[6] or neuroinflammation, in both juvenile and adult rodents.

Alteration of brain tissue was observed at very low dose in juvenile male rats (PND21) exposed to $MnCl_2 \cdot 4H_2O$ in water daily (one dose tested, reported as: 50 µg $MnCl_2 \cdot 4H_2O$ per rat per day) via gavage for various durations (15, 30, 45 or 60 days, i.e. up to PND80; 6 rats/group). Although only one administered dose was reported, considerable change can be expected in the actual dose on a mg/kg basis given the changing body weights of the growing young animals throughout the course of the study. The observed alterations include neuronal degeneration in the cerebral cortex of the frontal region and in the cerebellar cortex after 30, 45 and 60 days (no effect at 15 days), neuronal degeneration and neuroglial proliferation in the caudate nucleus after 60 days of exposure, and presence of astrocyte alterations reported to be similar to Alzheimer type-II cells (morphological change) in the area of neuronal degeneration (cerebral cortex) (Chandra and Shukla, 1978).

[5] Calculated dose assumes that the 25 mg/kg values reported are for $MnCl_24H_2O$, and not ionic Mn.

[6] Gliosis is an overgrowth of the glial cells (mainly the astrocytes) in a damaged area of the brain or spinal cord. It is a process of scarring in the CNS resulting from the proliferation of glial cells in an injured or diseased section of the brain, causing the formation of a fibrous glial scar.

Marked neuronal degeneration (gliosis, neuronal loss and depigmentation in the region of the substantia nigra) was observed in four adult male rhesus monkeys (*Macaca mulatta*) given 25 mg $MnCl_2•4H_2O$/kg bw per day orally (details on administration not specified), corresponding to 6.94 mg Mn/kg bw per day[7] for 18 months, when compared to four control monkeys (Gupta et al., 1980). Other brain regions were not examined.

In male and female rat pups exposed to manganese chloride *in utero* and through lactation (dams received daily water solution of manganese chloride in the first portion of their feed, leading to estimated doses of 10 or 20 mg $MnCl_2•4H_2O$/kg bw per day) for approximately 70 days (15-20 days before pregnancy, during pregnancy, and for one month after parturition with the first portion of food. A marked and dose-dependent gliosis was observed in the offspring at both doses in the caudate nucleus, dorsal and ventral septal nuclei, nucleus accumbens and cerebral cortex (Lazrishvili et al., 2009).

In two studies that exposed young adult rats to daily manganese (20 or 50 mg $MnCl_2H_2O$/kg) for 30 days via gavage, changes in the ultrastructure of neurons, interneuron contacts and glial cells were observed in the caudate nucleus, the substantia nigra and the fronto-parietal cortex area. These changes worsened by three months (i.e. after cessation of exposure), resulting in cellular degeneration. Both studies also reported destruction of most of the neurons or astrocytes mitochondria (Bikashvili et al., 2001; Shukakidze et al., 2002). The daily doses tested were 50 mg $MnCl_2•4H_2O$/kg (Bikashvili et al., 2001) and 20 or 50 mg $MnCl_2•4H_2O$ $MnCl_2$/kg bw per day (Shukakidze et al., 2002).

The differential effects of exposure of mice to manganese chloride in saline by gavage (10 or 30 mg Mn/kg bw per day was examined during three life-periods: juvenile (PND20-PND34), adult (PNW12-PNW20) and both juvenile and adult (Moreno et al., 2009a). At ≥ 10 mg Mn/kg bw per day, manganese increased the nitric oxide synthase 2 (NOS2) [8]expression in microglia and caused a slight activation of astrocytes (not statistically significant) in juvenile mice, and an increase in astrogliosis was seen [in] adult mice. The same alterations were observed in mice exposed for both periods, although the magnitude of changes observed was greater, and NOS2 expression was also increased in astrocytes (Moreno et al., 2009a).

Activated astrocytes (as indicated by increased levels of glial fibrillary acidic protein (GFAP) and/or impaired neurogenesis (as demonstrated by increased doublecortin-positive cells and reelin-positive cells, and decreased thyroid-related hormone concentrations) were observed in rats exposed to manganese chloride by micropipette on PND1-PND21 (25 or 50 mg Mn/kg bw per day, in a 25% sucrose solution; Kern et al., 2011) or *in utero* and through lactation (maternal diet concentrations: 32, 160, 800 or 1600 ppm of $MnCl_2•4H_2O$) on GD10-PND21 (Ohishi et al., 2012). An increase of GFAP (in the dentate gyrus) was also observed in adult rats following 10 weeks of exposure to manganese via gavage (15 and 59 mg $MnCl_2•4H_2O$/kg bw per day in distilled water) (Vezer et al., 2005; Vezer et al., 2007). Preweaning exposure to manganese resulted in increased expression of GFAP in the prefrontal cortex in rats exposed to 25 or 50 mg Mn/kg bw per day (PND 24), and "progressed" to also include increased astrocyte activation in other brain regions that control executive function: the medial striatum and nucleus accumbens at the 50 mg Mn/kg bw per day level (PND 107). These results indicate an effect of manganese exposure on astrogliosis that persisted and/or progressed to other brain regions in adult animals after blood manganese levels had returned to normal (Kern and Smith, 2011).

[7] Calculated dose assumes that the values reported are for $MnCl_24H_2O$, and not ionic Mn.

[8] NOS is a nitrosative stress marker. Enhanced expression of NOS2 is a typical inflammatory response of activated astrocytes.

In adult male mice, increased expression of mRNA GFAP and protein GFAP, heme oxygenase-1 (an oxidative stress marker) and inducible NOS was observed in the substantia nigra following 8 weeks of exposure to 0.4 g Mn/L through drinking water (Krishna et al., 2014).

In utero and lactational exposure (from GD10 to PND21) of mice to manganese through the diet (32, 160 or 800 ppm Mn from manganese chloride) resulted in an increased number of reelin-positive cells on PND21 for animals who received 160 ppm manganese and above. Additional neuronal alterations were also observed at the highest dose. The authors proposed that manganese targets immature granule cells and suppresses differentiation into mature granule cells, leading to apoptosis and neuronal mismigration (Wang et al., 2012).

A multigenerational study conducted in mice treated with 25 mg Mn/kg bw per day (as manganese chloride) in drinking water observed cell toxicity in 2 neonatal mice (3rd generation), which was evidenced by abnormal motion in gait. Losses of stainability in granular cells in the external layer of the cerebral cortex, Purkinje cells in the cerebellar cortex, and increases in stainability of the nerve fibers in the cerebellar medulla were reported (Ishizuka et al., 1991).

10.2.1.4 Neurochemical endpoints

An increase in monoamine oxidase (MAO) activity was observed in young male rats exposed to manganese daily over the early post natal period. The rats were exposed to manganese chloride tetrahydrate in distilled water (50 µg $MnCl_2 \cdot 4H_2O$ daily per rat; one dose tested) via gavage for various durations (15, 30, 45 or 60 days). An increase of monoamine oxidase (MAO) activity was observed in the brain in all treated groups (Chandra and Shukla, 1978). Given that MAO serves to metabolize (inactivate) monoamine neurotransmitters (noradrenaline, dopamine, epinephrine and serotonin), this finding is consistent with the results of other studies which report altered levels of neurotransmitters such as dopamine (DA) or serotonin. Decreased DA levels were reported in the striatum and hypothalamic region of young rats and mice exposed to ≥ 10 mg Mn/kg bw per dayay by gavage from PND1 to PND21 or from PND1 to PND24[9]. (Deskin et al., 1980; Moreno et al., 2009b). A dose-response depletion of striatal DA levels was also reported in young rats exposed to 0, 50, 250, or 500 µg Mn/day by gavage from PND 1-20) (Tran et al., 2002b). This decrease in DA was accompanied by adverse functional effects on motor development and behaviour, as mesured by the righting test (reflex), homing test, and passive avoidance test (Tran et al., 2002b).

Reduced striatal DA levels were reported in male and female mice exposed to 10 and 30 mg Mn/kg bw per day as manganese chloride in saline via gavage over two periods (as juveniles from PND20 to PND34 and as adults from PNW12 to PNW20) (Moreno et al., 2009b). Decreased DA levels were also reported in the brainstem of adult (3 month-old) rats following exposure to 20 mg $MnCl_2$/kg bw per day manganese chloride by gavage for 6.5 days (Desole et al., 1997). Long-term reduction in cocaine-evoked reflux of striatal dopamine as measured by *in vivo* microdialysis on PND90 was also documented following neonatal (PND1-21) exposure in rats (750 µg Mn/day) (McDougall et al., 2008).

At higher doses (approximately 20 mg Mn/kg bw per day and above), alterations of other neurotransmitter levels (e.g. GABA, serotonin, aspartate, Gln, Glu, taurine) or neurotransmitter enzyme (AChE) activity (Deskin et al., 1981; Lipe et al., 1999; Garcia et al., 2006), impaired DA transporter binding sites, D1-like DA receptors (Dorman et al., 2000; Liu et al., 2006; Reichel et

[9] Tested doses reported by the authors: 1, 10, 20 µg Mn/g-bw per day (Deskin et al. 1980); 50, 250 or 500 µg Mn per day per animal (Tran et al. 2002a,b).

al., 2006; McDougall et al., 2008; Kern et al., 2010; Kern and Smith, 2011) and aberrations in neurogenesis (Wang et al., 2012) were reported in the striatum of juvenile mice and rats.

The effects of early exposure to manganese in rats on behaviour and cognition were shown to be associated with significant alterations in D1 and D2 receptor proteins and dopanime transporter (DAT) measured in the dorsal striatum, prefrontal cortex, and nucleus accumbens (Kern et al., 2010). In this study, neonate rats were exposed to 25 and 50 mg Mn/kg bw per day (as $MnCl_2$) via micropipette over PND 1-21. The animals were subjected to a number of tests designed to assess executive function behaviours (n= 15-20 males/treatment) (details of this testing is provided in 'behavioural endpoints' subsection that follows), and immunohistochemistry was performed on a separate cohort of animals to assess D1, D2, and DAT levels in the brain (n=4-7 rats/treatment). Levels of D1 receptors were significantly lower in the dorsal striatum of treated animals (both dose groups), as were DAT levels in the high dose group. No change was measured for D2 levels in the striatum. A decrease in D1 receptors and DAT was also observed in the high dose group of the nucleus accumbens. Although D2 receptor levels did not change measurably in the striatum or nucleus accumbens, a significant increase in the high dose group was observed in the prefrontal cortex. These results suggest that manganese exposure during development alters dopaminergic synaptic environments in brain nuclei (Kern et al., 2010).

Neurochemical changes were also described in a subsequent study investigating whether early exposure to manganese would result in neurobehavioral and neurochemical effects lasting into adulthood (Kern and Smith, 2011). In this study,neonatal rats (PND1-PND21) were exposed to $MnCl_2$ (25 or 50 mg Mn/kg bw per day, in 25% sucrose solution) via micropipette. The rats were evaluated for brain dopamine D1- and D2-like receptors and dopamine transporter (DAT) densities in the prefrontal cortex, striatum, and nucleus accumbens on PND24 (as weanlings) and PND107 (to reflect an adult stage). Results indicated that preweaning manganese exposure led to increased D1 receptor levels in the nucleus accumbens on PND107 at the 25 mg Mn/kg bw per day exposure level (however on PND24, D1 receptor levels were decreased at the highest dose in this tissue and were decreased at both doses in the dorsal striatum). Significantly increased D2 receptor levels (to approximately 800% of controls) were observed in the prefrontal cortex at the highest dose on both PND24 and PND107. Levels of DAT were elevated on PND 24 in the dorsal striatum and nucleus accumbens at the highest dose levels, although no change in the transporter level persisted on PND107. It is interesting to note that the blood and brain manganese concentrations on PND 107 (after preweaning exposure on PND1-21) were not statistically different from control concentrations (despite the observed increase on PND24) (Kern and Smith, 2011), suggesting that early exposure to manganese results in effects on the dopanimergic system that persist even after levels of manganese return to pre-exposure levels. An earlier study by a different group exposed male pup mice to manganese in drinking water (5 mg $MnCl_2$/L) for up to 180 days. A transient increase in the content of DA, NE, HVA, and tyrosine was reported in the corpus striatum (Chandra et al., 1979a). The authors suggested that this transient elevation in striatal DA and NE was related to the hyperactivity observed following 60 and 90 days of treatment (Chandra et al., 1979a).

Decreased levels of DA in the serum, cerebellum, hypothalamus, cortex, hippocampus, mid-brain and/or striatum were reported in adult rats exposed to $\geq$ 22.5 mg Mn/kg bw per day (as manganese chloride or sulfate) via drinking water. Alterations of the levels of neurotransmitters or neurotransmitter metabolites (GABA, serotonin, norepinephrine (NE), DA, Glu, taurine), alterations of neurotransmitter transporters, alteration of enzymatic activities (TH) were also reported in adult rats and mice exposed to estimated doses ranging from 22.5 to 2 943.3 mg Mn/kg-day (as manganese chloride or sulfate) via drinking water or gavage for

durations varying from 7 days to 8 months (Bonilla, 1978; 1980; Chandra, 1983; Eriksson et al., 1987a; Subhash and Padmashree, 1991; Miele et al., 2000; Ranasinghe et al., 2000; Spadoni et al., 2000; Calabresi et al., 2001; Centonze et al., 2001; Montes et al., 2001; Anderson et al., 2007; 2008; 2009; Fordahl et al., 2010; Krishna et al., 2014). Exposure of 4 male rhesus monkeys to manganese chloride tetrahydrate (20 mg/kg bw per day, in distilled water) by gavage for 18 months resulted in an increase of tissue manganese concentrations. A decrease in the levels of DA and NE in the diencephalon, the corpus striatum, the midbrain and the pons was reported; the level of 5-hydroxytryptamine (5-HT) was decreased in the midbrain. In the medulla oblongata, DA and 5-HT levels were decreased, although the brain manganese content was similar to that for controls (Chandra et al., 1979b).

Altered GABA and other neurotransmitter levels were also reported in 30-day old weanlings and 90 day-old adult rats exposed to 10 or 20 mg Mn/kg bw per day (as manganese chloride in water) by gavage for 30 days. At the 20 mg Mn/kg bw per day dose level, juvenile rats exhibited an increase in GABA levels in the caudate nucleus, and increased levels of aspartate, glutamate (Glu), glutamine (Gln), taurine and GABA were reported in the cerebellum of adults; no dose-response was observed in the other brain regions examined (frontal cortex and hippocampus) (Lipe et al., 1999). Similarly, an alteration in levels of GABA and other neurotransmitters (i.e., increased serotonin and GABA levels and decreased acetylcholinesterase (AchE) levels) in the striatum, the hypothalamus or the overall brain were also reported in juvenile rats of both sexes exposed to $\geq$ 20 mg Mn/kg bw per day by gavage (as manganese chloride in a 5% sucrose solution; tested doses: 10, 15 and 20 µg Mn/kg bw per day; (Deskin et al., 1981) or through lactation (pups exposed PND 4-21, where dams were fed with a manganese supplemented diet at 100 ppm Mn) and then through the diet when capable (i.e. PND11) (Garcia et al., 2006).

Decreased levels of 3,4-dihydroxyphenylacetic acid (DOPAC) in the striatum and the hypothalamus, of 5-HIAA in the hippocampus, and of noradrenaline in the pons was documented in male rats exposed to manganese chloride in drinking water for 8 months (effects observed at both concentrations tested (0.1 and 1.0 mg Mn/mL) (Bonilla, 1984b).

Changes in neurotransmitter systems were suggested to vary with the duration of exposure during manganese intoxication. Such changes were observed in studies carried out by a group of researchers who exposed male pup mice to manganese chloride through lactation[10] and then drinking water containing 3 µg Mn/mL (3 mg/L) for up to 180 days (Chandra et al., 1979a) or male rats to drinking water containing 1 mg/mL (1000 mg/L) for up to 360 days (Chandra and Shukla, 1981). Manganese exposure increased the levels of DA, NE, HVA and tyrosine in the corpus striatum (Chandra et al., 1979a; Chandra and Shukla, 1981). It should be noted, however, that this increase was transient (levels declined under the control values after 300 and/or 360 days of treatment) (Chandra and Shukla, 1981). These alterations were not correlated with the level of manganese in the corpus striatum, which gradually increased up to 120 days in mice and up to 240 days in rats, and then remained constant (Chandra et al., 1979a; Chandra and Shukla, 1981). However, the altered levels of neurotransmitters were associated with the increased activity of MAO in the striatum of rats during early periods of manganese exposure (from day 15 to day 120 of treatment). In mice, the authors proposed that the initial elevation of striatal DA and NE levels might be related to the hyperactivity observed after 60 and 90 days of exposure (Chandra et al., 1979a). Similar results (transient elevated levels of DA in the caudate-putamen) were reported in

[10] 5 000 ppm in drinking water to the dam

rats exposed to a higher dose of manganese (2,8 mg/L) as manganese chloride tetrahydrate in drinking water (Eriksson et al., 1987a).

It has been suggested that manganese-induced alterations of rat brain synaptosomal uptake of amines may be age-dependent. In 70-90 day-old rats exposed *in utero* and throughout life to 1 mg $MnCl_2 \cdot 4H_2O$/mL manganese chloride in drinking water (corresponding to doses estimated at 33 or 36.1 mg Mn/kg bw per day for Lai et al. (1982)[11] and Lai et al. (1984)[12], respectively),a transient decrease of DA uptake by synaptosomes isolated from the hypothalamus, the striatum and the midbrain, and a decrease of synaptosomal choline uptake in the hypothalamus was observed. In older rats (aged 90-120 days), the synaptosomal choline uptake was increased in the striatum and the hypothalamus, though no changes were observed in DA uptake (Lai et al., 1982; Lai et al., 1984).

10.2.2 Reproductive toxicity

10.2.2.1Adult male reproductive system

Manganese was found to alter testicular functions and to induce testicular damages after short- and long-term exposures.

In male CD-1 mice exposed for 43 days to manganese acetate (7.5, 15.0 and 30.0 mg/kg bw per day), decreased testicular sperm counts (≥ 7.5 mg /kg bw per day) and decreased sperm motility (≥ 15.0 mg /kg bw per day) were observed; however, the ability of the exposed males to impregnate unexposed females was not impaired (Ponnapakkam et al., 2003a). Increased sperm head abnormalities and percentage of abnormal sperm were also noted in mice administered potassium permanganate (65 – 380 mg /kg bw per day) or manganese sulfate (102.5 - 610 mg/kg bw per day) by gavage for 21 days (Joardar and Sharma, 1990).

Testicular damage was reported in both monkeys and rats. In adult rhesus monkeys exposed orally[13] to manganese chloride at 25 mg $MnCl_2 \cdot 4H_2O$/kg bw per day for 18 months, the authors reported congested and swollen testes accompanied by a marked increase in testis weight, interstitial oedema, and degeneration of seminiferous tubules. Leydig cells did not show any abnormality. Activities of several enzymes (succinic dehydrogenase, glucose-6-phosphate dehydrogenase and acid phosphatase) were significantly inhibited in the seminiferous tubules. The authors of this study concluded that chronic exposure to manganese did not produce severe degenerative changes in the testis earlier than metal-enduced encephalopathy in primates (Murthy et al., 1980).

In Sprague-Dawley rats exposed to manganese acetate for 63 days, mild to moderate segmental degeneration of germinal epithelium within the seminiferous tubules occurred at ≥ 612 mg Mn/kg bw per day (no effect at 306 mg Mn/kg bw per day). These changes appeared to be reversible on cessation of manganese exposure (Ponnapakkam et al., 2003c).

Impaired male fertility was observed in male mice exposed to manganese chloride in drinking water (8 000 mg $MnCl_2$/L, corresponding to doses of 706 mg $MnCl_2$/kg bw per day or 309 mg Mn/kg bw per day if the dose reported by the authors reflects $MnCl_2$ and not elemental

[11] Default value for water intake: 0.062 L/d, provided value for body weight: 0.523 kg. Calculated dose assumes that the values reported are for $MnCl_24H_2O$, and not ionicl Mn.

[12] Default values (males/females mean value) for water intake: 0.049 L/d and for body weight: 0.38 kg. Calculated dose assumes that the values reported are for $MnCl_24H_2O$, and not ionicl Mn.

[13] No more information provided in the secondary reference (Health Canada 2007).

Mn) for 12 weeks before mating with unexposed females (no effect observed at 1 000, 2 000 and 4 000 mg $MnCl_2$/L) (Elbetieha et al., 2001).

10.2.2.2Adult female reproductive system

Several studies have been conducted in rats, mice and rabbits to assess the toxicity of manganese on the female reproductive system. Impaired fertility, increased post-implantation loss and decreased fetal viability were observed in some studies at elevated doses.

Decreased numbers of implantations and viable fetuses were observed in female Swiss mice exposed to manganese chloride tetrahydrate in drinking water (8 000 mg $MnCl_2$/L) for 12 weeks before mating with unexposed males (no effect 1000, 2000 or 4000 mg $MnCl_2$/L) (Elbetieha et al., 2001). Increased post-implantation loss was reported in pregnant rats given drinking water with concentrations 8000 mg Mn/L (Elbetieha et al., 2001). In contrast, no reproductive effect was observed in pregnant rabbits administered similar doses of manganese chloride on GD6-GD20 (Szakmáry et al., 1995).

Manganese did not adversely affect the health of the dams, the litter size or the sex ratios of the pups when pregnant rats were administered manganese chloride in drinking water (2 or 10 mg $MnCl_2$/mL) throughout gestation; more extensive analyses of female reproductive organs were not performed (Pappas et al., 1997). In another study, a decrease of the litter weight was reported in female rats exposed to manganese chloride through drinking water (20 mg $MnCl_2$/mL) (Kontur and Fechter, 1985); at this dose, water intake and body weight gain by the dams were severely reduced.

No effect of manganese on maternal weight gain, implantation number, resorptions, or percentage of dead fetuses was reported in female Sprague-Dawley rats administered varying doses manganese sulfate in the diet (4, 24, 54, 154, 504 and 1 004 mg Mn/kg dry diet) from weaning to mating until GD21 (Jarvinen and Ahlström, 1975).

10.2.3 Developmental toxicity

A number of studies have investigated developmental toxicity resulting from exposure to manganese in rats, mice or rabbits using comparable exposure periods over gestation and the postnatal period. Manganese readily crosses the placental barrier and is secreted in breast milk (Saric, 1986). Neonates are particularly sensitive to manganese exposure during development, as there is evidence that they absorb and accumulate more manganese, and excrete less due to their underdeveloped capacity for biliary excretion (Deskin *et al.*, 1980; Dorman *et al.*, 2000; Keen *et al.*, 1986).

Oral and/or inhalation exposure to manganese during gestation, lactation and through the postnatal period was shown to alter growth and/or survival, alter the reproductive performance and lead to neurotoxic effects in a number of studies. Exposure to manganese during gestation has also been linked to decreased pup body weight gain. This review focuses primarily on the developmental toxicity resulting from oral exposure to manganese. A detailed account of toxicity resulting from inhalation exposures is provided in Health Canada (2010).

10.2.3.1Altered growth and survival

No clearly discernible effect on implantation or on maternal and fetal survival was found in two studies investigating the developmental effects of soluble forms of manganese on rats, mice, hamsters and rabbits exposed to manganese sulfate monohydrate by gavage for 5 to 13 consecutive gestation days (mice and rats GD 6-15, hamsters GD 6-10, rabbits GD 6-18; doses

ranged from 0.783-1.36 (low) to 78.3-136.0 (high) mg/kg bw per day, depending on the species studied (NTIS, 1973).

In mice exposed to manganese chloride through the diet (0, 32, 160 or 800 ppm of Mn) from GD10 to PND21, reduced body weight was observed in male pups at the 160 ppm level (from PND21 to PND70) and at 800 ppm (from PND17 to PND63). In contrast, female pups showed no changes in body weight from PND2 to PND77 (Wang et al., 2012).

10.2.3.2Altered development of the reproductive system

Manganese-induced precocious pubertal development was reported in male and female rats exposed to 10-25 mg/kg $MnCl_2$ manganese by gavage early in postnatal development (Pine et al., 2005; Lee et al., 2006; Hiney et al., 2011).

Failure in reproductive performance as well as in neonatal growth and survival was reported in a study that exposed rats to manganese[14] in the diet (diet with basal manganese levels of 50 mg/kg bw per dayay plus 0, 500 or 1 000 mg/kg bw per dayay manganese, on a dry basis) for up to 7.5 months of treatment. As summarized in Gerber et al. (2002), histological studies revealed a reduction of spermatogenesis, epithelial alteration, atretic (degereated) ovarian follicles, and persistence of the corpus luteum, indicative of ovarian disfunction.

A decrease in male sexual development, as measured by decreased weights of testes, seminal vesicles and preputial organs was seen in mice given 1050 ppm of manganese in the diet as Mn_3O_4 who were on Fe deficient diets (Gray and Laskey, 1980).

10.2.3.3Teratogenicity

Only two studies investigated the teratogenicity of soluble forms of manganese administered orally and neither indicated increased abnormalities in either soft or skeletal tissues (NTIS, 1973; Grant et al., 1997). The first study was conducted in rats, mice, hamsters and rabbits exposed by gavage to manganese sulfate monohydrate for 5 to 13 consecutive gestation days (mice and rats GD 6-15, hamsters GD 6-10, rabbits GD 6-18; doses ranged from 0.783-1.36 (low) to 78.3-136.0 (high) mg/kg bw per day, depending on the species) (NTIS, 1973). The second study exposed rats to manganese chloride by gavage on GD6-GD17 (400 µmol/kg bw per day) (Grant et al., 1997).

10.2.3.4Developmental neurotoxicity

Exposure to manganese during gestation, lactation and/or through the postnatal period can result in several types of neurotoxic effects, including behavioural effects that are supported by observed neurochemical and neurostructural alterations in animals, as discussed in detail in Section 9.2.2. Reported effects include altered cognitive and behavioural functions that are consistent with developmental effects reported in epidemiological studies.

Neonates are particularly sensitive to manganese exposure during postnatal development, and there is substantial evidence that neonates absorb and retain more manganese than adults, leading to greater brain manganese levels and neurotoxicity during this period (Deskin et al., 1980; Kontur and Fechter, 1985; Keen et al., 1986; Kristensson et al., 1986; Brenneman et al., 1999; Dorman et al., 2000; Weber et al., 2002; Tran et al., 2002a). This increased susceptibility is likely due to several factors including elevated absorption of manganese from the gastrointestinal tract, an incompletely formed blood-brain barrier, the absence of biliary manganese excretion until weaning, and a greater propensity for disruption in the activity of various enzymes and

[14] Chemical form not specified

impaired neurotransmitter systems(Kostial et al., 1978; Shukla et al., 1980; Kristensson et al., 1986; Brenneman et al., 1999; Dorman et al., 2000; Moreno et al., 2009b; Health Canada, 2010). This last difference between developing animals and adults was observed in studies that have compared the effects of manganese exposure in neonate and adult animals (Kostial et al., 1978; Shukla et al., 1980; Dorman et al., 2000; Moreno et al., 2009b).

The effect of manganese on motion at higher doses was observed in a three generation study in mice: abnormal motion was reported in the gait of 2 neonates of the 3rd generation litter exposed to 25 mg Mn/kg bw per day (Ishizuka et al., 1991).

10.2.4 Other effects

The effects of dietary exposure (excluding neurotoxicity) to manganese are documented in a study conducted by the NTP (1993) in rats and mice fed manganese sulfate monohydrate in the diet for 14 days, 13 weeks, or 2 years. In the 2-year study, mice were exposed to 1 500 to 15 000 ppm in diet. The doses corresponding to the higher exposure level were not adjusted for body weight and therefore varied with growth (body weight increase) of the animals. The estimated range over the course of the study was from 1171 mg/kg bw per day (week 4) to 505 mg/kg bw per day (week 104) in male rats (1249-561 mg/kg bw per day in female rats). Similarly, doses corresponding to the higher dose level in mice ranged from 2263-1916 mg/kg bw per day in males and 3449-1983 mg/kg bw per day in females. In this study, no significant effect was observed on the respiratory system, the cardiovascular system, the liver, the eyes, the muscles or the bones (pathological lesions) in both species (NTP, 1993). It should be noted that exposure in this study was through diet, and not drinking water. As described in the Kinetics section of this assessment, the bioavailability of manganese exposure through drinking water (assuming fasted state) is expected to be greater than through food.

10.2.4.1Effects on bodyweight

Several studies conducted under a variety of conditions reported reduced body weight following oral exposure of rodents to manganese. In neonatal rats, significantly lower body weight was observed on PND21 following gavage with 250 or 750 µg Mn/day (as manganese chloride in a 10% sucrose solution) from PND1 to PND21 (Reichel et al., 2006). Reduced growth and body weight gain were also observed in neonate rats after oral exposure[15] to manganese chloride at doses of 25 or 50 mg/kg bw per day on PND1-PND49 and on PND21-PND49 (Brenneman et al., 1999; Dorman et al., 2000). In 90 day-old rats exposed to 10 or 20 mg Mn/kg bw per day by gavage (as manganese chloride in distilled water) for 30 days, decreased body weight was observed in both groups (Lipe et al., 1999). Higher doses (≥ 120 mg Mn/kg bw per day) of manganese in diet or drinking water were also shown to induce a decrease in body weight gain in rats and mice (Komura and Sakamoto, 1991; NTP, 1993; Torrente et al., 2005b; Avila et al., 2008).

In the NTP study (1993), mean body weight was decreased in female mice exposed to ≥ 1 500 ppm manganese through diet and in male rats exposed at the 15 000 ppm level. No effects on body weight were observed in male male mice or in female rats (NTP, 1993).

[15] In the Brenneman et al. (1999) study, the authors only indicated "exposed orally". In the Dorman et al. (2000) study, $MnCl_2$-$4H_2O$ dissolved in nanopure water was administered by gavage (adults) or by mouth using a micropipette (pups).

10.2.4.2Respiratory effects

Manganese has been shown to have effects on the respiratory tract following oral exposure (reduced lung weight) and inhalation exposure (nasal and pulmonary inflammation). A detailed assessment of the toxicological effects resulting from inhaled manganese is provided in Health Canada's *Human Health Risk Assessment for Inhaled Manganese* (Health Canada, 2010).

10.2.4.3Gastrointestinal effects

Guinea pigs administered 10 mg/kg manganese chloride by gavage for 30 days had patchy necrosis, in both the stomach and small intestine with decreased cellular adenosine triphosphatase and glucose 6-phosphatase activities (Chandra and Imam, 1973). However, it is possible that the gavage treatment in this study may have partially or completely contributed to the adverse effects seen in the stomach and small intestine of these animals. Hyperplasia of the forestomach associated with ulcers and inflammation (mostly in males) was observed in mice (but not in rats) fed with 15 000 ppm manganese sulfate monohydrate in the diet for 2 years (NTP, 1993).

In male mice exposed to manganese sulfate monohydrate (up to 50 000 ppm) in the diet for 13 weeks, mild hyperplasia and hyperkeratosis of the forestomach were observed in 3/10 animals at the highest tested dose (1950 mg Mn/kg bw per day). In contrast, no gastrointestinal effects were observed in female mice exposed under similar conditions, nor in rats fed up to 25,000 ppm (NTP, 1993).

10.2.4.4Cardiovascular effects

In two studies on weanling male Sprague-Dawley rats, dietary exposure to manganese (45-50 ppm in diet) for 15 weeks reduced the maximal vessel contraction (Kalea et al., 2005). It also led to aortic structural alterations (increase of the level of uronic acid, increased concentrations of total galactosaminoglycans and decreased concentration of hyaluronan and heparan sulfate in aortas) (Kalea et al., 2006).

10.2.4.5Hematological effects

In rats (particularly in males), an increase of total leukocyte and neutrophils counts was observed following dietary exposure to 50 000 ppm manganese sulfate monohydrate for 14 days. Hematological effects were also reported in rats following 13 weeks exposure (increased neutrophils counts from 1 600 ppm in males and from 6 250 ppm[16] in females) and mice (decreased hematocrit and hemoglobin concentrations at 50 000 ppm in males and females, respectively) (NTP, 1993).

No notable difference was observed in the hematology of rats and mice exposed to manganese though diet for 2 years; increased hematocrit, hemoglobin and red blood cell (RBC) count were the only hematological effects observed in 15 000 ppm male mice at the 15-month interim evaluation but their significance is uncertain (NTP, 1993). These results contrast with those obtained in mice fed diets containing 2 g Mn/Kg for 100 days: Red blood cell (RBC) levels were decreased following exposure to manganese acetate and chloride, the white blood cell count was decreased by manganese acetate, chloride and dioxide (Komura and Sakamoto, 1991). A decrease in hematocrit was observed following exposure to manganese carbonate (Komura and Sakamoto, 1991).

[16] Only the dose range are provided in the NTP report (13 weeks exposure).

10.2.4.6Hepatic effects

Exposure of rats to 16 mg $MnCl_2 \cdot 4H_2O$/kg bw per day (in a drinkable 10% sucrose solution) for 30 days induced alterations of several hepatic and serum enzyme levels (in the liver: decreased activities of succinic dehydrogenase and alcohol dehydrogenase and increased activities of monoamine oxidase (MAO), adenosine triphosphatase, arginase, alanine aminotransferase, ribonuclease and glucose-6-phosphatase; in the serum: increased activities of α-amylase and decreased activities of β-amylase) (Shukla et al., 1978). In another study, female rats exposed to higher doses of manganese in drinking water as manganese chloride tetrahydrate (1000, 10 000 or 20 000 mg $MnCl_2$/L) from conception through the age of 60 days, exhibited liver necrosis and ultrastructural alterations (Leung et al., 1982). In the NTP study (1993), reduced relative liver weight was reported in male rats fed manganese sulfate monohydrate at ≥ 12 500 ppm for 14 days. After 13 weeks exposure, decreased liver weights were also reported in male rats at ≥ 35.8 mg Mn/kg bw per day (≥ 1 600 ppm) and in female rats at 650 mg Mn/kg bw per day (25 000 ppm). In mice, only males exhibited a relative and absolute reduction of liver weights at 2 410 mg Mn/kg bw per day (50 000 ppm) (NTP, 1993).

10.4.2.7Renal effects

Male Sprague-Dawley rats orally treated (gavage) with high levels of manganese (306-1838 mg Mn/kg bw per day as manganese acetate) for 63 days developed severe renal disease (glomerulosclerosis/nephritis and urolithiasis [kidney stones]; Ponnapakkam et al., 2003b). Female animals did not show significant differences in tissue effects relative to controls, suggesting that males are more sensitive to this manganese-indced effect. Contrary to these findings, no significant renal histopathological changes were observed in mice and rats fed elevated doses of manganese sulfate (up to 2 410 and 650 mg Mn/kg bw per day, respectively) for 13 weeks (NTP 1993), nor in mice and rats fed manganese sulfate (up to 50 000 ppm in the diet) for 14 days (NTP, 1993). An increase in oxidative stress was not detected in the kidneys of rats exposed via drinking water at up to 25 000 ppm of $MnCl_2$[17] (estimated as 861 mg Mn/kg bw per day) for 30 days (Avila et al., 2008).

A marginal increase in the average severity of nephropathy (vs. control) was noted in male rats fed manganese sulfate monohydrate (15 000 ppm) for 2 years, while no significant renal histopathological changes were observed in female rats nor in mice of both sexes exposed under similar conditions (NTP, 1993).

10.2.4.8Neuroendocrine and endocrine effects

The effect of manganese (manganese chloride) on hormonal status was investigated by a group of researchers that conducted several studies with similar designs. The reported effects include an increase of gonadotropin-releasing hormone (GnRH[18]), luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol or testosterone levels in immature Sprague-Dawley rats exposed to $MnCl_2$ by gavage before puberty: effects were reported in females exposed to 10 mg $MnCl_2$/kg bw per day from PND12 to PND29 and at 25 mg $MnCl_2$/kg bw per day in males exposed from PND15 to PND48 or from PND15 to PND55 (Pine et al., 2005; Lee et al., 2006). At these doses, continued manganese exposure also induced a moderate but significant

[17] Dose calculated as 861 mg Mn/kg bw per day based on the average male/female Wistar rats water intake (0.0285 L/d) provided in U.S. EPA (1988) and on the average body weight (0.2297 kg) provided by the authors. For information, ATSDR (2012) reports a dose of 1 730 mg Mn/kg bw per day.

[18] Also known as LHRH

advancement in the age of vaginal opening in females (1.5 days) and an increase of both daily sperm production and efficiency of spermatogenesis in males (Pine et al., 2005; Lee et al., 2006).

In another study, the same group of researchers investigated the effects of prepubertal manganese exposure by gavage (saline solution; 10 mg $MnCl_2$/kg bw) of females (from PND12 to PND22 or from PND12 to PND29) on specific glial-derived puberty-related genes known to affect neuronal LH-releasing hormone (LHRH) release in the medial basal hypothalamus (MBH) and in the preoptic area/anteroventral periventricular (POA/AVPV) region. The authors noted increased expression of insulin-like growth factor-1 (IGF-1) and cyclooxygenase-2 (COX-2) genes in the MBH at PND22 and PND29, as well as of the LHRH gene in the POA/AVPV region at PND29 (Hiney et al., 2011).

The sensitivity of females to manganese during puberty was evidenced by the results of *in vitro* studies on sectioned basal hypothalami of adult male rats and of immature male and female rats (Pine et al., 2005; Lee et al., 2006; Prestifilippo et al., 2007). Manganese chloride stimulated LHRH release in adult males at a higher concentration (500 µM) than the one required in immature females (50 µM) and males (250 µM), respectively. Thus, the immature females more sensitive to this manganese-induced effect than immature and mature males (Pine et al., 2005; Lee et al., 2006; Prestifilippo et al., 2007).

In a 1993 NTP study, no manganese-related endocrine effects (histopathological lesions) were found in mice and rats fed manganese sulfate monohydrate (up to 25 000 ppm in rats and up to 50 000 ppm in mice) for 13 weeks. In mice fed manganese sulfate monohydrate (15 000 ppm) for 2 years, increased incidences of thyroid follicular hyperplasia and thryoid follicular dilatation were observed in both males and females; no endocrine effects were noted in rats exposed under similar conditions (NTP 1993).

10.2.4.9Carcinogenicity

In 1996, the U.S. EPA indicated that manganese was ''not classifiable as a human carcinogen'' (Group D) because existing studies were considered inadequate to assess its carcinogenicity (U.S. EPA, 2014, US EPA 1996). To date, the International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of manganese.

Clear evidence of carcinogenicity has not been established (Assem et al., 2011). In an NTP study, mice and rats were administered manganese sulfate monohydrate in their diet (0, 1 500, 5 000 or 15 000 ppm) for 2 years (NTP 1993). In rats of both genders (exposure up to 615/715 mg/kg bw per day for males/females), there was no evidence of carcinogenic activity. In mice of both genders (exposure up to 1800/2250 mg/kg bw per day for males/females), there was equivocal evidence of carcinogenicity based on a marginally increased incidence of thyroid gland follicular cell adenoma and a statistically significant increase in the incidence of follicular cell hyperplasia.

10.3 Genotoxicity

The genotoxic potential of manganese is not well understood, and results of genetic toxicity testing seem to depend upon the test system and associated protocol used. The results of *in vitro* studies have shown that at least some chemical forms of manganese (such as manganese sulfate) have a mutagenic/genotoxic potential. However, no overall conclusion can be made about the possible genotoxic hazard to humans from exposure to manganese compounds because results of *in vivo* studies in mammals are inconsistent (European Commission, 2000; Health Canada, 2010; Assem et al., 2011).

10.3.1 In vitro *findings*

10.3.1.1 Mutagenicity and cell transformation

In the Ames *Salmonella* mutagenicity assay carried out with and without metabolic activation, manganese sulfate was not mutagenic to *S. typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537 (Mortelmans et al., 1986) but it was mutagenic to strain TA97 in another study (Pagano and Zeiger, 1992). Manganese chloride was not found to be mutagenic to *S. typhimurium* strains TA98, TA100 and TA1535, but it was mutagenic to strain TA1537 (Wong, 1988; de Méo et al., 1991). Both manganese sulfate and chloride were positive when tested with strain TA102 without metabolic activation (de Méo et al., 1991). The lack of mutagenicity of manganese in some of the Ames assays may be due to the lack of bioavailability of the metal ion because components of the culture media have been shown to inhibit the mutagenic activity of metal ions by chelating them or because of competition for active transport sites (NTP, 1993).

Manganese chloride tested positive without metabolic activation in the mouse lymphoma assay (80, 60, and 40 µg/mL) (Oberly et al., 1982) and in the Comet assay (single cell gel assay) performed in cultured human lymphocytes (mutagenic potency of 2.4 revertant/nmole $MnCl_2$) (de Méo et al., 1991). It also induced cell transformations in Syrian hamster embryo cells (0.13mM $MnCl_2$) (Casto et al., 1979).

Manganese sulfate was slightly mutagenic and convertigenic when tested for the induction of gene conversion and reverse mutation in the strain D7 of *Saccharomyces cerevisiae* (Singh, 1984). In contrast it was negative for gene conversion in two other studies in yeast (Baranowska et al., 1977; Parry, 1977).

10.3.1.2 Sister chromatid exchange and chromosomal aberrations

Manganese sulfate (12 500 ppm) induced sister chromatid exchange (SCE) without metabolic activation in mouse fibroblasts (Andersen, 1983), Chinese hamster ovary (CHO) cells (Galloway et al., 1987) and human lymphocytes (Andersen, 1983) and with metabolic activation in CHO cells (NTP (1993)). Manganese sulfate also induced chromosomal aberrations without metabolic activation in CHO cells (Galloway et al., 1987; NTP 1993).

In contrast, potassium permanganate did not cause chromosomal aberrations in a primary culture of cells from Syrian hamster embryos when tested without metabolic activation (Tsuda and Kato, 1977).

10.3.2 In vivo *findings*

10.3.2.1 Mutagenicity

Manganese sulfate did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (Valencia et al., 1985; NTP, 1993). Manganese chloride did not produce somatic mutations in *D. melanogaster* (Rasmuson, 1985).

No heritable translocations (in mice) nor dominant lethal mutations (in rats) were detected following administration of manganese sulfate in the diet for 7 weeks in mice or by gavage once a day for 1 to 5 days in rats (Newell et al., 1974 as cited in NTP 1993).

10.3.2.2 Chromosomal aberration

Swiss albino mice orally exposed to manganese sulfate (ranging from 33 to 132 mg Mn/kg bw per day) for three weeks presented an increase of sperm head abnormalities and of the frequency of chromosomal aberrations and micronuclei in bone marrow cells (Joardar and

Sharma, 1990). In a similar study, swiss albino mice orally exposed to 22.6, 45.2 and 132.1 mg Mn/kg bw per day (as potassium permanganate) for three weeks exhibited an increase of sperm head abnormalities and in frequency of chromosomal aberrations in bone marrow cells (Joardar and Sharma, 1990).

No significant chromosomal damage occurred in either bone marrow or spermatogonial cells of male rats orally exposed to 0.014 mg Mn/kg bw per day (as manganese chloride) for 180 days (Dikshith and Chandra, 1978).

10.3.3 Epigenetics

Growing evidence suggests that exposure to toxicants such as metals early in life may influence gene expression later in life, possibly through epigenetics (Wright and Baccarelli, 2007). The change in gene expression without changes to DNA sequence has been suggested to ultimately alter the protein products of these genes. There is currently a knowledge gap surrounding whether elevated manganese exposure causes epigenetic modifications to DNA that may lead to altered gene expression, resulting in reported health effects. Exposure to manganese during development is reported to produce lasting changes in the expression of several dopamine system proteins, including D2, DAT, and catecholamine methyl transferase. These proteins are epigenetically regulated through CpG island methylation by the DNA methyltransferase protein DNMT (Kern et al. 2010, 2011; Shumay et al, 2010; Day et al., 2013). Manganese is a pro-oxidant at elevated exposure levels, and oxidative stress has been shown to inhibit DMNT or result in decreased DNMT protein levels (Han et al., 2011). In addition, altered DA system function has been linked to the behavioral and cognitive deficits produced by developmental manganese exposure (Kern et al., 2010, 2011; Beaudin et al., 2013, 2015; Reichel et al., 2006; McDougall et al., 2008).

11.0 Mode of action

The central nervous system is a critical target for manganese toxicity in humans, non-human primates and rodents. As discussed in sections 9 and 10 of this document, toxicological studies have shown that oral (and/or inhalation) exposure to manganese results in a variety of deleterious effects on behavior (e.g., impaired learning and memory), on motor function (e.g. altered reflex, altered activity), and on the ultrastructure of brain tissues.

Various mechanisms have been proposed to explain manganese neurotoxicity, although data suggest it involves a number of interrelated processes such as mitochondrial dysfunction (Gavin et al., 1992; Zheng et al., 1998), free radical formation (Desole et al., 1994; 1995; Hussain et al., 1997; Taylor et al., 2006) and neurotransmitter impairment (Chandra et al., 1979a; Deskin et al., 1980; Chandra and Shukla, 1981; Lai et al., 1982; 1984; Subhash and Padmashree, 1991; Komura and Sakamoto, 1994; Ranasinghe et al., 2000; Calabresi et al., 2001; Montes et al., 2001; Tran et al., 2002a; 2002b; Fitsanakis et al., 2006; McDougall et al., 2008; Peneder et al., 2011) that generate radicals, disrupt oxidative phosphorylation and ATP synthesis, and lead to cellular dysfunction, apoptosis/necrosis and cell death. Manganese exposure has also been reported to result in the disruption of Fe regulation, which may contribute to the mechanism of manganese neurotoxicity (Kwik-Uribe et al., 2003; Kwik-Uribe and Smith, 2006; Reaney et al., 2006; Crooks et al., 2007).

Elevated manganese levels can disrupt the regulation and interaction of neurotransmitters (DA, Glu and GABA) in the basal ganglia (Chandra et al., 1979a; Deskin et al.,1980; Chandra and Shukla, 1981; Lai et al., 1982; 1984; Subhash and Padmashree, 1991;Komura and Sakamoto,

1994; Ranasinghe et al., 2000; Calabresi et al., 2001; Montes et al., 2001; Tran et al., 2002a; 2002b; Fitsanakis et al., 2006; McDougall et al., 2008; Burton and Guilarte, 2009; Peneder et al., 2011).

DA plays a role in the regulation of cognition, behaviour, locomotor activity, and neuroendocrine secretion (Fitsanakis et al., 2006; Farina et al., 2013; Guilarte, 2013), while dopaminergic pathways are involved in the regulation of behaviours concerned with executive function (e.g. memory, learning, attention) (Kern et al., 2010). Approximately 80% of extracellular DA is recycled into presynaptic neurons through reuptake by dopamine transporters (Na^+/Cl^- dependent DAT and NET) that are principally located in the caudate, putamen and nucleus accumbens. DAT activity is critical for DA homeostasis in the brain as it contributes to DA cellular efflux (Roth et al., 2013) and helps regulate the duration and the dimension of dopaminergic signaling in the brain.

Reported neurological deficits in animal studies, including rodents and non-human primates, were accompanied by altered DAT and DA receptor levels, and altered response to DA antagonists. Since DAT levels increase throughout development, reaching maximal levels in adulthood (Roth et al., 2013), it has been suggested that the cognitive and neurobehavioural effects seen in children following exposure to manganese may be related to effects on the dopaminergic system during development (Neal and Guilarte, 2013).

Glutamate (Glu) is the most abundant excitatory neurotransmitter in the brain and may play a role in various CNS functions such as cognition, learning and memory, as well as in CNS development (Fitsanakis et al., 2006). Elevated levels of manganese in astrocytes appears to mediate neurotoxicity primarily through oxidative stress and mitochondrial dysfunction, but also appears to impair the Gln-Glu metabolic coupling cycle between astrocytes and neurons (i.e. the Gln/Glu-GABA cycle), which plays a critical role in normal brain function (Erikson and Aschner, 2003; Aschner et al., 2009; Sidoryk-Wegrzynowicz et al., 2009; Farina et al., 2013; Karki et al., 2013; Sidoryk-Wegrzynowicz and Aschner, 2013a; Sidoryk-Wegrzynowicz and Aschner, 2013b). The Gln/Glu-GABA cycle is crucial for optimal CNS function because it gives rise to the amino acid neurotransmitter Glu (excitatory) and GABA (inhibitory) via dynamic astrocyte-neuron interactions (Sidoryk-Wegrzynowicz and Aschner, 2013b). Disruption of this cycle leads to changes in Glu-ergic and/or GABA-ergic transmissions and Gln metabolism (Zwingmann et al., 2003; Sidoryk-Wegrzynowicz et al., 2009; Sidoryk-Wegrzynowicz and Aschner, 2013a; Sidoryk-Wegrzynowicz and Aschner, 2013b). Furthermore, disturbed astrocytic function and metabolism may prevent the astrocytes from providing substrates used by the neurons for the neurotransmitter metabolism, leading to impaired neuronal glucose oxidation, deterioration of neuronal energy metabolism and disturbance of the neurotransmission process (Zwingmann et al., 2003; Sidoryk-Wegrzynowicz and Aschner, 2013b).

Manganese exposure may increase the frequency and amplitude of spontaneous excitatory postsynaptic potentials in the striatum, resulting from hyperactivity of corticostriatal neurons (Centonze et al., 2001; Fitsanakis et al., 2006) and/or may promote excitotoxicity through over-activation of postsynaptic Glu receptors (Fitsanakis et al., 2006). Hyperactivity of the Glu receptor *N*-methyl-D-aspartate may lead to an increase in energy consumption due to an influx of Na+ and Ca2+ ions that must be actively pumped out of the cell. Energy-compromised cells may allow passive release of Glu, resulting in an increased extracellular Glu concentration and consequently an abnormal excitation of striatal neurons (excitotoxicity) (Erikson and Aschner, 2003; Fitsanakis and Aschner, 2005; Fitsanakis et al., 2006).

Conflicting data have been reported for GABA with some groups of researchers seeing manganese-induced increases in striatal GABA levels whereas other groups report no effects or a

decrease in GABA levels in the striatum and frontal cortex (Fitsanakis et al., 2006; Racette et al., 2012; Martinez-Finley et al., 2013; Michalke and Fernsebner, 2014). These contradictory conclusions could result from methodological differences (e.g., route and duration of exposure, age at time of exposure) and/or to the contribution and alteration of other neurotransmitter systems (Martinez-Finley et al., 2013).

12.0 Classification and assessment

Although manganese is an essential element, deficiency of manganese is very rare given that nutritional requirements are easily met through food consumption. Concern surrounding manganese-induced toxicity pertains primarily to excess exposures, particularly in infants, who lack homeostatic controls to maintain stable tissue levels of manganese. (Costa and Aschner, 2014).

Existing studies in humans and experimental animals were considered inadequate to suggest carcinogenicity as a key endpoint of concern in the risk assessment of manganese. The U.S. EPA (1999) considers that there is "inadequate information to assess human carcinogenic potential" for manganese. Manganese has not been classified by the International Agency for Research on Cancer. Consequently, a non-cancer endpoint was selected for the risk assessment of manganese in drinking water.

The central nervous system appears to be the primary target of manganese toxicity in mammals, followed by reproductive systems. Manganese has been shown to be readily taken up into the central nervous system following oral exposure, although increased levels can also occur in other tissues including the lungs, kidneys, and testes (Aschner et al., 2005; Bock et al., 2008).

Several epidemiological studies suggest an association between exposure to manganese in drinking water and neurological effects in children (Bouchard et al., 2011; Khan et al., 2011; Roels et al., 2012; Oulhote et al., 2014). These effects include intellectual impairment and poorer neurobehavioural function (memory, attention, motor function, hyperactivity) between the lowest and highest quintiles of observed exposure to manganese in drinking water, where median levels ranged from 1 to 216 µg/L (Bouchard et al., 2011; Oulhote et al., 2014).

Limitations in these studies, including potential confounding factors, inadequate exposure estimates, risk of bias, absence of a determination of the temporality of effects, in addition to the absence of a clear point of departure needed for dose-response analysis, prevent their use in a quantitative risk assessment. However, the results of these studies can be used to qualitatively support the choice of the key endpoint used for quantitative assessment in animals, as similar endpoints that reflect executive function behaviours have been studied in rodents (e.g. behavioural hyperactivity (measured using the open arena assessment) and learning deficits (measured using the 8-arm radial maze; Kern et al., 2010). Further, it has been suggested that the cognitive and neurobehavioural effects seen in children following exposure to manganese may be related to effects on the dopaminergic system during development (Neal and Guilarte, 2013), and mechanistic data appears to suggest common elements between rodents and non-human primates with respect to involvement of the dopaminergic system in manganese-induced neurotoxicity (Neal and Guilarte, 2013). Use of a rat model for extrapolation of developmental neurotoxicity to humans is recommended as the species of choice by the OECD (2007).

A number of animal studies have identified LOAELs following oral exposure to manganese. Although there has been concern in the published literature over the human relevance of some of the endpoints studied, and many of the studies only examine effects following a short duration without long-term follow-up. However, three animal studies in particular collectively

stand out as closely assessing and quantifying neurological effects consistent with those reported in the epidemiology studies, with consideration of observed effects measured over a long term (Kern et al., 2010; 2011; Beaudin et al., 2013).

The Kern and Beaudin studies were chosen as a basis for the current risk assessment because of their thoroughness in assessing neurodevelopmental endpoints (observed neurobehavioural effects are supported with corresponding neurochemical findings) in early life that are consistent with the findings reported in epidemiological studies (Bouchard et al., 2011; Khan et al., 2011; Roehls et al., 2012; Oulhote et al., 2014). These studies identified a LOAEL of 25 mg Mn/kg bw per day for various neurological endpoints in rats. In addition to demonstrating that exposure to manganese in early life can result in behavioural and sensori-motor effects, these studies provided mechanistic support by demonstrating corresponding neurostructural and neurochemical changes. Further, Kern et al. (2011) and Beaudin et al. (2013) demonstrated the ability of manganese exposure in early life to result in effects that persist into adulthood, after levels of manganese in the brain have returned to normal.

Despite their above-mentioned strengths, it should be noted that the key studies chosen do not reflect the lowest LOAELs for neurological effects following oral exposure to manganese reported in the literature, and that benchmark dose analysis was not possible given that only two doses were tested. Other studies indicated neurotoxicity resulting from oral exposure to manganese in rats, mice, and non-human primates at levels ranging from 0.106 mg/kg bw per day in non-human primates (Golub et al., 2005) to 6.5 mg/kg bw per day in young adult rats (Vezer et al., 2005, 2007), however these studies were not considered strong candidates for development of a risk assessment on their own (Chandra and Shukla, 1978; Chandra et al., 1979a,1979b; Deskin et al., 1980; Gupta et al., 1980; Oner and Senturk, 1995, 1996; Shukakidze et al. 2002, 2003; Tran et al., 2002b; Larishvili et al., 2009; Moreno et al., 2009a, 2009b). Various study limitations include the lack of a clear account of animal dosing, lack of information concerning long-term effects, and confounding factors that hindered the interpretation of study results. Nonetheless, these studies support the choice of neurotoxicity as the key endpoint of concern for this risk assessment.

It is important to be mindful that a number of factors may influence the extent of toxicity specific to drinking water exposure in infants, including increased bioavailability of manganese when ingested in a fasted state, differing chemical form and valence states in drinking water, and the higher absorption and increased retention of manganese in infants compared to adults (Dorothy Klimis-Zacas, 1993; Costa et al., 2014; Aschner and Aschner, 2005; Keen et al., 1986). It should also be noted that the current risk assessment considered studies that were most appropriate in the context of establishing a guideline for manganese in drinking water. Differences in bioavailability of manganese between food and water have been acknowledged in the literature and in previous risk assessments (Ruoff et al., 1995; IRIS, 2002; U.S. EPA, 2004; Bouchard et al., 2011), and quantitative data concerning the differences in bioavailability of manganese between exposure sources in infants is not available. Levels of manganese in children's hair (a biomarker of manganese exposure) have been found to correlate with exposure to manganese from drinking water, though not with exposure to manganese in food (Bouchard et al., 2011). Taking the differences in bioavailability between different routes and sources of exposure into account, in addition to the limited ability of the susceptible population to maintain manganese homeostasis, caution was exercised in selecting studies with the most appropriate route and source of exposure to manganese for derivation of a health-based value for drinking water.

Given the challenges with using the existing human epidemiological studies for quantitative risk assessment, animal studies that were representative of effects reported in humans were used to quantify risk in this assessment. The Kern et al. (2010, 2011) and Beaudin et al. (2013) studies were conducted in neonatal rats to reflect developmental risk in infants (the most sensitive subpopulation). Infants (and neonates) are particularly sensitive to the effects of manganese because of their increased capacity for absorption and reduced ability for biliary excretion. Evidence also suggests that exposure to manganese in early life, during a critical period of development of the dopaminergic system, may result in lasting neurotoxic effects in adults.

Using the most appropriate LOAEL as described above, the tolerable daily intake (TDI) for manganese is calculated as follows:

$$\text{TDI} = \frac{25 \text{ mg/kg bw per day}}{1000}$$

$$= 0.025 \text{ mg/kg bw per day}$$

where:

- TDI is the tolerable daily intake; the dose of manganese from drinking water that is not expected to pose a risk to human health. It should be noted that significant differences exist between the bioavailability of manganese from various routes and sources of exposure (including food, air, and water);
- 25 mg/kg bw per day is the LOAEL from the Kern et al.. (2010, 2011) and Beaudin et al. (2013) studies, based on neurological effects occurring from postnatal exposure to manganese in rats; and
- 1000 is the uncertainty factor, selected to account for interspecies variation (×10), intraspecies variation (×10), and the use of a LOAEL rather than a NOAEL (×10)

Using this TDI, the proposed HBV for total manganese in drinking water is calculated as follows:

$$\text{HBV} = \frac{0.025 \text{ mg/kg bw per day} \times 7 \text{ kg} \times 0.5}{0.75 \text{ L per day}}$$

$$= 0.117 \text{ mg/L}$$

$$\approx 0.1 \text{ mg/L (100 µg/L) (rounded)}$$

where:

- 0.025 mg/kg bw per day is the TDI derived above;
- 7 kg is the average body weight of an infant (0-6 months) (Health Canada, 1999);
- 0.5 is the allocation factor estimated for drinking water. Given that formula represents the total diet in non-breast fed infants for the first few months of life, potentially increased levels of manganese in both the water used to prepare formula as well as powdered formula itself are considered the main sources of exposure. Due to the high variability of manganese in drinking water and formula, the source allocation from drinking water is assumed to be half of the total potential exposure, with the balance from the formula itself. Contributions from other sources are not expected to be significant for this age group; and

- 0.75 L per day is the estimated daily volume of tap water consumed by a bottle-fed infant in the 0-6 months age group (Health Canada, 1999).

12.1 International considerations

Other agencies have established limits for manganese in drinking water. Generally, two different values are established: one for aesthetic or operational limits, and one based on human health.

The Minnesota Department of Health developed a tiered guidance document based on the same endpoint and key study (Kern et al., 2010) used by Health Canada to derive its proposed HBV. A level of 0.1 mg/L was established for infants less than 1 year old, and 0.3 mg/L for children >1 year old and adults (MDH, 2012). Health Canada's approach differs from that of the MDH in that an additional uncertainty factor is applied to account for database deficiencies with respect to adequate dose-response information.

The U.S. EPA established a secondary maximum contaminant level for manganese in drinking water of 0.05 mg/L, based on aesthetic considerations. In addition, a non-regulatory health advisory of 0.3 mg/L was published, which was based on absence of effects in dietary intake studies (U.S. EPA, 2004).

The World Health Organization established a health based value of 0.4 mg/L, based on an absence of effect in a composite of dietary studies (WHO, 2011). WHO determined that it was not considered necessary to establish a formal guideline given that this health-based value is well above concentrations normally found in drinking water.

The Australian Drinking Water Guidelines report a health-based guideline of 0.5 mg/L, which was derived from an amount of manganese exposure that was considered safe from all sources by the WHO, and an aesthetic guideline of 0.1 mg/L for manganese in drinking water based on plant experience with respect to consumer acceptance (NHMRC, 2011).

13.0 Rationale

Manganese occurs naturally in the environment under several oxidation states. It is widely distributed in air, water and soil, and may be present in water from natural sources, such as rock and soil weathering, or as a result of human activities. Manganese is generally more prevalent in ground waters than in surface waters.

Manganese is an essential element for humans. Deficiency is considered unlikely in Canada, as adequate amounts are obtained from food. Existing studies are inadequate to determine whether manganese could be carcinogenic, and it has not been classified with respect to carcinogenicity by IARC or by the U.S. EPA. Manganese is more readily bioavailable from drinking water than from food. Levels of manganese in children's hair correlate with exposure to manganese from drinking water, but not with exposure to manganese in food.

The central nervous system appears to be the primary target of manganese toxicity in both animals and humans. Several epidemiological studies suggest an association between exposure to manganese in drinking water and neurological effects in children, such as intellectual impairment and poorer neurobehavioural function. Although the limitations of these studies prevent their use to establish a proposed MAC, they can be used to qualitatively support the choice of the key end-point in animal studies. The reported neurological effects observed in children are consistent with the neurological effects reported in the key animal studies used as a basis for the calculation of the health-based value.

Infants are the most sensitive subpopulation to the health effects of manganese, having higher absorption and retention of manganese than adults. Although established for the most sensitive subpopulation, the HBV is also protective for chronic exposure in children and adults. In addition, exposure to manganese in drinking water at levels at or below the proposed HBV is not expected to result other types of toxicity that have associated with exposure to manganese. A health-based value of 0.1 mg/L has been calculated for manganese in drinking water.

A MAC of 0.1 mg/L (100 µg/L) and an AO of 0.02 mg/L (20 µg/L) are proposed for total manganese in drinking water. The proposed MAC is established at a level to be protective of neurological effects in infants, the most sensitive population, and the proposed AO will reduce consumer complaints regarding discoloured water and staining of laundry. The proposed MAC and AO for manganese can be measured by available analytical methods and are achievable by municipal and residential treatment technologies. As part of its ongoing guideline review process, Health Canada will continue to monitor new research and recommend any change to the guideline that is deemed necessary.

14.0 References

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Appendix A: List of Acronyms

AI	adequate intake
ANSI	American National Standards Institute
AO	aesthetic objective
ATP	adenosine triphosphate
BBB	blood-brain barrier
CAS	Chemical Abstracts Service
CI	confidence interval
CNS	central nervous system
CSF	cerebral spinal fluid
DBP	disinfectant by-product
DO	dissolved oxygen
DOC	dissolved organic carbon
EPA	Environmental Protection Agency (U.S.)
GAC	granular activated carbon
GCI	McCarthy general cognitive index
HAAs	haloacetic acids
HBV	health-based value
ICP-AES	inductively coupled plasma–atomic emission spectroscopy
ICP-MS	inductively coupled plasma–mass spectrometry
IQ	intelligence quotient
LOAEL	lowest-observed-adverse-effect level
MAC	maximum acceptable concentration
MDL	method detection limit
MnB	manganese concentration in blood
MnH	manganese concentration in hair
MnUmbi	manganese concentration in umbilical serum
MnW	manganese concentration in water
MOB	manganese oxidizing bacteria
MRL	minimum reporting level
MIREC	Maternal-Infant Research on Environmental Chemicals
NOAEL	no-observed-adverse-effect level
NBNA	neonatal behavioural neurological assessments
NOM	natural organic matter
NSF	NSF International
ORP	oxidation/reduction potential
PBPK	physiologically based pharmacokinetic
POE	point-of-entry
POU	point-of-use
PQL	practical quantitation level
PVC	polyvinyl chloride
RO	reverse osmosis
SCC	Standards Council of Canada
SD	standard deviation
SM	Standard Method
TDI	tolerable daily intake

TDS	total diet study
Tf	transferrin
THMs	trihalomethanes
UCMR3	third Unregulated Contaminant Monitoring Rule
UL	tolerable upper intake level
WHO	World Health Organization

Appendix B: Provincial/territorial cost estimates

Prince Edward Island

Newfoundland and Labrador

Nova Scotia

New Brunswick

Quebec

Ontario

Manitoba

Saskatchewan

Alberta

British Columbia

Yukon

Northwest Territories

Nunavut

4- Parameters - Chemical

4-B Lead

Reference/Action:

- Verbal update on the standards and US legislation and Canadian impacts related to lead
- For information only

Notes:

4- Parameters - Chemical

4-C PFOS, PFOA and chemical specific adjustment factors

Reference/Action:

- Oral presentation on the draft guideline technical documents for PFOS and PFOA in drinking water
- Attached: Draft guideline technical documents for PFOS and PFOA in drinking water
- Status: The documents on PFOS and PFOA have gone through internal and external peer-review processes. The comments from these reviews were integrated, and the documents are presented at the meeting for approval by CDW for a 2 month public consultation period.
- For CDW discussion/approval

Notes:

4- Parameters - Chemical

4-D Chromium

Reference/Action:

- Oral presentation on the revised chromium guideline technical document
- To be sent prior to meeting: Revised Guideline Technical Document on chromium and table of comments and responses from public consultation
- Status: The draft document on chromium has gone through a public consultation on the website. The comments from the consultation have been integrated, where relevant, and the document is presented at the meeting for final approval by CDW.
- For CDW discussion/approval

Notes:

4- Parameters - Chemical

4-E Benzo[a]pyrene

Reference/Action:

- Oral presentation on the revised B[a]P guideline technical document
- The Revised Guideline Technical Document on Benzo[a]pyrene was sent 7 weeks prior to CDW meeting, along with the table of comments and responses from public consultation
- Status: The draft document on B[a]P has gone through a public consultation on the website. The comments from the consultation have been integrated, where relevant, and the document is presented at the meeting for final approval by CDW.
- For CDW discussion/approval

Notes:

4- Parameters - Chemical

4-F Uranium

Reference/Action:

- Verbal update on the draft guideline technical document on uranium
- Status: The document on uranium is being drafted and will go through internal and external peer-review processes. Once the comments from these reviews are integrated, the document is expected to be presented to CDW at the May 2016 meeting.
- For information only

Notes:

4- Parameters - Chemical

4-G Strontium – problem formulation

Reference/Action:

- Oral presentation on the problem formulation for strontium
- Status: Strontium is currently number 3 on the priority list. Work on the technical document for strontium was recently initiated. A problem formulation is presented in order to get CDW's input very early in the process.
- CDW to discuss

Notes:

4- Parameters - Chemical

4-H Copper

Reference/Action:

- Verbal update on the draft guideline technical document on copper
- Status: The document on uranium is being drafted and will go through internal and external peer-review processes. Once the comments from these reviews are integrated, the document is expected to be presented to CDW at the May 2016 meeting.
- For information only

Notes:

4- Parameters - Chemical

4-I Total organic carbon

Reference/Action:

- Oral presentation on the total organic carbon (TOC) document
- Status: The document on TOC is being drafted and will go through internal and external peer-review processes. Once the comments from these reviews are integrated, the document is expected to be presented to CDW at the May 2016 meeting.
- For information only

Notes:

4- Parameters - Chemical

4-J Microcystins

Reference/Action:

- Verbal update on the draft microcystins guideline technical document
- Status: The draft guideline technical document for microcystins in drinking water was approved in principle by CDW members at the May 2015 meeting to undergo a 2 month public consultation period. The appendix B of the document: "*Considerations for implementing the guideline for total microcystins in treated drinking water supplies*" was circulated and approved by CDW members by email during the month of July 2015. The guideline technical document on microcystins is being prepared to be posted for public comment.
- For information only

Notes:

4- Parameters - Chemical

4-K Other chemical/radiological

Reference/Action:

- Verbal update on other work in the area of chemical and radiological parameters
- Other parameters in development or to discuss include bromate, chloramines, barium, etc.
- For information only

Notes:

5- Secretariat projects

5-A PHAC project on the burden of acute gastrointestinal illness attributable to drinking water

Reference/Action:

- Oral presentation on publication of articles for the PHAC project on the burden of acute gastrointestinal illness due to drinking water in Canada
- For information only

Notes:

5- Secretariat projects

5-B Antimicrobial resistance

Reference/Action:

- Oral presentation on the results of a literature review and report on the presence of antimicrobial resistant bacteria in water, the impacts of water treatment practices on these microorganisms and the implications for human health risk in drinking water
- For information only

Notes:

5- Secretariat projects

5-C Certification and standards

Reference/Action:

- Oral presentation on certification and standards
- For information only

Notes:

5- Secretariat projects

5-D National drinking water conference

Reference/Action:

- Oral presentation on the 2016 National Drinking Water Conference
- Status: S.McFadyen is working closely with an organizing committee to prepare the 17th National Conference on Drinking Water. A meeting location has been reserved (Delta Ottawa, October 16 - 18, 2016); the CDW meeting will take place immediately following the conference. CDW will be updated on the proposed conference format and registration costs. Announcements will be made publically in early November, including a web site hosted by Dalhousie University Center for Water Resource Studies. A CDW member is needed to act as co-host during the event.
- CDW to discuss and nominate a co-chair

Notes:

5- Secretariat projects

5-E Update on CNPHI tools

Reference/Action:

- Oral presentation to provide an update on CNPHI tools and initiatives
- For information only

Notes:

5- Secretariat projects

5-F Hydraulic fracturing

Reference/Action:

- Verbal update on initiatives related to hydraulic fracturing (mainly short updates from CDW members, if any)
- For information only

Notes:

5- Secretariat projects

5-G Criteria for a sampling list of pharmaceutical compounds for the next National Drinking Water Survey

Reference/Action:

- Oral presentation by Anca-Maria Tugulea (EHSRB) on "*Proposed criteria for creating a sampling list for pharmaceutical compounds for the next National Drinking Water Survey*"
- For information only

Notes:

5- Secretariat projects

5-H Disinfection by-product research highlights from the DBP Gordon Research Conference

Reference/Action:

- Oral presentation by Anca-Maria Tugulea (EHSRB) on "*Disinfection by-product research highlights from the DBP Gordon Conference*"
- For information only

Notes:

5- Secretariat projects

5-I Safe Drinking Water for First Nations Act

Reference/Action:

- Oral presentation from Tracy Lavallée (AANDC) and Jamie Lafontaine (Health Canada - FNIHB) on the Safe Drinking Water for First Nations Act
- For information and discussion

Notes:

6- Committee Liaison Reports

6-A CRCP / CACP report

Reference/Action:

- Verbal update on activities and an update on the National Plumbing Code as it relates to standards
- Status: France Lemieux will provide an update with respect to various standards and the activities of the Canadian Regulatory committee for plumbing (CRCP) and the Canadian Advisory Committee on Plumbing (CACP) Report.
- For information only

Notes:

6- Committee Liaison Reports

6-B Certification body reports

Reference/Action:

- Oral presentation on certification activities
- Status: France Lemieux will provide an update with respect to activities within the area of drinking water material standards. Accredited Certification Body organizations will be attending the meeting and reporting on their certification activities and possible issues. Organizations may be handing out material for CDW information.
- For information only

Notes:

6- Committee Liaison Reports

6-C FNIHB report

Reference/Action:

- Kristina Taracha will provide an oral update on activities related to drinking water from First Nations and Inuit Health Branch
- For information only

Notes:

6- Committee Liaison Reports

6-D WHO report

Reference/Action:

- Verbal update on WHO-related activities
- For information only

Notes:

6- Committee Liaison Reports

6-E CHE report

Reference/Action:

- Verbal update on CHE activities by Gary O'Toole (Nova Scotia Environment)
- For information only

Notes:

6- Committee Liaison Reports

6-F CCME report

Reference/Action:

- Verbal update on CCME activities by Environment Canada
- For information only

Notes:

7-A Member's Reports

Reference/Action:

- Verbal update by all CDW members

Notes:

8-A Future meetings

Reference/Action:

- Future meetings

Notes:

Fishwick, David HLTH:EX

From: Anne Vezina <anne.vezina@hc-sc.gc.ca>
Sent: May 5, 2015 12:24 PM
To: POLEGAAR@gov.ns.ca; Caroline.Robert@mddelcc.gouv.qc.ca; Fishwick, David HLTH:EX; donald.reid@gov.ab.ca; Peter_Workman@gov.nt.ca; ghsomers@gov.pe.ca; hkhan@gov.nl.ca; Kevin.Gould@gnb.ca; Kim.Philip@gov.mb.ca; pat.brooks@gov.yk.ca; sam.ferris@wsask.ca; Satish.Deshpande@ene.gov.on.ca; MLeBlanc-Havard@GOV.NU.CA
Cc: WQHB@hc-sc.gc.ca; kristina.taracha@hc-sc.gc.ca; Gary.OToole@gov.ns.ca; philippa.cureton@ec.gc.ca; rocio.aranda-rodriguez@hc-sc.gc.ca; Anca-Maria Tugulea
Subject: Presentations CDW meeting
Attachments: Presentations CDW.pdf

CDW folks and secretariat,

Attached is a file with all presentations for the meeting. Don't worry, we have paper copies for the all members who requested them.
(See attached file: Presentations CDW.pdf)

See you all tomorrow,
Anne

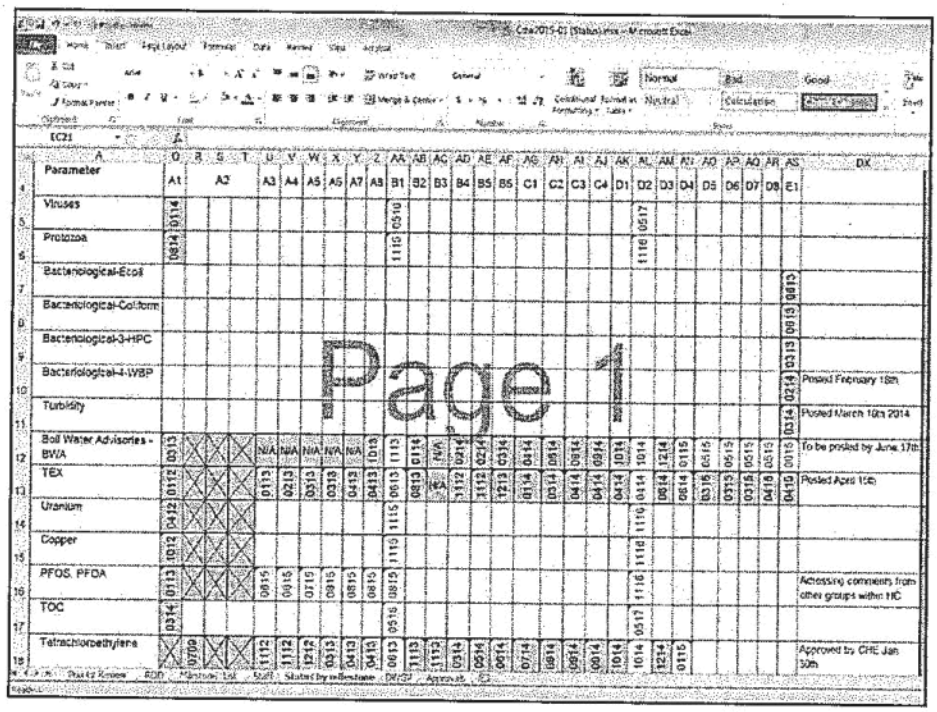
Anne Vézina
Coordinator of the F/P/T Committee on Drinking Water
Coordonatrice du Comité F/P/T sur l'eau potable
Water and Air Quality Bureau
Bureau de la qualité de l'eau et de l'air
Safe Environments Directorate
Direction de la sécurité des milieux
Health Canada
Santé Canada
Ottawa
Tel.: (613) 957-3130
Fax: (613) 952-2574

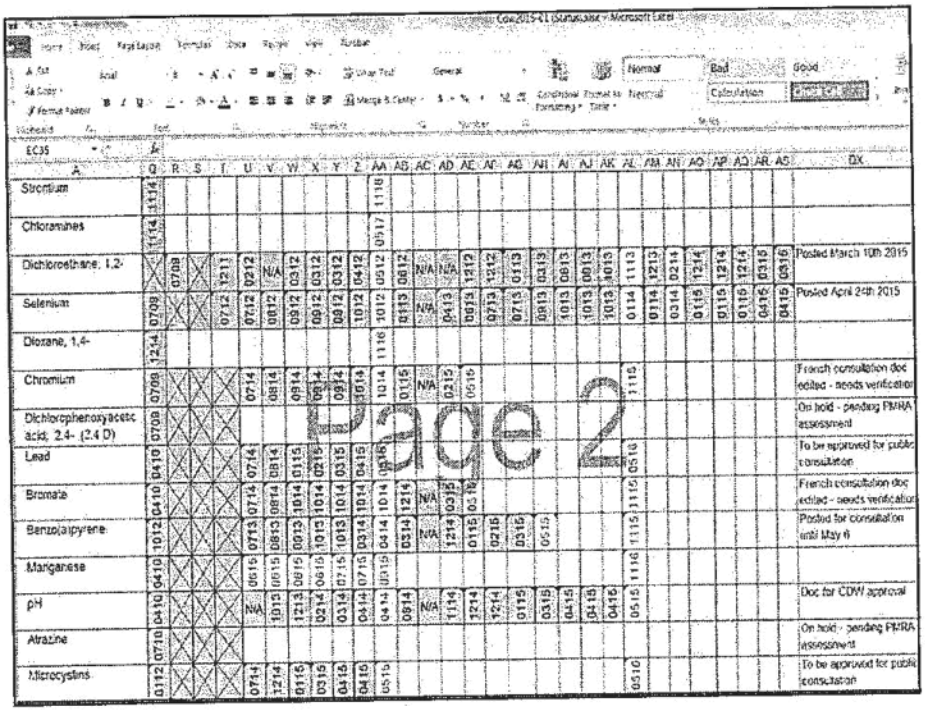
Item 2-C
CDW Status

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario





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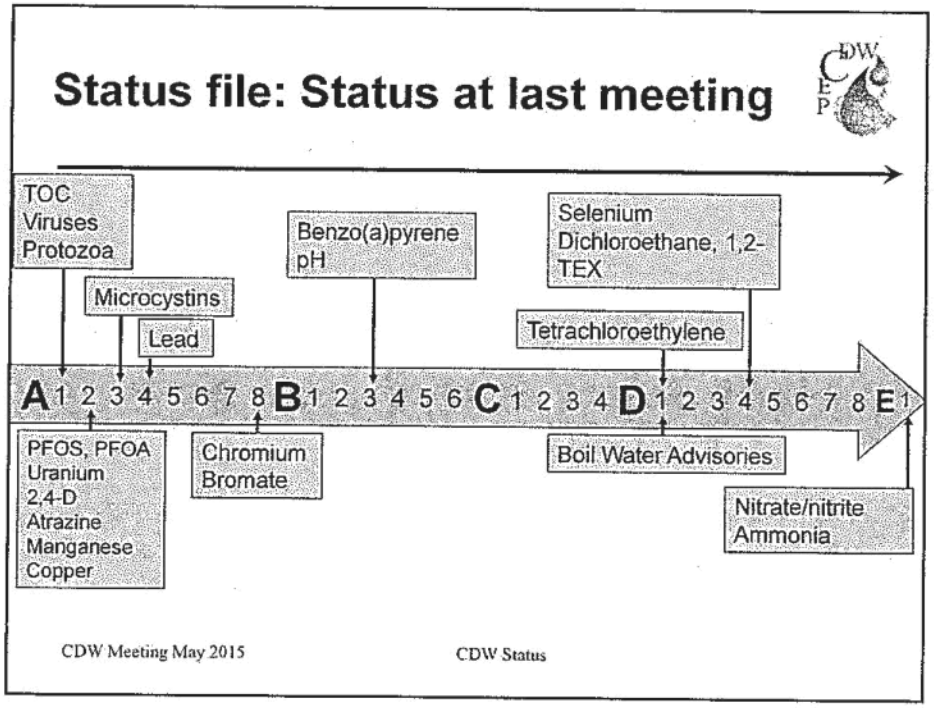
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Protozoa
Microcystins
Lead
Benzo(a)pyrene
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Selenium
Dichloroethane, 1,2-
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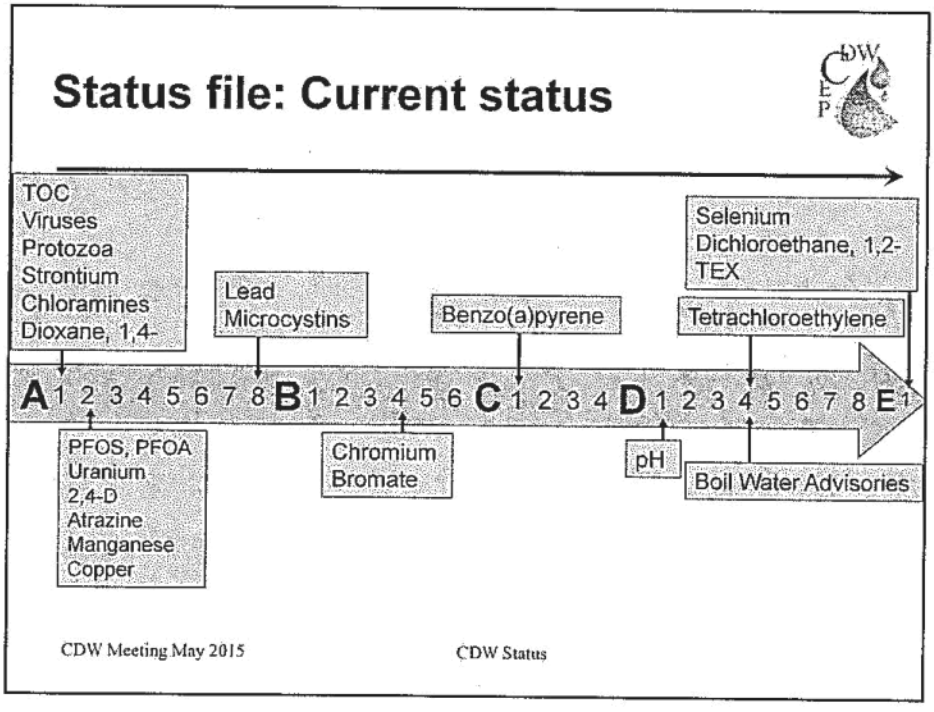
Tetrachloroethylene
A 1 2 3 4 5 6 7 8 B 1 2 3 4 5 6 C 1 2 3 4 D 1 2 3 4 5 6 7 8 E 1
PFOS, PFOA
Uranium
2,4-D
Atrazine
Manganese
Copper
Chromium
Bromate
Boil Water Advisories
Nitrate/nitrite
Ammonia
CDW Meeting May 2015
CDW Status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Protozoa
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Chloramines
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Microcystins
Benzo(a)pyrene
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Dichloroethane, 1,2-
TEX
Tetrachloroethylene
A 1 2 3 4 5 6 7 8 B 1 2 3 4 5 6 C 1 2 3 4 D 1 2 3 4 5 6 7 8 E 1
PFOS, PFOA
Uranium
2,4-D
Atrazine
Manganese
Copper
Chromium
Bromate
pH
Boil Water Advisories
CDW Meeting May 2015
CDW Status

CHE approvals

	BWA		PERC		TEX		Selenium		1,2-DCA		Ammonia		Nitrate/ nitrite		Overarching doc		Vinyl chloride		WBP		Turbidity	
Jurisdiction	H	E	H	E	H	E	H	E	H	E	H	E	H	E	H	E	H	E	H	E	H	E
Alberta		x		x				x	x								x		x			
British Columbia									x										x	x	x	x
Manitoba																						
New Brunswick																					x	x
Newfoundland and Labrador	x	x	x	x		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Northwest Territories	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Nova Scotia	x	x	x	x											x	x	x	x				
Nunavut																						
Ontario								x		x						x		x				
Prince Edward Island	x	x	x	x	x	x	x	x			x	x	x	x	x	x	x	x				
Quebec	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Saskatchewan	x	x	x	x	x	x	x	x	x		x	x		x		x		x	x	x	x	x
Yukon					x	x									x	x	x	x			x	x

CDW Meeting May 2015 CDW Status

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
1	Draft priority list - April 2014								NL		SK		ON		QC		PEI		AB		YK		BC		N
2	Parameter	Priority	Total score	Health	Analytical Treatment	P/Ts total score*	P/Ts Exposure	P/Ts Need	E	N	E	N	E	N	E	N	E	N	E	N	E	N	E	N	E
3	Arsenic	1	2.81	3.00	3.00	2.44	2.44	2.44	2	2	2	2	3	2	2	3	2	2	2	3	3	3	3	3	3
4	Trihalomethanes - total (THMs)	2	2.44	3.00	2.00	2.33	2.33	2.33	3	3	3	3	2	2	3	2	1	1	2	3	1	1	3	3	3
5	Strontium	3	2.17	3.00	2.00	1.50	1.33	1.67	2	2	1	1	1	2	2	2	1	1	1	2	2	2	1	1	1
6	Chloramines (DBP)	4	2.13	3.00	1.50	1.89	1.67	2.11	3	3	2	3	2	3	1	1	1	1	1	3	1	1	3	3	1
7	Dioxane 1,4-	5	2.11	2.00	3.00	1.33	1.22	1.44	1	1	1	1	3	2	1	2	1	1	1	3	1	1	1	1	1
8	Haloacetic acids (HAAs)	6	2.06	3.00	1.00	2.17	2.00	2.33	3	3	2	2	1	2	2	2	1	1	2	3	2	2	2	3	3
9	Barium	7	1.89	3.00	1.00	1.67	1.78	1.56	2	1	1	1	2	1	3	2	3	2	1	3	1	1	1	1	2
10	Aluminum	8	1.85	2.00	2.00	1.56	1.56	1.56	1	2	3	2	2	1	2	2	1	1	1	2	1	1	1	1	2
11	Cadmium	9	1.85	3.00	1.00	1.56	1.56	1.56	1	1	2	1	2	2	2	2	1	1	1	2	2	2	1	1	2
12	Boron	10	1.81	3.00	1.00	1.44	1.33	1.56	1	1	1	2	2	1	1	1	1	1	1	2	1	1	2	3	2
13	Acrylamide	11	1.80	3.00	1.00	1.39	1.22	1.56	1	1	1	1	2	2	2	2	2	1	1	3	1	1	1	1	1
14	Pentachlorophenol	12	1.78	3.00	1.00	1.28	1.11	1.44	1	1	1	1	2	2	1	2	1	1	1	3	1	1	1	1	1
15	Trichloroethylene	13	1.72	2.00	2.00	1.17	1.11	1.22	1	1	1	1	1	1	2	3	1	1	1	1	1	1	1	1	1
16	Zinc	14	1.67	2.00	1.50	1.50	1.56	1.44	1	1	3	1	2	2	1	1	2	1	1	3	1	1	1	1	2
17	Iron	15	1.65	1.00	2.00	1.94	2.56	1.33	2	1	3	2	2	1	3	1	3	1	2	2	2	2	3	1	3
18	Formaldehyde	16	1.57	2.00	1.50	1.22	1.11	1.33	1	1	1	1	1	1	2	2	1	1	1	3	1	1	1	1	1
19	Hydrocarbons, F2, F3, F4	17	1.50	2.00	1.00	1.50	1.33	1.67	1	1	2	1	2	3	2	2	1	1	1	3	1	1	1	1	1
20	Odour (AO)	18	1.46	1.00	2.00	1.39	1.33	1.44	1	1	2	2	2	2	1	1	1	1	2	2	1	1	1	1	1
21	Benzo(a)pyrene	19	1.44	1.00	2.00	1.33	1.11	1.56	1	1	1	1	1	3	1	3	1	1	2	2	1	1	1	1	1
22	Asbestos	20	1.44	2.00	1.00	1.33	1.33	1.33	1	1	2	2	2	1	1	2	1	1	1	1	2	2	1	1	1
23	Nanosilver	21	1.43	2.00	1.00	1.28	1.00	1.56	1	1	1	1	1	3	1	2	1	1	1	3	1	1	1	1	1
24	Taste (AO)	22	1.43	1.00	2.00	1.28	1.22	1.33	1	1	2	2	1	1	1	1	1	1	2	2	1	1	1	1	1
25	Dichlorobenzene 1,4-	23	1.41	2.00	1.00	1.22	1.22	1.22	1	1	1	1	2	2	2	2	1	1	1	1	1	1	1	1	1
26	Tricopyr	24	1.33	2.00	1.00	1.00	1.00	1.00	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Priority list (May 2014)

1) Arsenic
2) Trihalomethanes (THMs)
3) Strontium
4) Chloramines
5) Dioxane, 1,4-
6) Haloacetic acids (HAAs)
7) Barium
8) Aluminum
9) Cadmium
10) Boron
11) Acrylamide
12) Pentachlorophenol
13) Trichloroethylene
14) Zinc
15) Iron
16) Formaldehyde
17) Hydrocarbons, F2, F3, F4
18) Odour (AO)
19) Perchlorate
20) Asbestos

Item 2-D
Pesticides - Priority List Discussion

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Background

- Some pesticide guidelines are >20 years old
  - A number were reaffirmed in 2005 based on a review of new toxicological data and PMRA assessment updates
- As part of the priority review, Secretariat wants to re-examine these older pesticides for possibility of 'withdrawing' some of them
  - No longer registered, or registration due to expire in the next couple of years, for use in Canada
  - No exposure from drinking water expected/seen
- Work with PMRA on advice for new or for pesticides under reevaluation (presentation agenda item 4-D)

Already withdrawn/archived

- Aldicarb (2010)
- Aldrin + dieldrin (2011)
- Bendiocarb (2011)
- Chlordane (1987)
- Cyanazine(2011)
- DDT (1993)
- Dinoseb (2011)
- Endrin (1987)
- Heptochlor + Heptochlor epoxide (1987)
- Lindane (1987)
- Methoxychlor (2011)
- Methyl-parathion (1987)
- Parathion (2011)
- Pentachlorophenol (2014)*
- Pesticides (total)
- Temephos (1993)
- Toxaphene (1987)
- Triallate (1993)**
- 2,4,5-T (1993)
- 2,4,5-TP (1987

* Assessed as an organic chemical
** For further discussion

Pesticides with guidelines

- Atrazine (1993)
- Azinphos-methyl (1989/2005)
- Bromoxynil (1989/2005)
- Carbaryl (1991/2005)
- Carbofuran (1991/2005)
- Chlorpyrifos (1986)
- Diazinon (1986/2005)
- Dicamba (1987/2005)
- Diclofop-methyl (1987/2005)
- Dimethoate (1986/2005)
- Diquat (1986/2005)
- Diuron (1987/2005)
- 2,4-D (1991)
- Glyphosate (1987/2005)
- Malathion (1986/2005)
- MCPA (2010)
- Metolachlor (1986)
- Metribuzin (1986/2005)
- Paraquat (1986/2005)
- Phorate (1986/2005)
- Picloram (1988/2005)
- Simazine (1986
- Terbufos (1987/2005)
- Trifluralin (1989/2005)

Status of pesticides – 1

- Atrazine (1993)
  - Currently under assessment; awaiting PMRA special review
- Azinphos-methyl (1989/2005)
  - Propose withdrawal
  - Last date of use of product – 31/12/2012
- Bromoxynil (1989/2005)
  - No PT exposure data; request made to PMRA for any data (monitoring or modelled) they have
- Carbaryl (1991/2005)
  - No recent assessment from PMRA (last update 2009); request made to PMRA for any data (monitoring or modelled) they have
- Carbofuran (1991/2005)
  - Propose withdrawal
  - Last date of use of product – 31/12/2012

Status of pesticides – 2

- Chlorpyrifos (1986)
  - Many uses discontinued, however, is used as a mosquito larvicide and aerial spraying (vector control);
  - request made to PMRA for any data (monitoring or modelled) they have
- Diazinon (1986/2005)
  - Propose for future withdrawal of guideline; low potential for exposure and limited uses (most uses expire 31/11/2016); request made to PMRA for any data (monitoring or modelled) they have
  - New IARC assessment (March 2013) group 2A (limited evidence of carcinogenicity)
- Dicamba (1987/2005)
  - Suggest updating guideline depending on exposure assessment;
  - request made to PMRA for any data (monitoring or modelled) they have
- Diclofop-methyl (1987/2005)
  - Expiry date of last registered product was 31/12/2014
  - Acceptable for continued registration

Status of pesticides – 3

- Dimethoate (1986/2005)
  - Many uses discontinued (expiry date for last domestic product was 2004)
  - request made to PMRA for any data (monitoring or modelled) they have
- Diquat (1986/2005)
  - request made to PMRA for any data (monitoring or modelled) they have
- Diuron (1987/2005)
  - Use in dugouts and ponds no longer supported and being phased out
  - request made to PMRA for any data (monitoring or modelled) they have
- 2,4-D (1991)
  - Currently under assessment; awaiting PMRA special review
- Glyphosate (1987/2005)
  - New IARC assessment (March 2013) group 2A (limited evidence of carcinogenicity)
  - Suggest updating guideline depending on exposure assessment;
  - request made to PMRA for any data (monitoring or modelled) they have

Status of pesticides – 4

- Malathion (1986/2005)
  - Many uses discontinued (last PMRA update 2012), however, may be used for vector control, hence potential for exposure;
  - request made to PMRA for any data (monitoring or modelled) they have
  - New IARC assessment (March 2013) group 2A (limited evidence of carcinogenicity)
  - Suggest updating guideline depending on exposure assessment
- Metolachlor (1986)
  - No longer registered for use (since 2006)
  - Propose withdrawal of guideline
- Metribuzin (1986/2005)
  - request made to PMRA for any data (monitoring or modelled) they have
- Paraquat (1986/2005)
  - All domestic use products expired in 2005;
  - request made to PMRA for any data (monitoring or modelled) they have

Status of pesticides – 5

- Phorate (1986/2005)
  - Propose eventual withdrawal of guideline as last date for use by end users is 01/08/2015
- Picloram (1988/2005)
  - request made to PMRA for any data (monitoring or modelled) they have
- Simazine (1986)
  - request made to PMRA for any data (monitoring or modelled) they have
- Terbufos (1987/2005)
  - Propose withdrawal of guideline
  - Last date of use of product – 01/08/2012
- Trifluralin (1989/2005)
  - request made to PMRA for any data (monitoring or modelled) they have
- Triallate – Guideline archived in 1993
  - Reason for archiving unknown; may need to revisit based on exposure/uses
  - PMRA confirmed it is still acceptable for continued registration (registration was never suspended
  - request made to PMRA for any data (monitoring or modelled) they have

Next steps

- Review the list
  - Identify pesticides for possible guideline withdrawal or for update where needed
  - Identify pesticides where additional monitoring data is needed to determine if guideline needs updating based on exposure
    - Either provincial/territorial data or PMRA generated data

Item 3-A
Enterococcus

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Background

- Fall 2014 Meeting:

  Decision/Action:

  – Members to advise by December 15, 2014 how having an *enterococcus* guideline would impact their jurisdiction

Background

Part A. Guidance on enterococci in Canadian drinking water supplies

- From this review, *E. coli* currently remains the best available indicator of recent faecal contamination in drinking water systems.
- For decision-making, the focus is the positive detection of *E. coli*.
- Testing for enterococci could be used as a complement to, but not a replacement for *E. coli* monitoring - for assessing general bacteriological water quality throughout the treatment and to provide further information as to its microbial acceptability.

Results from CDW votes

P-T	GTD: yay	GTD: nay
AB	x	
QC	x	
NS	x	
NB	Vote is with HC	Vote is with HC
BC	x	
MB	Depends on cost and if specific recs. were made	
P.E.I.		Guidance doc and supplemental parameter
SK	Neutral – would duplicate cost and test time may affect reporting time	Neutral – would duplicate cost and test time may affect reporting time
ON	Neutral – adopt own regs...impact minimal	Neutral – adopt own regs...impact minimal
Need votes:		
NL		
Yukon		
NWT		
Nunavut		

Summary:
- 4 PTs wanting a GTD
- 3 PTs neutral
- 1 PT wanting a guidance document
- 4 PTs did not respond

Discussion / next steps



- Seeking CDW decision on format for Enterococcus document.
- Document to be Activated (A1) – July, 2015

Item 3-B
Total coliforms

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Background

- Fall 2014 Meeting:

  Decision/Action:

  – Members to advise the technical secretariat by December 15, 2014 on the best option for their jurisdiction for the update of the document on total coliforms:

  1) a guideline technical document with a MAC;
  2) a guideline technical document without a MAC; or
  3) a guidance document.

Current guideline statement

The maximum acceptable concentration (MAC) of total coliforms in water leaving a treatment plant and in non-disinfected groundwater leaving the well is none detectable per 100 mL.

Total coliforms should be monitored in the distribution system because they are used to indicate changes in water quality. Detection of total coliforms from consecutive samples from the same site or from more than 10% of the samples collected in a given sampling period should be investigated

Status

P-T	GTD-MAC	GTD (No MAC)	Guidance Doc.
SK	1		
P.E.I.	1		
NL			1
ON	1		
AB		2	1
QC		1	2
NS	undecided	undecided	undecided
NB	3/Side with maj.	1	2/Side with maj.
BC	1 (MAC or treat.obj.)		
MB	1		
Yukon	Needs more time	Needs more time	Needs more time
NWT		1	
Nunavut		1	
1st place votes	5	4	2
2nd place votes	0	1	2
3rd place votes	1	0	0

Summary:
- 9 PTs prefer a GTD

Current examples

Current Examples:

GTD - MAC

- *E. coli;* Enteric protozoa, Enteric viruses (health-based treatment goals)

GTD - no MAC

- Ammonia (2013) ...not necessary to establish a health-based guideline for ammonia, based on low toxicity at concentrations found in drinking water. Levels can affect water quality in distribution...should be monitored.
- Chlorine (2009)...not considered necessary to establish a guideline for chlorine in drinking water, based on low toxicity at concentrations in drinking water as result of treatment. Any measures ..must not compromise disinfection.

Guidance

- Use of heterotrophic plate counts; Waterborne bacterial pathogens; Controlling corrosion in drinking water distribution systems

Discussion / next steps

- The GTD-MAC vs GTD-no MAC vs Guidance format will have little impact on the overall advice provided by Health Canada, but #2 or #3 would not have a MAC.
- Seeking CDW decision on format for Total Coliforms document.
- Document to be Activated (A1) – September 2015

Item 4-A
Lead

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Status

- Guideline technical document has been peer-reviewed and comments received have been incorporated into the document
- Guideline technical document has been provided to CDW in the Agenda Package
- Seeking CDW approval for public consultation

Refresher

- Current guideline (1992) is 0.010 mg/L (after flushing), based on PQL
- Current intervention level in blood (10 µg/dL) is no longer considered protective of health
- Lead service lines can contribute 50–75% of lead in drinking water
- Lead in drinking water needs to be measured at the tap. Levels can be highly variable and dependent on number of factors
- Lead exposure is associated with many health effects, including cancer; decreased IQ was retained as the critical effect:
  - Strongest evidence for a causal effect
  - Children were affected at the lowest blood lead levels studied

Refresher: HBV calculation

IQ decrements in school-aged children; Pooled longitudinal data from seven studies of 1,333 children (Lanphear et al., 2005)

→ Blood lead concentration BMDL of 1.2 µg/dL associated with 1% change in IQ (EFSA, 2013)

PBPK model →

Oral dose of 0.4 µg/kg-bw/day associated with drinking water ingestion

Linear low-dose extrapolation →

Health-Based Values: 0.08 – 0.008 µg/L associated with 10^{-4} and 10^{-5} risk of decrease in IQ

Analytical methods

- U.S. EPA approved methods for total lead
  - EPA Method 200.5 Rev. 4.2 (ICP AES)
  - EPA Method 200.7 Rev. 4.4 (ICP AES)
  - EPA Method 200.8 Rev. 5.4 (ICP GC/MS)
  - EPA Method 200.9 Rev. 2.2 (GFAAS)
  - Standard Method SM 3113B (GFAAS)
  - ASTM Method D3559-96D/-03D (GFAAS/ ASV)
  - Palintest Method 1001 (ASV; portable; MDL 2 µg/L)
- MDLs range from 0.00002 to 0.010 mg/L (0.02 to 10 µg/L) for laboratory methods
- Current PQL is 0.005 mg/L (5 µg/L)
  - Based on US EPA Second Six Year Review (2009)

Considerations for sampling

- Sampling protocol for average exposure
- Fully flushed protocol not representative of typical exposure
- RDT and 30MS protocols both representative of average exposure
  - 30MS representative and reproducible
  - 30MS also representative of average inter-use stagnation time of water in a residential setting
  - RDT representative but less reproducible

Strategies to reduce lead

- Full lead service line replacement is best approach
- Partial lead service line replacement reduces lead but may cause release of lead for several months
- Corrosion control
  - Maintain non-corrosive water quality to the tap (pH and alkalinity adjustment; corrosion inhibitors)
  - May not be sufficient to reduce lead concentrations when water is supplied through a lead service line
- Use of low lead materials for distribution and plumbing systems (Comply to NSF 372 and NSF 61)

Treatment considerations

- Municipal treatment to reduce lead at source
  - Adsorption, Membrane, Ion exchange
- Certified residential treatment devices for lead removal
  - Adsorption, reverse osmosis, distillation
  - Point-of-use treatment devices can achieve proposed MAC

Peer reviewers – treatment, analytical and sampling

- Dr. Michèle Prévost
  - Professor, École Polytechnique de Montréal
  - Expertise in corrosion, sampling in schools and large buildings, analysis of lead; IEUBK modelling
- Michael Schock
  - US EPA, Chemist, Office of Research and Development;
  - Expertise in corrosion control, sampling and analysis of lead
- Dr. Simoni Triantafyllidou
  - Post Doctoral Fellow, US EPA Office of Research and Development;
  - Expertise in corrosion and sample preparation for analysis of lead

Peer review comments – treatment, analytical & sampling

- Positive feedback
  - Strong support for lower MAC
  - Proposed sampling protocol is justified on basis of typical exposure
- Suggested revisions
  - Suggests including an equivalent to an MCLG of zero
  - Add more information on release of lead from lead service lines relative to other sources
  - Strengthen justification for protocol selection in background info
  - Five minute flush prior to 30MS should maintained (one minute flush increases variability);
- Suggested additional references

Peer review comments (cont'd)

- Specify sampling type locations and number
  - Identify priority sites & locations; homes with LSLs (full or partial) should be prioritized
  - Provide guidance on site selection when homes with LSLSs not possible
- RDT may be a better protocol for large buildings and schools
  - 30MS good for homes with LSLs but may not represent typical exposure or be practical/realistic for large buildings and schools
  - RDT could be used for homes but requires many more samples
- One reviewer recommended hot digestion of sample (rather than 2% nitric)

Proposed MAC

- An HBV range of 0.08 – 0.008 µg/L is derived for non cancer effects
  - Based on reductions of IQ in school aged children
  - Corresponds to risk levels ranging from 10^{-4} - 10^{-5}
- MAC of 0.005 mg/L (5 µg/L) using the appropriate protocol for the type of building being sampled is proposed based on analytical feasibility

International considerations

- US EPA (1991; rev. 2007): MCLG = zero; Treatment technique i.e., Action Level of 15 µg/L (90th percentile; 1 L first-draw; 8 hr stagnation)
  - Major revision of Lead and Copper Rule underway with consideration of different sampling and sample sites; Draft expected in 2015
- WHO (2011): Guideline value of 10 µg/L based on achievability
  - The PTWI established by JECFA is no longer considered health protective and has been withdrawn (JECFA, 2010)
- European Union: 10 µg/L sampled at consumer's tap; Sampling protocol left to individual member countries
  - U.K. uses Random Daytime Sampling

Next steps

- Seeking CDW approval for a 2-month public consultation period

Item 4-B
Manganese

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Status

- For information only
- Risk assessment is under development
  - DWSV prepared as requested, based on new information
- Draft guideline technical document expected for CDW review and approval for public consultations in early fall 2015

Refresher

- Manganese is an essential element that exists in a number of oxidation states, Mn(II) is the most common form that is soluble in water and readily bioavailable. Deficiency is very rare.
- Food is the major source of exposure, although bioavailability from water appears to be greater.
- The most sensitive endpoint in animals is neurotoxicity, which is supported by available epidemiological studies
- Manganese is not classifiable with respect to human carcinogenicity (Group D, US EPA)

Exposure - water

- National Drinking Water Survey, 2009-2010; levels in 65 systems :
  - undetected in 63% samples; 75% under 8-11 µg/L; mean 11-16 µg/L; max 160-440 µg/L
- Data provided by CDW members: wide ranges reported (<detection – > 10 000 µg/L)

P/T	Source	Median concentration (µg/L)
AB	Dissolved and total Mn in raw water, treatment plant effluents and distribution system	0.5-0.60
BC	Total and dissolved Mn	8
NB	Crown lands distribution systems Municipal ground or surface water sources	5 50
NL	Tap water Source water	120 115
ON	Raw water Treated water, Distribution system	6.8 1.2, 1.5
QC	Raw water Treated water	4.3 2.9
SK	Distribution system and treated water	10
YT	Raw drinking water Treated drinking water	20 6

Risk assessment

- Will be based on an animal neurotoxicity study
  - Consistent with endpoints seen in epidemiology studies
- Confirmation of reported dosing has been significantly more involved than anticipated
  - Lack of consistency among authors in what the reported numbers in studies mean, several have been contacted for clarification
  - Needed to verify interpretation of dosing in studies from consultant's report (return to primary literature for most studies)
- Internal peer review of the proposed risk assessment strategy is currently underway

Analytical methods

- Several U.S EPA, APHA, and ASTM methods based on atomic absorption (AA), inductively coupled plasma with mass spectrometry (ICP/MS), or atomic emission spectrometry (ICP-AES):
  - Method detection limits range from 0.002 to 10 µg/L
- Determining different forms (dissolved, colloidal, particulate) is recommended:
  - Requires filtering and may require acid digestion for total Mn

Treatment

- Municipal-scale treatment effective for Mn removal to below 0.05 mg/L:
  - Oxidation/filtration: Oxidize Mn(II) using $KMnO_4$, ClO_2, or O_3 followed by conventional or membrane filtration
  - Adsorption/oxidation: Mn oxides on filter media adsorbs and catalyzes oxidation
  - Biological filtration, dissolved air flotation, and softening
- Research indicates <0.02 mg/L can be achieved by most utilities by optimizing existing treatment
- WRF recommends treated water Mn target of 0.015 mg/L
- Residential-scale treatment devices can be certified under NSF/ANSI Standard 42: Drinking Water Treatment Units-Aesthetic Effects
  - No treatment units currently certified for Mn removal

Distribution System

- Deposition
  - Physical deposition, phys-chem sorption, biological accumulation
- Release - multiple mechanisms
  - Mn accumulates in tubercles in iron vs. surface deposits on PVC pipes; surface deposits easily dislodged with flowing water
  - Associated with organic and mobile phases of corrosion scales with 9 % Mn in exchangeable fraction
  - Mn accumulates in biofilm and susceptible to release with inactivation

Distribution System

- Other operational considerations
  - Scavenging of other metals (e.g., lead, arsenic) in manganese and iron oxides in distribution system
  - Inhibition of stable Pb(IV) scale formation
  - Potential presence (source) of Mn in ferric chloride
- Manganese management options
  - Prevent from entering distribution system (most effective)
  - Uni-directional flushing
  - Stable water chemistry
  - Resuspension Potential method for discolouration risk

Next steps

- Complete the risk assessment
- External peer review to be conducted in Summer 2015
- CDW approval to be sought in early Fall 2015 for a 2-month public consultation

Item 4-C
1,4-dioxane
(problem formulation)

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Problem formulation

- Modern way of looking at data for chemicals, focussing on issues directly related to drinking water and human health risk assessment
- Based on early development of a targeted report to identify critical issues, using readily available information
- Allows for the early identification of expertise needed
  - For specific sections of the document (e.g., BMD, PBPK)
  - To ensure appropriate groups within HC are consulted early (e.g., Foods, CMP)
- Enables the evaluator to focus the assessment on critical issue(s)/endpoints

Problem formulation example:

1,4-dioxane

Use, sources and exposure

- Use and sources
  - Leaching into groundwater (resists biodegradation) of industrial stabilizers, manufacturing solvents and consumer products.
- Exposure
  - **Levels in Canadian water:** unavailable; 1 µg/L (USA, 1980s).
  - **Main source of exposure/likely proportion of total intake from DW:** consumer products/No information (likely low)
  - **Additional inhalation/dermal exposure likely from showering or bathing:** No

Kinetics

- **Parent compound or metabolite toxic entity:** Parent; metabolic process may become saturated at higher doses.
- **Toxicokinetic data or PBPK models available to address interspecies differences or human variability:** No

Health effects

- **Likely critical effect(s):**
  - Liver carcinogenicity in rats, mice & guinea pigs
  - Liver & kidney toxicity in humans & animals
- **MOA analysis available:** No; strong evidence to suggest a threshold carcinogen in animals with a non-genotoxic MOA
- **New studies likely to have impact since last assessments:** Yes; MOA analysis of liver tumors supports threshold approach
- **Likely POD:** NOAEL of 9.6 mg/kg bw/day based on liver & kidney toxicity in male rats (Kociba et al., 1974) is lower than doses found to cause significant tumour incidence

Analytical and treatment considerations

- Analytical methods
  - EPA Method 522; solid phase extraction & GC/MS analysis with selected ion monitoring. Specific for analysis of drinking water.
    - MRLs: 0.036-0.047 µg/L; MDL: 0.010 µg/L
  - EPA Methods 1624 (MDL = 0.010 µg/L) and 8015C (MDL = 0.015 mg/L) for surface and groundwater
- Treatment plant achievability
  - Limited full-scale data
  - Advanced oxidation (UV/H_2O_2 or H_2O_2/O_3) capable of achieving between 0.002 - 0.010 mg/L in treated water
  - Membrane filtration achieved 0.080 mg/L

National and international considerations

- Currently no regulatory limits

Agency	Year	Value (µg/L)	Basis
HC - DWGV	2013	90	NOAEL 9.6 mg/kg bw/day based on liver & kidney toxicity (Kociba et al., 1974)
U.S. EPA – Health Advisory	2013	35 µg/L (10^{-4} risk level)	- Chronic oral RfD of 0.03 mg/kg bw/day based on liver toxicity (Kociba et al., 1974) - Oral slope factor of 0.10 mg/kg bw/day based on liver cancer (Kano et al., 2009)
WHO - Guideline	2005	50	NOAEL 16 mg/kg bw/day based on liver cancer (Yamazaki et al.,1994)

Potential issues/focus

- **Consistency:** All assessments considered the same potential critical effects and key studies
- **Uncertainty in previous assessments:**
  - Linear vs. threshold approach based on MOA
  - Choice of key study (Kociba et al., 1974 vs. Kano et al., 2009)
  - No multi-generation reproduction studies
  - Choice of species/gender
- **Critical issues on which to focus the assessment:**
  - MOA analysis (liver toxicity vs. liver tumors; sensitive species & gender)
  - Need for PBPK model with saturable kinetics?
- **Need to engage cancer MOA & PBPK experts early**

Next steps

- Secretariat to send request for CDW exposure data
- Development of proposed guideline technical document – expected fall 2016

Item 4-E
Uranium

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Status

- For information only
- Risk assessment under development
- Draft guideline technical document expected for CDW review and approval for public consultations at fall 2015 meeting

Background

- Current MAC (2001) of 0.02 mg/L (20 µg/L)
  - Based on chemical toxicity of uranium (radiological risk not relevant at environmental levels)
  - Based on a subchronic study showing kidney toxicity in rats (Gilman, 1998)
  - Risk managed based on both treatment costs
- A number of new studies are available since 2001
  - 9 month animal studies
  - Epidemiology studies

Sources

- Uranium is widespread and naturally occurring, consists of 3 isotopes: U-238, U-235, U-234
- Canada is the second largest producer in the world
  - Mostly in Saskatchewan
- Present in water as a result of leaching from natural deposits, its release in mill tailings, emissions from the nuclear industry, combustion of coal and other fuels, and from phosphate fertilizers

Exposure

- Food
  - Plant and animal sources
  - Average intake for Canadians is 0.07 µg/kg bw/d
  - Highest intake in infants under 3 months
- Consumer products
  - Only in certain antiques
- Ambient air
  - Environment Canada does not monitor uranium in ambient air
  - Values available for Port Hope, ON: 0.3 – 6 ng/m^3
- Soil
  - Varies with mineral deposit types (SK, ON, QC, NB, NT)
  - Average background level 2 mg/kg soil

Exposure levels – water

2000 – 2015*

P/T	Water Source/Range (ug/L)	Average (ug/L)
AB*	Raw 0.1 - 11	0.8
	Treated 0.1 - 34	0.7
NB	Raw 0.05 - **165**	1.06
	Treated 0.1 – 25.7	0.9
NL	Raw 0.1 – 20	1.5
NS	Raw <0.1 – 16.3	2.0
	Treated <0.1 - 19	2.4
NU	Raw <0.01 – 2.19	0.34
QC	Treated Max* 360	6.7
SK	Raw/Treated 0.01 - **183**	5.4

Health considerations

- Target organs
  - **Kidney: proximal tubules**
  - Bone: storage site
  - Reproductive system: effects seen in animal studies only, no well-conducted human studies
- Carcinogenicity
  - Natural uranium is not classified by IARC, NTP or EPA

Analytical Methods

- Several U.S. EPA approved methods based on:
  - ICP-MS (EPA 200.8; ASTM D5673 and SM 3125)
  - Fluorimetric Method (EPA 908.1; ASTM D 2907; SM 7500 U C; USGS R-1181-76)
  - Laser Phosphorimetry (ASTM D 5174)

Treatment technologies

- EPA considers the following processes as BATs/SSCTs (2000)
  - Enhanced coagulation/filtration
  - Lime softening
  - Ion exchange
  - Reverse osmosis
- Adsorptive Media Technology
  - Iron modified IX resin, iron-based media
- Residuals management

Residential scale

- No certified devices currently available
- Point-of-use reverse osmosis and ion exchange treatment systems may reduce uranium concentrations in drinking water

International considerations

- WHO (2011) provisional 30 µg/L
  - Up from 15 µg/L (2004)
- US EPA (2000) MCL 30 µg/L
- Australia (2011) 17 µg/L

Next steps

- Complete the risk assessment
- External peer review to be conducted in summer 2015
- CDW approval to be sought in fall 2015 for a 2-month public consultation

Item 4-F
pH

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Status

- Public consultation ended March 16th, 2015
- Seven sets of comments were received and addressed
- Seeking final CDW approval

Refresher

- pH range of 7.0 to 10.5 was proposed for drinking water based on:
  - Ability to achieve treatment objectives and corrosion control
  - Minimize leaching of lead in distribution system
  - Allow flexibility for pH of finished water
  - Minimize potential for increased skin and eye irritancy (pH > 11.0)

Consultation comments

- Clarify that this is an operational guideline
  - Guideline statement was clarified
- Strengthen justification for the upper and lower limits of the proposed pH range
  - Information added, need CDW discussion
- Concern with reduced chlorine disinfection efficiency at pH greater than 8.5
  - Relevant information already in document – clarified that guideline applies to finished drinking water
- Wanted more emphasis on the need to adjust pH during treatment processes
  - Relevant information already in document – clarified that guideline applies to finished drinking water

Consultation comments (cont'd)

- Suggested adding information in Section 6.0
  - UV lamp fouling rates
  - Bromate formation during UV/chlorine treatment
  - pH affects membrane performance
- Raised concerns with potential health effects at higher end of pH range
  - Verified original references – no additional information available

Next steps

- CDW discussion – upper bound of range
- Seeking CDW approval of the final Guideline Technical Document for publication
- Next steps:
  - final CHE approval
  - Publication

Item 4-G
Aluminum – problem formulation

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Status

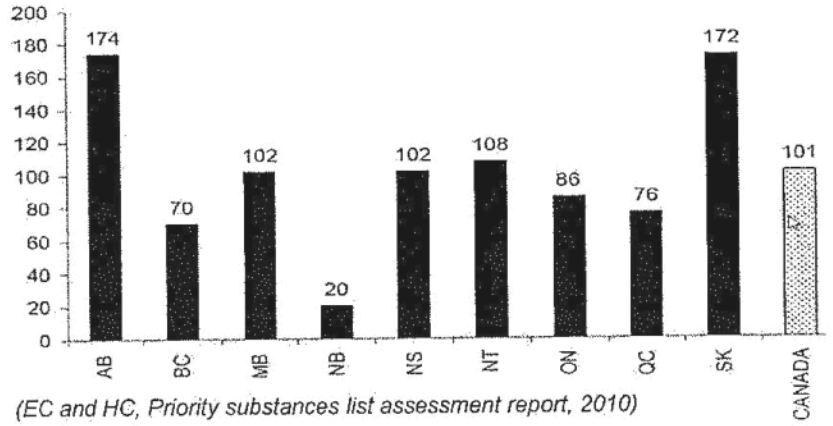
- For information only
- Risk assessment in early stages
- Aluminum currently #8 on priority list
- Problem formulation for aluminum being presented to CDW at their request

Use, sources and exposure

- Use and sources
  - Municipal water treatment facilities (78% of estimated 16.1 kilotonnes of 2006 domestic consumption)
  - Industrial water & wastewater treatment (additional 20%).
  - Natural aluminum (rocks) releases much greater than anthropogenic releases
- Exposure
  - **Main source of exposure/likely proportion of total intake from DW:** Food & beverages / <2% from DW
  - **Additional inhalation/dermal exposure likely from showering or bathing:** Not likely

Exposure

Mean total Al µg/L in Al-treated DW (1990-2007)



(EC and HC, Priority substances list assessment report, 2010)

Exposure (continued)

Table 3.2 Contribution (%) of each source of exposure based on Canadian mean daily intake of total aluminum

Source of exposure	Contribution (%) of each source of exposure						
	Infants (0–6 months)		Toddlers (0.5–4 years)	Children (5–11 years)	Teens (12–19 years)	Adults (20–59 years)	Seniors (> 60 years)
	Breastfed (exclusively)	Non breastfed					
Drinking water	0.00	4.1	0.84	0.83	0.70	1.31	1.69
Food and beverages	6.80	32.4	49.5	78.9	92.2	87.7	85.0
Ambient air	0.030	0.02	0.02	0.02	0.02	0.02	0.02
Indoor air	0.21	0.14	0.14	0.14	0.12	0.18	0.20
Soils	92.7	63.4	49.5	20.1	7.17	11.0	12.8
TOTAL	100.00	100.00	100.00	100.00	100.00	100.00	100.00

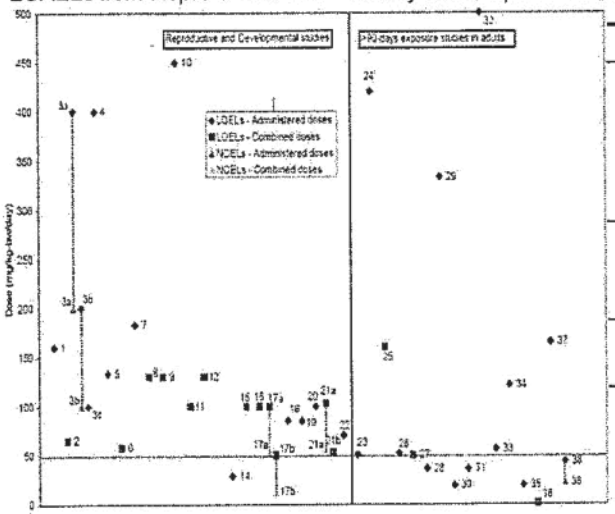
(EC and HC, Priority substances list assessment report, 2010)

Kinetics

- **Endogenously produced:** No
- **Toxic entity:** Parent compound
- **TK data or PBPK models available to address interspecies differences or human variability:** Yes, but necessary? Need to be evaluated
- **Other related info:** Low oral bioavailability of Al in DW (0.3%), no likely interspecies differences

Health effects

LOAELs from Repro & Dev and > 90 day adult exposure studies (EC & HC, 2010)



- **Likely critical effect(s):** Neurotoxicity, Reproduction & neurodevelopment
- **MOA analysis available:** No consensus
- **New studies likely to have impact:** NO
- **Likely POD:** 50 mg Al/kg-bw/day as a combined dose of total Al (LOAEL)

7

Analytical and treatment considerations

- **Analytical methods:**
  - EPA 200.5 MDL = 2.2 µg/L
  - EPA 200.7 MDL = 0.02 mg/L (20 µg/L)
  - EPA 200.8 MDL (total recoverable)= 1.7 µg/L; (direct analysis)= 0.04 µg/L
  - EPA 200.9 MDL = 7.8 µg/L
- **Treatment achievability:**
  - 0.1 mg/L or less in systems using aluminum based coagulants
  - 0.2 mg/L or less for treatment systems with direct or in-line filtration or lime
  - A concentration of 0.050 mg/L in finished water is considered optimal

National & international considerations

Agency	Year	Value (mg/L)	Basis
HC	1998	0.1-0.2	Operational objective. No HBV or aesthetic objective
HC-DWGV	2007	0.6	Cal/EPA
HC/EC – priority substances list assessment report	2010	NA	• Not entering environment at a level of concern to human health • 50 mg/kg-bw/day lower bound of LOAELS for neuro, repro & developmental effects.
U.S. EPA – Secondary MCL	2012	0.05-0.2	Aesthetic objective – coloured water (>200 µg/L) Range addresses varying water quality and treatment situations.
WHO -PTWI	2010	0.9	LOAEL 50 mg/kg bw/day based on rodent repro & neurotoxicity.
Cal EPA - PHG	2001	0.6	• LOAEL 45 µg/kg bw/day based on neurodevelopment in premature infants • LOAEL/NOAEL125 mg/kg bw/day based on Al metabolism in male adults.
Australia	2001	0.2	Aesthetic objective

Potential issues/focus

- **Consistency in previous assessments:**
  - All considered the same potential critical effects
  - LOAEL of 45 or 50 mg/kg bw/day (of those that selected a POD)
- **Uncertainty in previous assessments:**
  - Need for a HBV when aesthetic/operational objectives are in same range or lower than likely critical effects?
- **Critical issues on which to focus the assessment:**
  - Need for a HBV when aesthetic/operational objectives are in same range or lower than likely critical effects?
  - Lower bound of range of LOAELs vs. lower single dose studies
  - Are children more susceptible than adults to Al toxicity? Comparison of health effects & kinetics suggest→ No (but should look at potential for differences in MOA)

CDW discussion



- Current priority is #8, mostly based on health, analytical and treatment.
- The health-based value would be higher than the current operational guidance value.
- What is the path forward ?

Item 4-H
Microcystins

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Status

- Guideline technical document has been revised and peer reviewed
- Peer-review comments have been incorporated into the document
- Guideline technical document has been provided to CDW

Peer review comments – Identity, exposure

- No major content changes
- Address benthic cyanobacteria
- Organism name changes (e.g., *Anabaena* now *Dolichospermum*)
- Discuss additional tools: phycocyanin probes
- Minor text changes re: ecology, environmental influences; Additional references suggested
- Question for CDW emerged: extent of use of dugouts as drinking water sources?

Peer reviewers – analytical and treatment

- Dr. Arash Zamyadi:
  - Sr. Research Associate, School of Civil and Environmental Engineering, UNSW, Australia
- Dr. Judy Westrick:
  - Director of Lumigen Instrumentation Center, Dept. of Chemistry, Wayne State University
- Dr. Jussi Meriluoto:
  - Dept. of Biosciences, Abo Akademi University, Finland
- Dr. Rocio Aranda-Rodriguez: Research Chemist, Health Canada
- U.S. EPA Review:
  - 8 EPA reviewers: analytical chemists & engineers in OGWD, OST, and USGS

Peer review comments – analytical

- Peer reviewers supported the recommendations on the use of laboratory based ELISA and PPIA for screening with LC-MS/MS or HPLC-PDA analyses on a portion of positive samples:
  - ELISAs are not selective, different cross-reactivity for variants; can be affected by pH, chemical oxidation and temperature
  - Knowledge of variants important for interpreting ELISA results and treatment plant performance
  - Recognized that LC-MS/MS not routinely used in commercial laboratories
- Supported use of field test kits for qualitative information on bloom toxicity and treatment plant operations:
  - Not designed for compliance monitoring

Peer review comments, treatment – 1

- Peer reviewers supported assessment of treatment plant achievability:
  - Optimized treatment plants using combination of methods (conventional filtration and oxidation or PAC) can achieve total microcystin concentrations well below proposed MAC (<0.1 µg/L)
  - Cells removed effectively when conventional filtration optimized
  - May need to adjust oxidant dose or add PAC based on dissolved microcystin concentration
- Requested additional information on cyanobacterial cell removal:
  - Added information on factors affecting cell removal (e.g., coagulant type, dose, cyanobacterial genera, operational parameters)

Peer review comments, treatment – 2

- Requested additional information on the fate of cells and microcystins within conventional filtration plants:
  - accumulation of cells in clarifiers (scums and sludge) and breakthrough into filtered water
  - potential release of dissolved toxins from sludge
- Added percent removal information from full-scale studies:
  - implications when high cell and microcystin concentrations present in raw water
- Requested information on DAF, riverbank filtration, and ballasted flocculation be added:
  - DAF and riverbank filtration effective for cell removal (>95%)

Peer reviewers – health effects

- Dr. Emanuela Testai:
  - Mechanisms of Toxicity Unit, Istituto Superiore di Sanità, Rome, Italy
- Dr. Leonard Ritter:
  - Professor Emeritus in the School of Environmental Sciences at the University of Guelph
  - Fellow of the Academy of Toxicological Sciences
- Dr. Ronald W. Brecher, PhD, DABT, CChem, QPRA:
  - Toxicology, Risk Assessment and Risk Communication Specialist
- The U.S. EPA Peer Review Process

Peer review comments, health – 1

- A short-term guideline for total microcystins is supported based on the scenario of exposure in Canada:
  - support Heinze et al. (1999) as the key study – study duration appropriate for proposed seasonal MAC;
  - supportive of a MAC for total microcystins – most practical approach due to lack of science on variants.
- No MACs for anatoxin-a and cylindrospermopsin also supported:
  - for cylindrospermopsin, supported due to lack of detection in Canada, not for inadequate science.

Peer review comments, health – 2

- Supportive of a proposed MAC based on adults as sufficiently protective of children due to:
  - scientific evidence for liver effects in young animals (5-6 weeks old), and developmental toxicity in fetuses (following *in utero* exposure) suggests that these age groups are less sensitive to MC-LR compared to adults; and
  - the use of a 10-fold UF to account for variations in sensitivity within humans (intraspecies UF).

Derivation of the HBV

- Heinze et al. (1999) represents the best available study for the basis of a short-term HBV due to:
  - the duration of the study (28 days);
  - the mode of administration (oral exposure via drinking water);
  - the use of an adequate number of animals; and
  - the analysis of organ weights, hematology, serum biochemistry and histopathology of the liver and kidneys.

$$TDI = LOAEL / UF$$

$$= \frac{50\ \mu g/kg\ bw}{900}$$

$$= 0.056\ \mu g/kg\ bw$$

$$HBV = (TDI \times BW \times AF) / DWC$$

$$= \frac{0.056\ \mu g/kg\ bw \times 70\ kg \times 0.8}{1.5\ L/d}$$

$$\approx 2\ \mu g/L$$

Infant exposure

- Animal evidence indicates that young animals and fetuses are less sensitive to MC-LR than adults, thus HC supports that the proposed MAC based on adults is protective of the Canadian population:
  - however, since infants can consume up to 5 times more drinking water for their body weight, and there is no scientific evidence to indicate decreased sensitivity in infants, a reference value for bottle-fed infants can be derived as follows:

$$RV = (TDI \times BW \times AF) / DWC$$

$$= \frac{0.056\ \mu g/kg\ bw \times 7\ kg \times 0.8}{0.75\ L/d}$$

$$\approx 0.4\ \mu g/L$$

Proposed MAC

- During a conference call on March 19th, CDW members and HC agreed that the current MAC of 1.5 µg/L be proposed as the new seasonal MAC:
  - since changing the guideline would not increase health protection and the 1.5 µg/L is already being achieved by P/Ts
- In a follow-up conference call on April 14th, CDW members and HC discussed providing the precautionary approach of recommending an alternative source of drinking water be used for reconstituting infant formula:
  - such advice addresses the increased intake per kilogram body weight in infants (0-6 months) and aligns with EPA approach

Next steps

- Seeking CDW approval for a 2-month public consultation period

Item 4-I
Copper

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Status

- For information only
- Risk assessment is under development and will be peer-reviewed over the summer
- Draft guideline technical document expected for CDW review and approval for public consultations at fall 2015 meeting

Background

- Current aesthetic guideline of ≤ 1.0 mg/L (1992)
  - based on palatability and to minimize laundry and fixture staining
- Cooper is an essential micronutrient
- Occurs naturally as mineral in rocks and soil
- Used extensively in industry and household products
  - **Plumbing:** copper tubing (malleable, ductile); alloys (brass and bronze fittings)

Sources and exposure

- Natural sources
  - Windblown dusts, volcanoes, decaying vegetation, forest fires, sea spray
- Anthropogenic activities
  - Industrial and mining operations
  - Municipal incinerators, water treatment plants (sewage sludge, water plumbing systems, algaecides)
  - Fertilizers, fungicides, pesticides, copper-made utensils
- Found in food, drinking water, copper-containing supplements (negligible contribution from air)

Drinking water contribution

- Usually < 10% daily intake (0.1-1 mg/day); however, up to 50% with levels > 1-2 mg/L
- In some cases could be higher (homes with new copper tubing, certain water quality)
- Copper speciation is different in drinking water than in food (most likely bound to organic complexes)

Drinking water exposure

- Copper in tap water varies widely and depends on many factors
  - Pipe age, corrosion scale composition
  - pH, alkalinity
  - Dissolved inorganic carbon
  - Oxidant level
  - Copper tubing, brass fittings can be important sources of copper in drinking water
- Limited copper exposure data from water
  - Request data from CDW

Health effects – humans

- Cu toxicity is very rare
- Short-term exposure
  - Exposure: mostly adults, 2 wks – 2mo, copper sulfate up to 12 mg /L
  - Acute GI effects: nausea, abdominal pain, vomiting and diarrhea
  - Nausea : transient, within first 15 min expo, threshold = ~ 4 mg Cu/L
  - GI effects generally with levels > 6 mg Cu/L
- Long-term exposure
  - Case reports, 2 studies in infants (up to 12 mo)
  - Mainly liver damage (kidney); need more data
  - No evidence of carcinogenicity
  - Neurotoxicity (Alzheimer): equivocal evidence

Health effects - animals

- Adverse health effects
  - Mainly liver, kidney, rodent forestomach
  - Other target organs: bone, CNS, immune system
  - Dietary copper less toxic than DW & gavage copper (WHO, 2004)
- Acute toxicity
  - GI irritation, liver and kidney
  - Usually copper sulfate
  - Subchronic and chronic toxicity
  - Hepatotoxicity, nephrotoxicity, hematotoxicity (RBC lysis)
  - Rat more sensitive than mice
  - No evidence of carcinogenicity, repro/developmental toxicity

Analytical Methods

- EPA approved methods based on
  - Inductively coupled atomic energy spectrometry (ICP-AES)
  - Inductively coupled plasma mass spectrometry (ICP-MS)
  - Graphite furnace atomic absorption spectrometer(GFAA)
  - Flame atomic absorption (FLAA)
- MDLs range from 0.5 µg/L – 3 µg/L
- Current PQL is 50 µg/L
  - Based on US EPA Second Six Year Review (2009)

Considerations for sampling

- Sampling protocols depend on objective(s)
  - Worst-case scenario?
  - Average exposure scenario?
  - Targeted to specific material
  - Sampling site (old vs. newer buildings)
- Flushed samples are not representative of typical exposure to copper

Treatment and distribution

- Municipal treatment to reduce copper at the source
  - Coagulation
  - Lime precipitation followed by settling
  - Membrane
  - Adsorption
  - Ion exchange
- Certified residential treatment devices for copper
  - Filtration (NSF 53)
  - Reverse Osmosis (NSF 58)
  - Distillation (NSF 62)

Strategies to reduce copper

- Corrosion control
  - Maintaining non-corrosive water quality to the tap
  - pH and alkalinity adjustments
  - Corrosion inhibitors
- Point-of-use treatment devices

International considerations

- US EPA (2002): MCLG = 1.3 mg/L; Secondary MCL = 1 mg/L
  - Based on 90th percentile of samples, 1L first-draw, 8 hour stagnation
  - Major revision of Lead and Copper Rule underway with consideration of different sampling and sample sites; draft expected in 2015
- WHO (2011): Guideline = 2 mg/L
  - Noting that there may be aesthetic impacts at levels below this value
  - 2-3 L per day consumption, tolerable uptake of 10 mg/day
  - Laundry staining above 1 mg/L; Taste and colour issues > 2.5 mg/L
- Australia (NHMRC, 2011): Guideline = 2 mg/L, aesthetic value = 1 mg/L
  - Tolerable daily intake from WHO

Next steps

- Complete the risk assessment
- External peer review to be conducted in summer 2015
- CDW approval to be sought in Fall 2015 for a 2-month public consultation

Item 4-J
PFOS, PFOA

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Status

- For information only
- Risk assessment is under development
- Draft guideline technical document expected for CDW review and approval late summer/early fall 2015

Refresher

- PFOS and PFOA are perfluoroalkylated compounds with long environmental half-lives and high partitioning to water
- Contamination of drinking water has occurred in Canada when the compounds are components of firefighting foams
- Half-lives in humans are much longer than in animals
  - This needs to be addressed to ensure that risk assessments are sufficiently protective for humans

Exposures in Canada

- Largest source of exposure for most Canadians is food
- Little information available on levels in Canadian raw water or drinking water supplies
  - Some data on raw and treated water from Alberta and Quebec
  - National Survey: treated and raw water samples obtained in winter and summer from 35 sites in 2009; 30 sites in 2010
- PFOS and PFOA were included in cycles 1 (2007-2009) and 2 (2009-2011) of the Canadian Health Measures Survey
  - the compounds were detected in the serum of almost all participants

Health effects – PFOS

- Lowest effect in animals is immune suppression
  - NOAEL: 0.000166 mg/kg bw/day; LOAEL: 0.00166 mg/kg bw/day — decreased IgM in mice exposed for 28 days
  - Not appropriate as basis of guideline (Only 5 mice per group, inconsistent with other studies, and not overt adverse outcome)
- Proposed basis for guideline: liver histological effects
  - Hepatic cystic degeneration in M rats exposure for 2 years
  - LOAEL: 0.024 mg/kg bw/day; no NOAEL (Butenhoff et al., 2012)
  - Lowest effect in only 2-year study with multiple treatment groups
- Cancer
  - Hepatocellular adenoma in M rats exposed for 2 years
  - Non-mutagenic; $BMDL_{10}$ of 0.318 mg/kg bw/day

Health effects – PFOA

- Lowest effect in animals is delayed mammary gland development
  - Effect observed at lowest doses in all studies; lowest LOAEL: 0.001 mg/kg bw/day
  - However, this endpoint will not be used as the basis of a guideline (Not overt adverse outcome, and effect only studied in one mouse strain
- Proposed basis for guideline: hepatocellular hypertrophy
  - In rats and mice exposed for 29 days (Loveless et al., 2008)
  - LOAEL: 0.3 mg/kg bw/day; no NOAEL
  - Not the lowest LOAEL, but most overt at lowest levels
- Cancer
  - Leydig cell adenoma in M rats exposed for 2 years
  - Non-mutagenic; $BMDL_{10}$ of 1.13 mg/kg bw/day

Deriving TDIs

- Substantial pharmacokinetic differences between animals and humans
  - A few days to weeks in animals; several years in humans
  - Traditional risk assessment approaches are not expected to be sufficiently protective of humans
- Two approaches are being considered to account for these differences
  - PBPK modelling
  - Application of chemical-specific adjustment factors

Analytical methods

- U.S. EPA Method 537 (LC/MS/MS)
  - PFOA detection limit = 1.7 ng/L; LCMRL = 5.1 ng/L
  - PFOS detection limit = 1.4 ng/L; LCMRL = 6.5 ng/L

Municipal treatment

- Conventional treatment not effective
- GAC (94-96%)
  - Efficiency affected by the regeneration rate
  - PFOS preferably adsorbed by GAC
- Membrane filtration
  - RO effectively remove PFOA/PFOS (92-99%)
  - Nanofiltration promising technology (97-99%)
- Anion exchange (75 - >92%)
  - PFOS were preferably removed by anion exchange resin
- Oxidative processes not effective due to strong carbon fluorine (C-F) bonds

Residential scale treatment

- No certified devices currently available
- Study on effectiveness of POU devices (MDH, 2008)
  - Point-of-use reverse osmosis and GAC treatment systems may reduce PFOA and PFOS concentrations in drinking water

International considerations

- Few drinking water values (all non-regulatory) for PFOS and PFOA

	PFOS	PFOA
Health Canada drinking water guidance values (2008, 2010, 2011)	**0.3 µg/L** Various effects (thymus, cholesterol, liver, thyroid) in monkeys	**0.7 µg/L** Liver weight in monkeys
	Animal-to-human extrapolation using classical PK calculations	
UK Health Protection Agency Maximum acceptable concentrations (2007, 2009)	**0.3 µg/L** Thyroid effect in monkeys	**10 µg/L** Liver weight in rats
	Animal-to-human extrapolation using default UF of 10	
U.S. EPA Provisional Health Advisories (2009)	**0.2 µg/L** Various effects in monkeys	**0.4 µg/L** Liver weight in mice
	Animal-to-human extrapolation using CSAFs	

Next steps

- Completion of risk assessment
- External peer review
- CDW approval for a 2-month public consultation to be sought late summer/early fall 2015

Item 5-A
National Drinking Water Conference

FPT Committee on Drinking Water

56th Meeting / May 6-7, 2015

Ottawa, Ontario

Background

- At the Fall meeting, CDW confirmed its preference for a drinking water focussed event in the tradition of the National Conference on Drinking Water
- New partnership opportunities are needed to help organize and administer the event

Potential partners approached

- Canadian Water Network
- Canadian Institute of Public Health Inspectors
- National Research Council Research Chairs in Drinking Water
  - Dalhousie University
  - École polytechnique de Montréal
  - University of Toronto
  - Waterloo University

Reactions

- CWN : Declined, citing potential conflicts
- CIPHI: Declined for 2016, interest in drinking water session at future events
- NSERC Chairs: High level of interest and commitment in drinking water conference
- Canadian Water and Wastewater Association: invitation to participate in broader water event in 2016 and ongoing

Option A - NSERC Chairs

- Drinking water and treatment focus
- Commitment to low registration fees
- Jointly administered by HC and Chairs
- 2016 in Ottawa, coordinate with CDW Fall meeting but need to move to mid-October
- CDW funds may be needed

Option B - CWWA

- Collaborate with CWWA every 2nd year as part of their new broader water event
- 2016 in Toronto, late November
- Less focus on drinking water overall, but offer of specialized drinking water session(s)
- Organized by CWWA with CDW input to drinking water session(s)

Option C – HC staff

- Workshop on one or two specific topic(s)
- Meet a need to be identified by CDW
- Organized by Health Canada staff
- One day event, held in Ottawa
  - Attached to CDW Meeting
  - 35 – 50 participants (invited experts)
  - Moderate cost (CDW funds)

Option D

- No CDW led Canadian drinking water event
- Is the gap already filled by the national water event (CWWA), numerous regional industry events (ACWWA, ResEAU, OWWA, WCWWA, BCWWA) and International events (AWWA, IWA)?

Next steps

- CDW decision needed:
  - Option A: NSERC Chair partnership
  - Option B: CWWA partnership
  - Option C: One day workshop
  - Option D: No CDW drinking water event
- Note that options A, B and C may require CDW decision on spending

Health Canada Santé Canada

Your health and safety... our priority. Votre santé et votre sécurité... notre priorité.



Iodo-THM Formation in High Sodium Source Waters

A.-M. Tugulea, R. Aranda-Rodriguez, M. Giddings, F. Lemieux, J. Hnatiw
Health Canada, Ottawa, Canada



Background

National Survey of Disinfection by-Products in Canadian Drinking water (2009-2010)

- First Canadian study of iodo-DBP (iodo-THMs and selected iodo-HAAs) occurrence in water treatment and distribution systems.
- 65 water treatment plants (WTPs) across Canada were investigated.
- Bromide, iodide ion, total bromine and total iodine concentrations were determined.



2

Background (cont.)

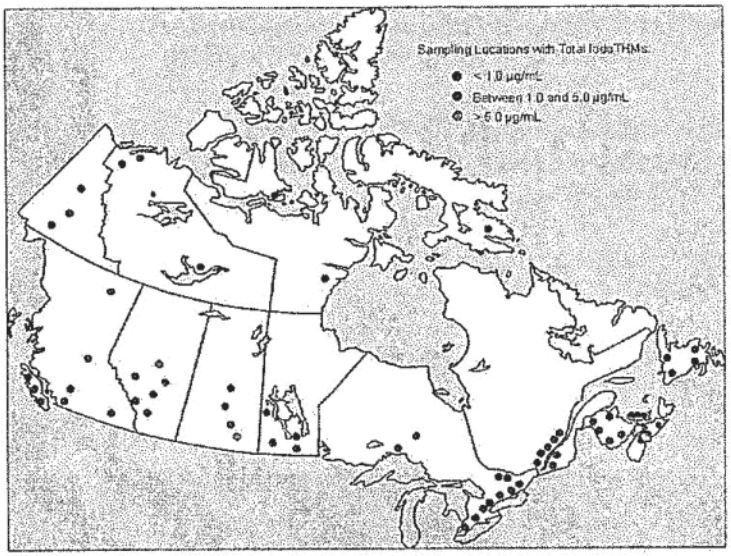
Findings:

- Iodo-THMs were found in 74% (48/65) of the water systems tested under summer conditions.
- Total iodo-THM concentration range: 0.02 µg/L to 21.66 µg/L.
- The median value of the maximum total iodo-THM concentrations in systems with detectable concentrations was 0.17 µg/L, while the average value for the same data set was 1.2 µg/L.
- In 2 WTPs the maximum total iodo-THMs was higher than 5 µg/L



3

Geographic distribution of total Iodo-THM concentrations (2009-2010 National Survey)



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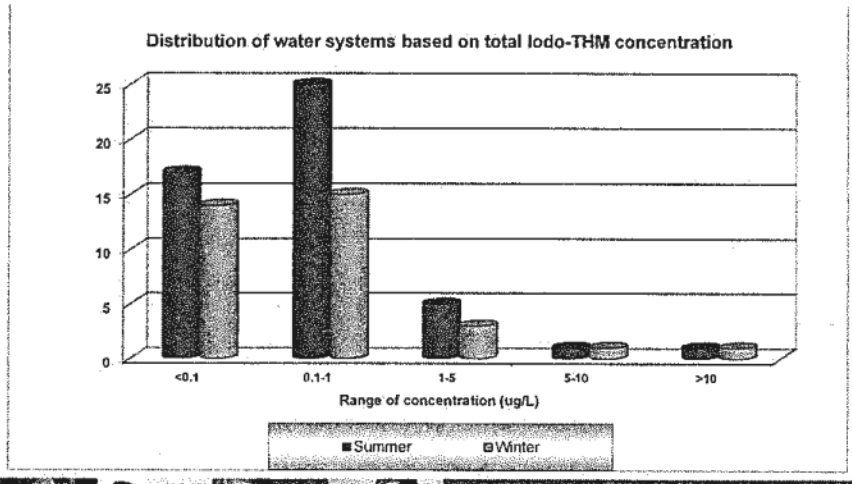
Background (cont.)





5

Background (cont.)

Findings:

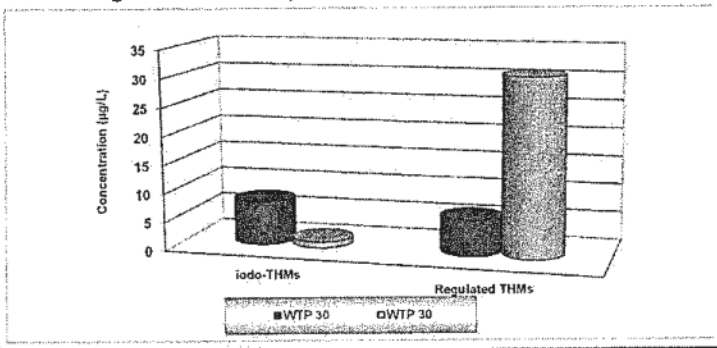
- The highest total iodo-THM concentrations were found in the Canadian Mid-West, in non-coastal locations.
- No correlation of total iodo-THM concentrations with Br^- concentrations was found.
- Total iodo-THM concentrations showed a good correlation with total iodine and iodide concentrations.
- At locations where elevated levels of iodide were present in the source water, the total iodo-THM concentration was inversely correlated with the free chlorine concentration in the treated water.



6

Iodo-THM formation correlation to low free chlorine in treated water

- WTP 30: Total iodo-THMs: 7.56 µg/L. The free chlorine concentration was 0.03 mg/L. Iodide was present in raw and treated water.
- WTP 31: Total iodo-THMs: 1.2 µg/L. The free chlorine concentration was 0.89 mg/L. Iodide was present in raw water only.





7

How do we identify water systems with potential for high iodo-THM formation?

- Is the potential to form iodo-THMs equally relevant for all treatment systems using chloramines?
- Iodide or total iodine determinations, with required MDLs, are not part of routine water quality analysis in many water treatment systems.
- Total iodo-THM concentrations higher than 5 µg/L were found at WTPs using source water with Na^+ conc. >200 mg/L, and where chloramines were formed (from added or naturally present NH_4^+).
- Na^+ concentration is considered in this study as a marker for higher bromide and iodide concentrations in the source water.



8

Current study: a survey targeting water treatment systems using water sources with high sodium content.

Hypothesis:

- High Na^+ concentrations and the presence of ammonium in the source water can be a marker for water treatment systems that can be expected to have a high potential for the formation of iodo-THMs.
- Total iodo-THM concentration and speciation in such systems are correlated to the free chlorine concentration in the treated water.
- Iodo-THM speciation in such systems is correlated to the bromide concentration in the source water.



9

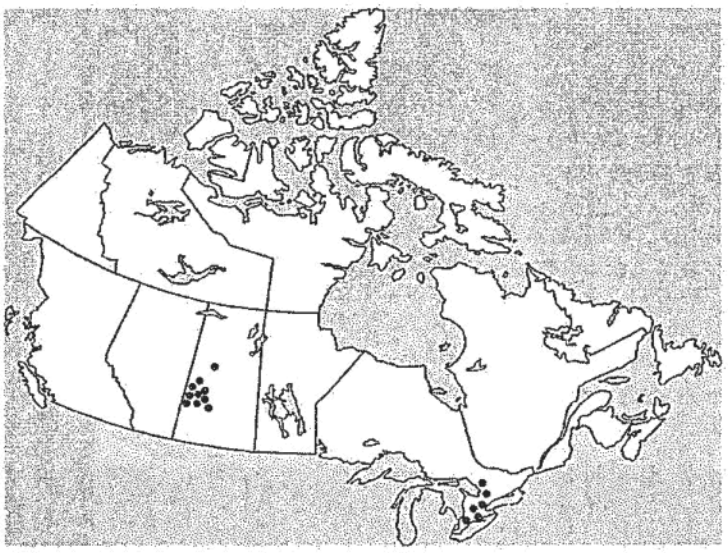
Current study: design

- 16 WTPs in two Canadian Provinces, with source water DOC ranging from 0.62 mg/l to 17 mg/L.
- Na^+ concentrations in source water ranged from 10 mg/L to 760 mg/L
  - 10 systems have Na^+ concentrations >200 mg/L.
- Source water has naturally occurring NH_4^+ ranging from <0.05 mg/L to 2.7 mg/L.
- All WTPs in the study use ammonium in the treatment train and/or have naturally occurring ammonium.
- This study also investigated other potential water contaminants: CNCl; CNBr; nitrosamines, bromate, perchlorate.



10

Study locations: map



11

Sampling and analytical method

- Sampling protocol: 65 mL brown glass bottles; no headspace, 0.114 M ascorbic acid for quenching; pH lowered to 4.5 using 0.1 N HCl.
- Stability studies: iodo-THM concentrations were stable for more then 2 weeks, if samples were kept cool (< 10^0C) and in the absence of light.

Chemical name		MDL (µg/L)
Dichloroiodomethane	DCIM	0.02
Bromochloroiodomethane	BCIM	0.05
Dibromoiodomethane	DBIM	0.03
Chlorodiiodomethane	CDIM	0.05
Bromodiodomethane	BDIM	0.05
Triiodomethane (iodoform)	TIM	0.02

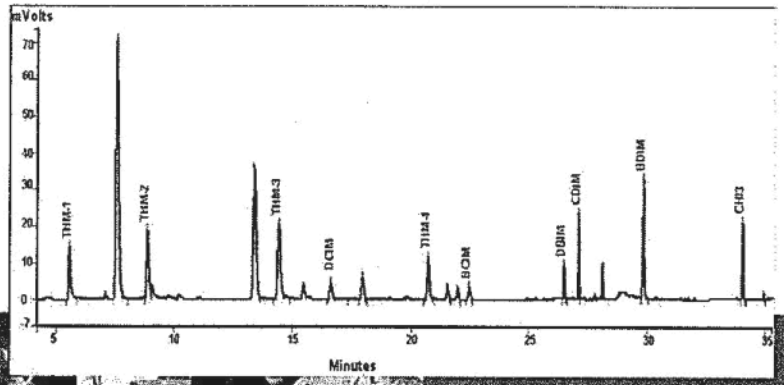


12

Sampling and analytical method

- Iodo-THM samples were analysed using an automated SPME-GC-ECD method.
- Possible interference by 32 other neutral DBPs was assessed.

Fig 1. Chromatogram of iodo-THMs separated from a solution containing 32 other neutral DBPs (iodo-THMs 10 µg/L, except iodoform 2 µg/L; other DBPs 5 µg/L, except THM-1 25 µg/L)

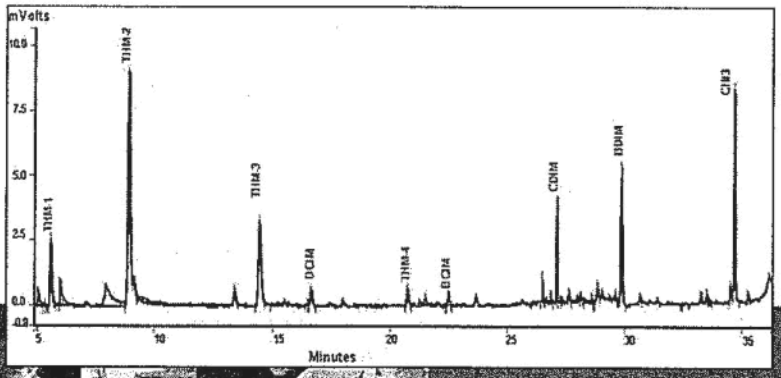


13

Sampling and analytical method

- Presence of the analytes in the sample was confirmed by spiking the samples with the iodo-THM standard mix.

Fig 2. Overlay of a sample spiked with iodo-THM standard mix (0.25 µg/L iodo-THM, except iodoform 0.125 µg/L) chromatogram (red) over original sample chromatogram (blue)for confirmation

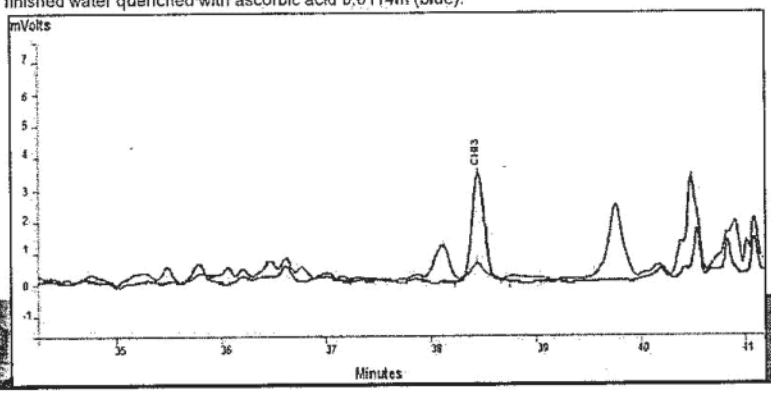


14

Quenching and iodo-THM stability

- Laboratory experiments demonstrated that iodoform is not stable in drinking water, if free chlorine is present. Recovery of spiked iodoform concentrations were much lower in unquenched drinking water samples as compared to quenched samples.

Fig. 3 Chromatogram of iodoform spiked (0.125 µg/L) in unquenched finished water (red) and finished water quenched with ascorbic acid 0.0114m (blue).



15

Results: concentration range and speciation

- For WTPs with Na^+ source water concentrations >200 mg/L, the range of maximum total iodo-THM concentration formed was 0.76 µg/L to 26.82 µg/L, with an average of 8.11 µg/L and a median value of 3.16 µg/L. These values were much higher than the average and the median value obtained during the 2009-2010 National Survey.

	2009/2010 National Survey	2012/2013 Targeted Survey
Number of sites investigated	65	16
% of sites with Na^+ concentration>200 mg/L	6.2	62.5
Maximum total iodo-THM concentration - Average value	1.2 µg/L	8.11 µg/L
Maximum total iodo-THM concentration - Median value	0.17 µg/L	3.16 µg/L



16

Results: concentration range and speciation

- 8/10 WTPs with high sodium source water had maximum total iodo-THM concentrations > 1 µg/L and 4/10 WTPs had concentrations > 10 µg/L.
- In the 4 WTPs with total iodo-THM concentrations > 10 µg/L, the dominant species formed was iodoform (CHI_3). The highest iodoform concentration, 16.28 µg/L, was found in treated water from WTP7, in the summer.



17

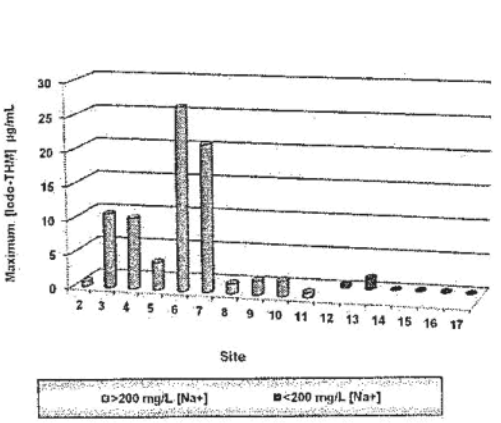
Results: Maximum total iodo-THM concentration and dominant species formed in the treated water from 16 WTP

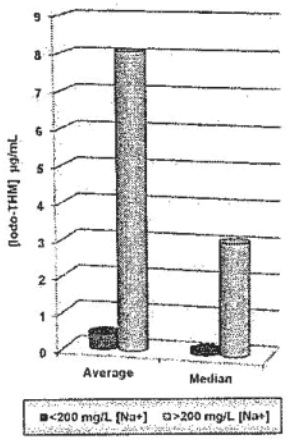
Site	Max. total Iodo-THM in treated water (µg/L)	Dominant Iodo-THM	[Na+] In source water (mg/L)	Free chlorine in Treated water (mg/L)	Bromide in source water (mg/L)
2	0.73	DCIM	620	1.55	no sample
3	10.92	CHI3	580	0.38	0.9
4	10.48	CHI3	530	0.05	1.3
5	4.08	DBIM	410	0.64	0.67
6	26.82	BCIM; CHI3	420	2.5	0.73
7	21.54	CHI3	440	0.06	1.49
8	1.47	DCIM	390	0.8	0.42
9	2.07	CHI3	760	0.03	2.55
10	2.25	DBIM	420	1.38	0.84
11	0.76	DCIM	240	0.19	0.59
12	0.4	DBIM	54	0.11	0.08
13	1.59	DCIM	51	2.08	0.09
14			44	1.32	0.12
15	0.09	DBIM	11	1.35	0.05
16	0.2	DCIM	32	1.5	0.05
17			80	0.72	0.29



18

Results: Maximum iodo-THM concentrations in treated water in correlation to sodium content of the source water.

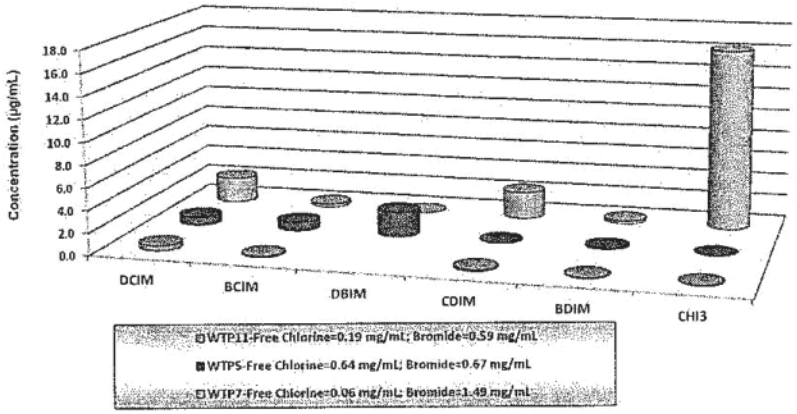






19

Results: Iodo-THM speciation and free chlorine concentration in treated water





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Conclusions

- Na^+ concentrations > 200 mg/L and the presence of ammonium in the source water are good markers for water treatment systems that can be expected to have a high potential for the formation of iodo-THMs.
- These results underline the importance of knowing and taking into consideration the concentration of ammonium in the source water, especially if high sodium concentrations are present (an indication of potential increased iodine presence).
- Iodo-THM total concentration and speciation in such systems are correlated to the free chlorine concentration.
- Iodo-THM speciation in such systems does not appear to be directly correlated to the bromide concentration in the source water.



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Food for thought

- Ammonium is not the only factor that can keep free chlorine concentration low for a part of the contact time. Other factors can play the same role (e.g. high concentration/highly reactive DOC or even iodide in high concentrations, not usually found, but possible).
- In cases of low free chlorine and high iodide in the raw water, there is a considerable proportion of the iodide still remaining in the water after treatment.
- The balance of iodide is oxidized to iodate. Iodate is typically considered to be reduced back to iodide in the human stomach.
- In the case of extremely high iodide concentrations of iodide in the source water, the long term exposure to iodide should be discussed and, maybe, even the chance that not all of it may be reduced in the stomach.



22

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- Data presented here were collected as part of the Targeted Survey of Selected Disinfection By-Products in source waters with high saline concentrations, a 3 year study funded by the Health Canada Monitoring and Surveillance Fund as part of the Chemical Management Plan (CMP).
- The authors would like to thank the members of the Canadian Federal-Provincial-Territorial Committee on Drinking Water for their gracious help in providing data for the site selection and the water plant operators for agreeing to participate in the study.
- The authors would like to thank Ashley Cabecinha and Zhiyun Jin for their technical support.



24

Fishwick, David HLTH:EX

From: Zubel, Marc <Marc.Zubel@fraserhealth.ca>
Sent: January 16, 2014 2:25 PM
To: Fishwick, David HLTH:EX
Cc: XT:HLTH Lem, Marcus
Subject: RE: Health Canada - PFOS + PFOA sampling data

Sorry Dave, but we are not aware of any of our water systems, including MetroVan to have tested for these parameters.

Marc Zubel, P.Eng
Regional Manager
Drinking Water Program
Office: 604-870-7917
Cell: 604-613-0145

From: Fishwick, David HLTH:EX [mailto:David.Fishwick@gov.bc.ca]
Sent: January 16, 2014 10:49 AM
To: [VCH-PHC] Clarkson, Len [STS]; 'Magee, Lynne'; Zubel, Marc; [IHA] Norlin, J Ivor; [NHA] Gaunt, Bruce
Subject: Health Canada - PFOS + PFOA sampling data

Hi Everyone:

The Health Canada Committee on Drinking Water is looking for sampling data on perfluorooctane sulfonate (PFOS) and perfluorooctanic acid (PFOA) from the past 10 years. Are any of you aware of whether your health authority has any sampling data for these chemicals?

Thanks, Dave

David Fishwick | *Drinking Water Manager* | *Ministry of Health* |*1515 Blanshard St 4-2* | *Victoria BC V8W 3C8*

Phone: Please note this is a new number: (250) 952-1110 | *Fax:* (250) 952-1713 | *E-mail:* david.fishwick@gov.bc.ca |
Please consider the environment before printing this email

Fishwick, David HLTH:EX

From: Magee, Lynne <Lynne.Magee@viha.ca>
Sent: January 16, 2014 2:12 PM
To: Fishwick, David HLTH:EX
Subject: RE: Health Canada - PFOS + PFOA sampling data

Hi Dave

I don't believe any of the systems in Island Health are or have sampled for PFOS or PFOA.

Lynne

From: Fishwick, David HLTH:EX [mailto:David.Fishwick@gov.bc.ca]
Sent: Thursday, January 16, 2014 10:49 AM
To: 'Clarkson, Len [STS]'; Magee, Lynne; 'Zubel, Marc'; 'Norlin, J Ivor'; XT:HLTH Gaunt, Bruce
Subject: Health Canada - PFOS + PFOA sampling data

Hi Everyone:

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Phone: Please note this is a new number: (250) 952-1110 | *Fax:* (250) 952-1713 | *E-mail:* david.fishwick@gov.bc.ca |
Please consider the environment before printing this email

Fishwick, David HLTH:EX

From: Gaunt, Bruce <Bruce.Gaunt@northernhealth.ca>
Sent: January 16, 2014 10:58 AM
To: Fishwick, David HLTH:EX
Cc: XT:HLTH Thibault, Greg; Wheeler, Angela; Brown, Crystal; Chen, Dale; Jang, Kira
Subject: RE: Health Canada - PFOS + PFOA sampling data

I seriously doubt that we have any water chemistry data on these compounds in Northern Health.

Bruce Gaunt, B.Sc., C.P.H.I.(C)
Drinking Water Planner
Public Health Protection, Northern Health
4th Floor, 1600 3rd Ave., Prince George, BC V2L 3G6
phone: (250) 645-6239 fax: (250) 565-2144
email: bruce.gaunt@northernhealth.ca

From: Fishwick, David HLTH:EX [mailto:David.Fishwick@gov.bc.ca]
Sent: Thursday, January 16, 2014 10:49 AM
To: 'Clarkson, Len [STS]'; 'Magee, Lynne'; 'Zubel, Marc'; [IHA] Norlin, J Ivor; Gaunt, Bruce
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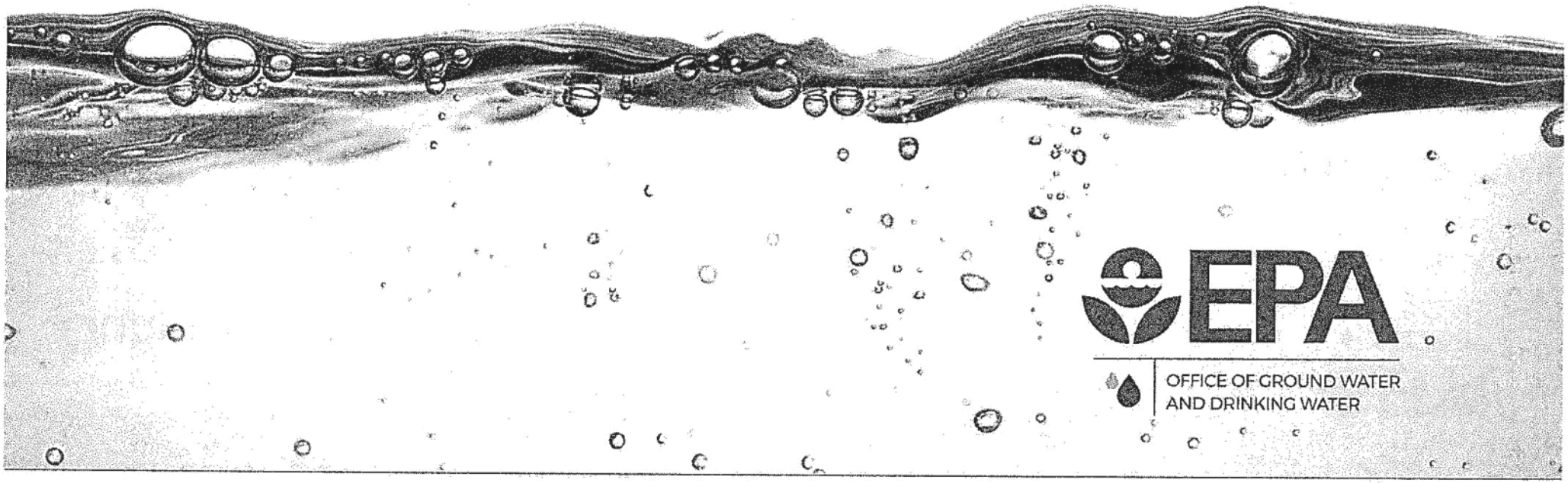
David Fishwick | *Drinking Water Manager* | *Ministry of Health* |*1515 Blanshard St 4-2* | *Victoria BC V8W 3C8*

Phone: Please note this is a new number: (250) 952-1110 | *Fax:* (250) 952-1713 | *E-mail:* david.fishwick@gov.bc.ca |
Please consider the environment before printing this email

EPA Activities on Per- and Polyfluoroalkyl Substances (PFAS)

15th Annual EPA Drinking Water Workshop
| August 28, 2018



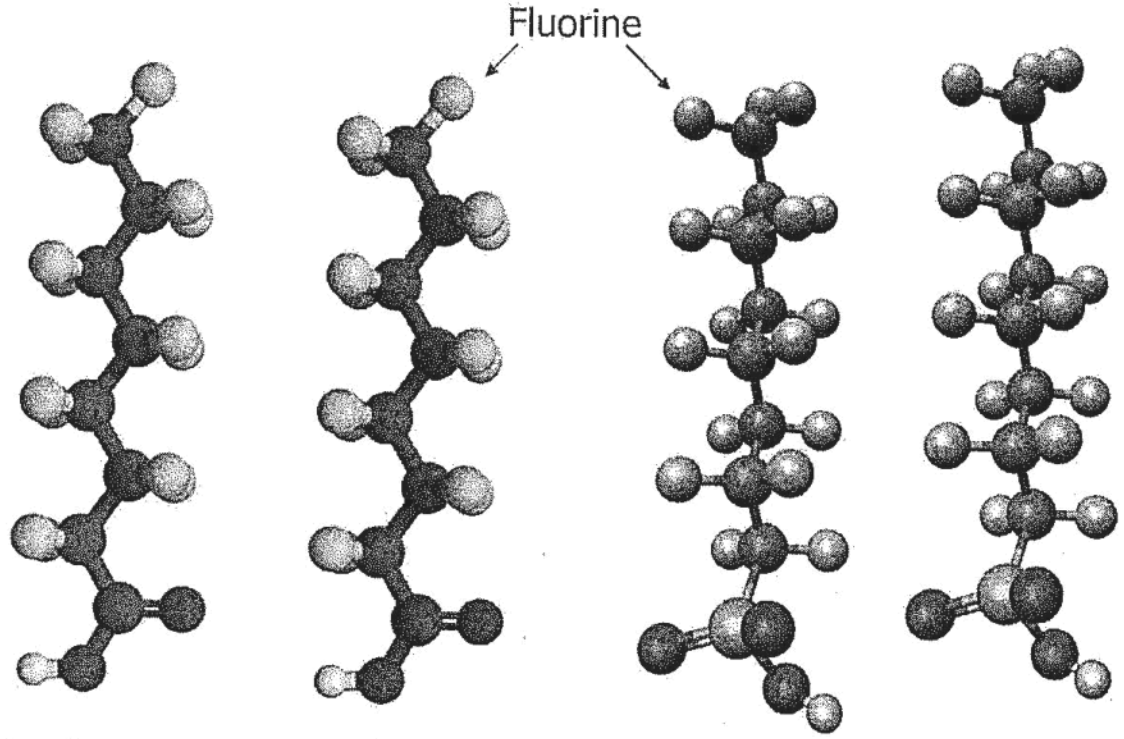
Outline

EPA
OFFICE OF GROUND WATER AND DRINKING WATER

- What are Per- and Polyfluoroalkyl Substances (PFAS)?
- How are PFAS used?
- What is EPA doing about it?

Per- and Polyfluoroalkyl Substances (PFAS)

EPA
OFFICE OF GROUND WATER AND DRINKING WATER



Perfluorooctanoic acid (PFOA)

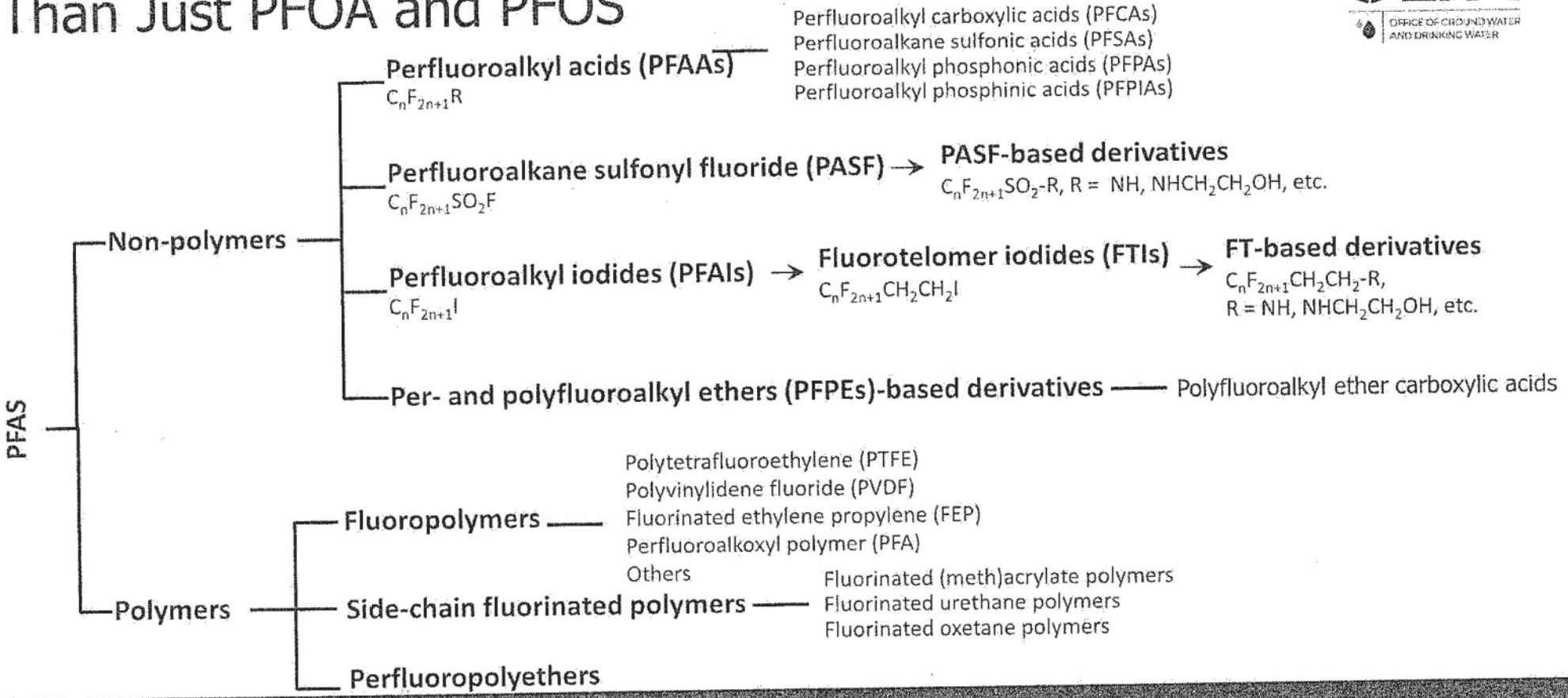
Perfluorooctanesulfonic acid (PFOS)

A class of man-made chemicals

- Chains of carbon (C) atoms surrounded by fluorine (F) atoms
  - Water-repellent (hydrophobic)
  - Stable C-F bond
- Some PFAS include oxygen, hydrogen, sulfur and/or nitrogen atoms, creating a polar end

PFAS: More Than Just PFOA and PFOS

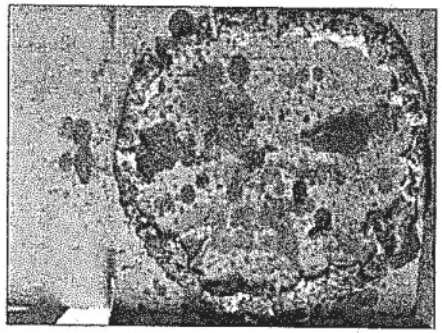
EPA OFFICE OF GROUND WATER AND DRINKING WATER

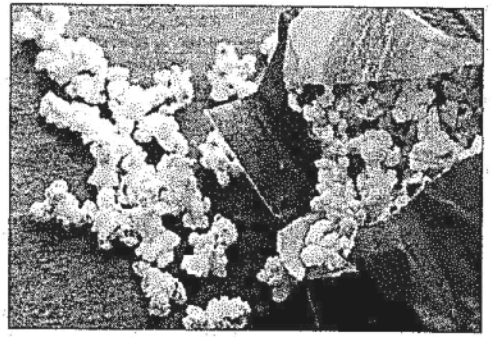


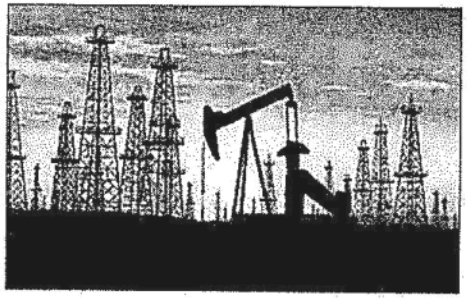
Used in Homes, Businesses & Industry

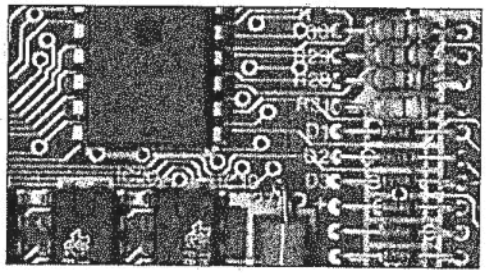
EPA
OFFICE OF GROUND WATER AND DRINKING WATER

- Food contact surfaces such as cookware, pizza boxes, fast food wrappers, popcorn bags, etc.
- Polishes, waxes, and paints
- Stain repellants for carpets, clothing, upholstered furniture, etc.
- Cleaning products
- Dust suppression for chrome plating
- Electronics manufacturing
- Oil and mining for enhanced recovery
- Performance chemicals such as hydraulic fluid, fuel additives, etc.



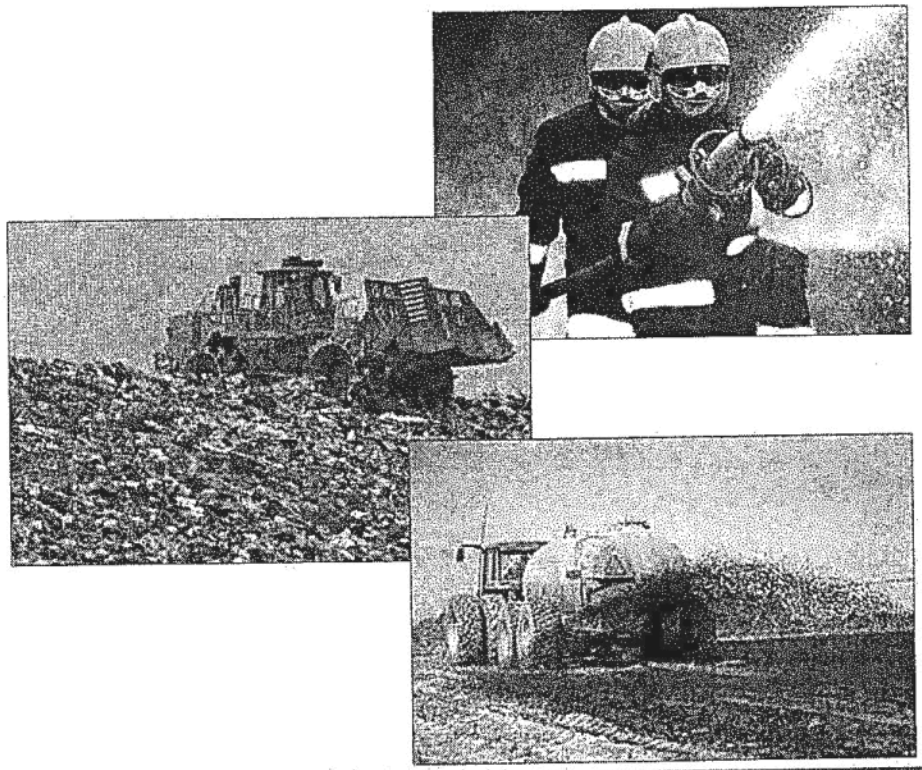






Sources of PFAS in the Environment

EPA
OFFICE OF GROUND WATER AND DRINKING WATER



- Direct release of PFAS or PFAS products into the environment
  - Use of aqueous film forming foam (AFFF) in training and emergency response
  - Release from industrial facility
- Chrome plating and etching facilities
- Landfills and leachates from disposal of consumer and industrial products containing PFAS
- Wastewater treatment effluent and land application of biosolids

Potential Reasons for Concern

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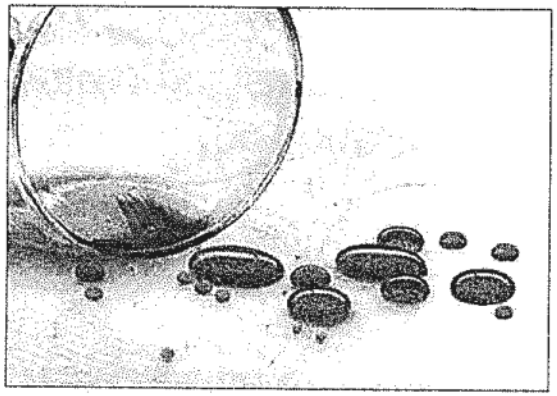
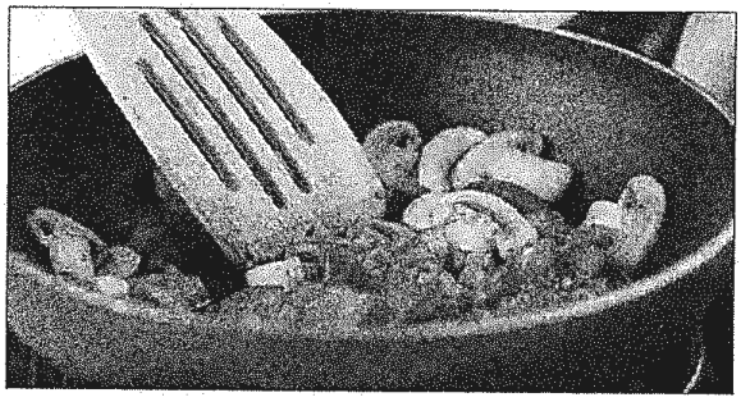
- Known or suspected toxicity
- PFAS and/or breakdown products are persistent in the environment
- Persistence in biota vary greatly across PFASs and species
- Used by a variety of industries
- Found in a variety of consumer products
- Most people have been exposed to PFAS





Dietary Exposure

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- In areas where drinking water has been contaminated, ingestion is a primary route of exposure to PFAS.
- In some states, the consumption of certain types of fish and shellfish caught from contaminated bodies of water has led to public health advisories for some PFAS, particularly PFOS*.
- Some States such as New Jersey, Michigan, and Minnesota have guidelines for PFAS that provisionally recommend maximum frequencies at which specific fish species caught in those water bodies can be eaten with no adverse effects on health.
- Communities living on subsistence economy may not have food habits that reflect those of the general population.

*See summary: EPA 823-N-16-003, August 2016, *Fish and Shellfish Program Newsletter*

EPA's Current PFAS Activities

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- **Issues related to PFAS involve most EPA Programs and Regions**
- **Four broad goals:**
  - Fill data gaps related to human health toxicity to inform public concerns and risk mitigation
  - Establish validated methods for measuring many PFAS in different media
  - Reduce environmental exposures
  - Assure accurate and timely risk communications

EPA's PFAS Coordinating Committee

EPA
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- **EPA announced cross-Agency effort to address PFAS in December 2017**
- **Focus on near-term actions to support states, tribes and local communities, including:**
  - Fill data gaps related to toxicity of additional PFAS compounds
  - Develop analytical methods to expand the capacity for analysis of PFAS compounds in drinking water and other contaminated media
  - Provide treatability information for PFAS compounds in contaminated media
  - Expand tools for proactive risk communication with communities impacted by PFAS compounds
- **EPA's Office of Water is leading these efforts**
  - Includes members from EPA's air, chemicals, land, water, enforcement, and research offices as well as EPA regions to enhance cooperation with partners at the state and local level

Current PFAS Activities in Water

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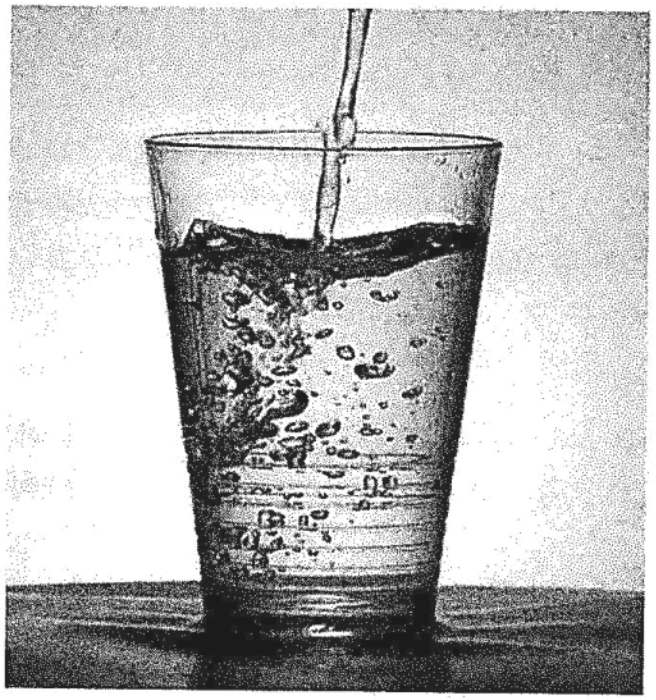
- **Published Drinking Water Health Advisories (HA) in 2016 for PFOA and PFOS**
  - HAs are non-regulatory information for federal, state and local officials to consider when addressing drinking water contamination
  - Identified 0.07 µg/L (70 ppt) as the HA level for PFOA and PFOS combined and provided information about treatment and monitoring



Current PFAS Activities in Water

EPA
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- **Evaluating PFOA and PFOS for regulatory determination under the Safe Drinking Water Act (SDWA)**
  - PFOA and PFOS are on the fourth Contaminant Candidate List (CCL 4) published in November 2016. OW is assessing PFOA and PFOS against the three SDWA regulatory determination criteria
    - *May have an adverse effect on the health of persons*
    - *Is known to occur or there is a substantial likelihood that it will occur in public water systems with a frequency and at levels of public health concern*
    - *In the sole judgment of the Administrator, regulating the contaminant presents a meaningful opportunity for health risk reductions for persons served by public water systems*
  - From 2013 to 2015, EPA collected nationally representative data on the occurrence of six PFAS in public water systems (including PFOA and PFOS)

Current PFAS Activities for Waste Sites

EPA
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- **EPA Federal Facility Superfund Program**
  - Actively engaged PFAS activities at 58 Federal Facility NPL Sites
  - It is anticipated that this number will grow since there are known or suspected contaminations of PFAS at many of the 140 DoD Federal Facility NPL Sites
  - PFAS detections in groundwater range from non-detect (based on analytical method limitations) or slightly exceeding the Drinking Water Health Advisory of 70 ppt (PFOA and PFOS combined) to 2,000,000 ppt
  - Drinking water has been potentially impacted at 22 of these Federal Facility NPL sites

Current PFAS Activities for Waste Sites

EPA
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- **Office of Superfund Remediation and Technology Innovation (OSRTI)**
  - 29 known impacted non-Federal NPL sites
  - 100s of potential NPL sites (e.g., 100 metal plating sites, 300 landfills)

- **Regional Assistance**
  - OLEM offices hold site-specific consultations with EPA Regions on investigations of PFAS contamination
  - OSRTI/FFRRO provides ongoing technical assistance on PFAS issues and also coordinates with the Regions on their needs and priorities on PFAS issues
  - Develop cleanup recommendations for PFOA/PFOS contaminated groundwater

Current PFAS Activities in Chemical Use

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- **PFOA Stewardship Program**
  - Eight companies participated in the program and successfully eliminated production of PFOA
  - Resulted in phase-out of PFOA and related PFAS, including potential PFOA precursors, by these companies by the end of 2015
- **EPA's New Chemicals Program**
  - Since 2000 have reviewed hundreds of pre-market alternatives for PFOA and related chemicals
  - Most were approved with restrictions and data-generation requirements

Current PFAS Activities in Chemical Use

EPA
OFFICE OF GROUND WATER AND DRINKING WATER

- **Significant New Use Rule (SNUR)**
  - Proposed on January 21, 2015, to require manufacturers, importers, and processors of PFOA and related chemicals (including as part of articles), to notify EPA at least 90 days before starting or resuming new uses of these chemicals in any products
  - Notification provides EPA opportunity to conduct risk assessment/management for the new use
- **Gen X**
  - EPA is revising the GenX risk assessment originally done for its pre-market approval, based on data received by the company and other information arising from the NC situation

Current PFAS Research Activities

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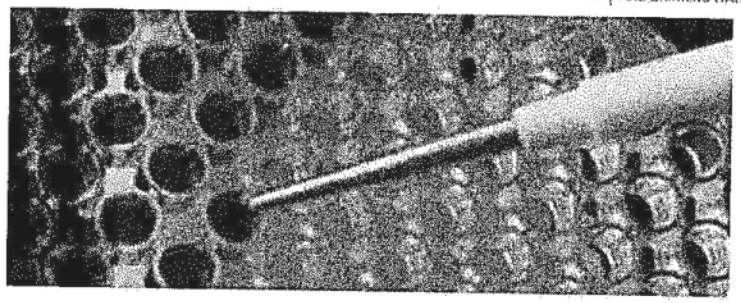
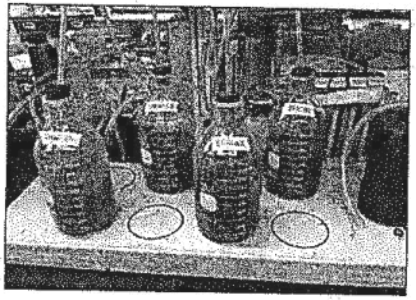
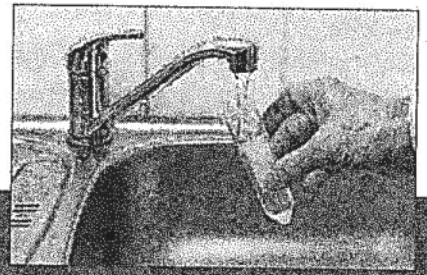
- **Human Health/Toxicity**
  - Understand human health toxicity
  - Inform risk mitigation activities
  - Chemical library and high throughput toxicity testing



- **Analytical Methods**
  - Establish validated methods for measuring PFAS in different environmental media



- **Site Characterization/Exposure**
  - Develop sampling methods to characterize sources and contaminated sites
  - Identify and estimate human exposure to PFAS from different sources
- **Treatment/Remediation**
  - Identify/evaluate methods to reduce PFAS exposures
  - Identify/evaluate methods to treat and remediate drinking water and contaminated sites



EPA's PFAS National Leadership Summit

EPA OFFICE OF GROUND WATER AND DRINKING WATER

- **Included representatives from over 40 states, tribes, and territories; 13 federal agencies; congressional staff; associations; industry groups; and non-governmental organizations.**
- **EPA provided the opportunity for the public to join in a portion of the meeting via streaming online and is asking the public to send written input to EPA**
  - visit https://www.regulations.gov/ enter docket number: OW-2018-0270
- **During EPA's PFAS National Leadership Summit, participants worked together to:**
  - Share information on ongoing efforts to identify PFAS in communities and characterize risks from PFAS
  - Identify specific near-term actions, beyond those already underway, that are needed to address challenges currently facing states and local communities
  - Develop risk communication strategies that will help communities to address public concerns with PFAS

EPA's PFAS Summit/Engagement

EPA OFFICE OF GROUND WATER AND DRINKING WATER

- **EPA announced four actions the Agency will take following the Summit:**
  - EPA will initiate steps to evaluate the need for a maximum contaminant level (MCL) for PFOA and PFOS.
  - EPA is beginning the necessary steps to propose designating PFOA and PFOS as "hazardous substances" through one of the available statutory mechanisms, including potentially CERCLA Section 102.
  - EPA is currently developing groundwater cleanup recommendations for PFOA and PFOS at contaminated sites and will complete this task by fall of this year.
  - EPA is taking action in close collaboration with our federal and state partners to develop toxicity values for GenX and PFBS by this summer.

EPA's PFAS Community Engagement

EPA OFFICE OF GROUND WATER AND DRINKING WATER

- **EPA's Community Engagement**
  - Following the Summit, EPA traveled to communities impacted by PFAS to further engage on ways the agency can best support work occurring at state, local and tribal levels
    - June 25-26: Portsmouth, NH
    - July 25: Horsham, PA
    - August 7-8: Colorado Springs, CO
    - August 14: Fayetteville, NC
    - September 5: Leavenworth, KS

- **EPA plans to develop a PFAS Management Plan using information gained from the Summit, community engagements, and public docket**

Risk Communication

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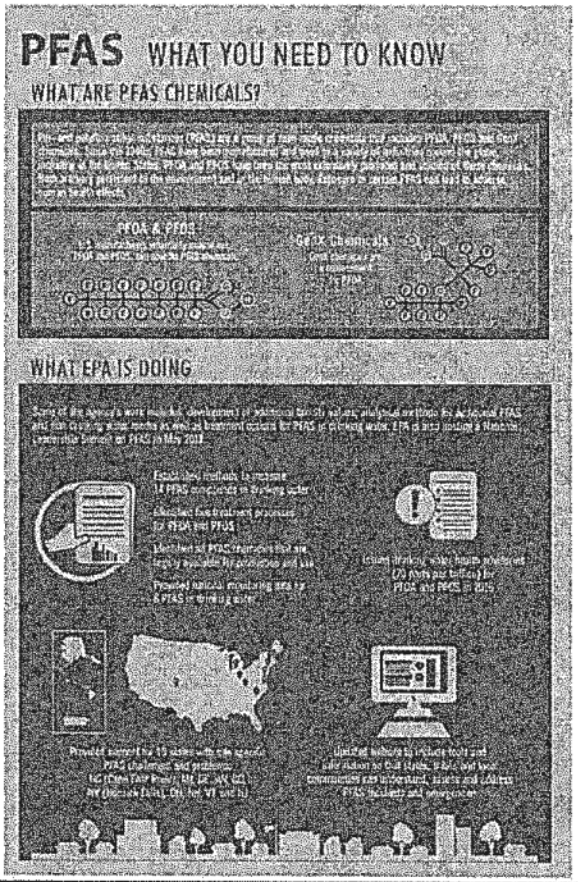
- **Case Studies**
  - In collaboration with ECOS and ASTHO, EPA worked with States to compile case studies of risk communication around PFAS

- **EPA's PFAS Website**
  - One central location for information on PFAS and EPA actions to address PFAS
  - Infographic on PFAS and PFAS factsheet
  - Links to state programs and site-specific resources

- **Risk Communication Strategy**
  - Part of PFAS National Management Plan to help states, tribes, and local officials communicate PFAS issues to the public



Contact

Ryan Albert, PhD
Acting Branch Chief
Standards and Risk Reduction Branch
Office of Ground Water and Drinking Water
Albert.ryan@epa.gov

Input may be submitted to the public docket at:
https://regulations.gov
docket number: OW-2018-0270

Treatment Options for PFAS at a Surface Water Treatment Plant

Carel Vandermeyden, P.E.

Director of Engineering

Cape Fear Public Utility Authority

Stewardship. Sustainability. Service.

Cape Fear Public Utility Authority

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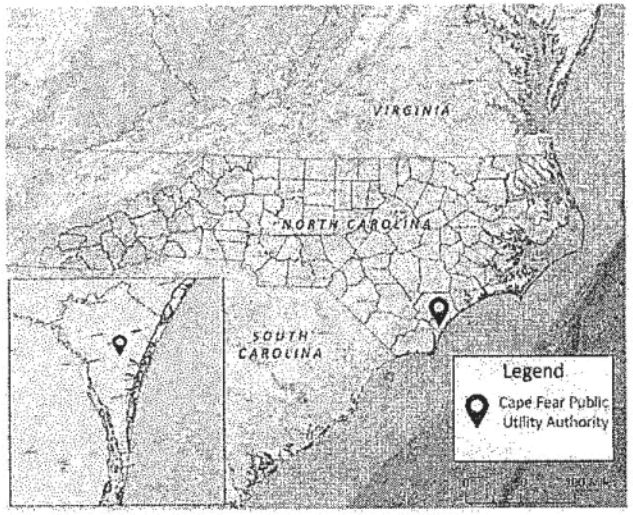
- Located in Wilmington, North Carolina
- 200,000 customers
- Two groundwater systems (7 mgd)
- One surface water system (35 mgd) - Cape Fear River raw water supply
- Per- and Polyfluorinated compounds (PFAS) detected in source and drinking water, including GenX



Existing Sweeney Water Treatment Plant

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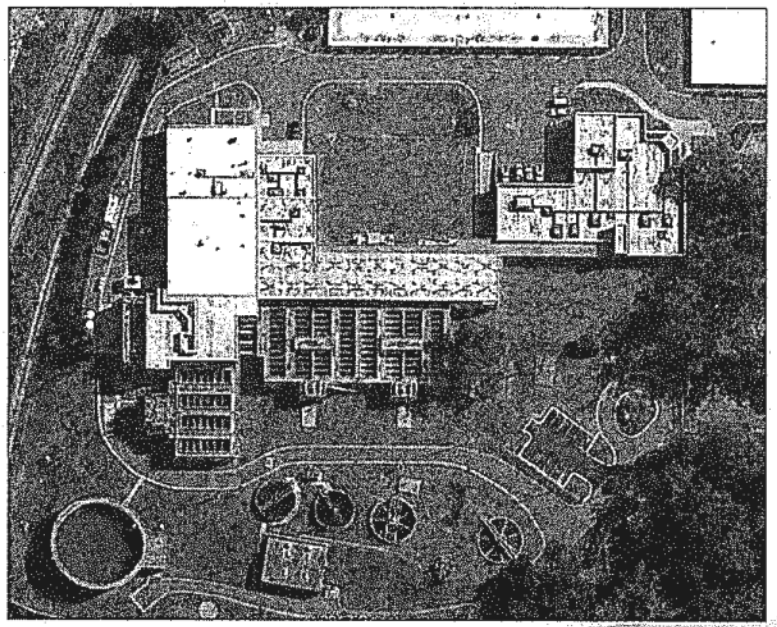
- Conventional treatment
- Raw water ozonation
- Pre-filter ozonation
- Biofiltration with GAC
- UV
- Chlorine disinfection
- More advanced treatment methods required for PFAS



Per-Fluorinated Compounds in the Cape Fear River

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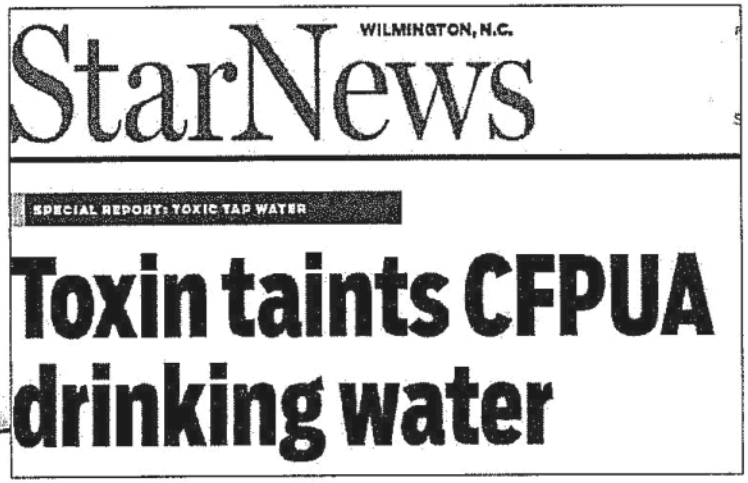
- June 2017 - *Wilmington StarNews* article on the presence of GenX in the Cape Fear River and in CFPUA drinking water.
- GenX is only about 12% of all PFCs quantified in source water.
- No MCL for GenX or other PFAS.
- NC-DHHS issued a preliminary health advisory level of 140 ppt for GenX.
- Customer Concerns:
  - Thousands of calls from concerned customers.
  - Numerous public forums, media interviews. Weekly press releases by CFPUA.
  - 9,800 people are members of the on-line "North Carolina Stop GenX in our Water" community organizing group.
  - Awareness of emerging contaminants has decreased consumer confidence in drinking water.
  - Utilities (ratepayers) should not bear the cost to address source water contamination by others.


WILMINGTON, N.C.

StarNews

SPECIAL REPORT: TOXIC TAP WATER

Toxin taints CFPUA drinking water

CFPUA Action on PFAS — 14 Months

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- For over one year, we have worked on the issue of GenX and other PFAS compounds.
- We have:
  - Worked with UNCW to identify new compounds.
  - Worked with NCDEQ to remain informed on regulatory actions.
  - Worked with NCDHHS to understand the health impacts.
  - Continuously monitored levels of PFAS in drinking water.
  - Taken legal action against Chemours.
  - Set up free water stations in our groundwater areas.
  - Conducted a full pilot study to investigate treatment options.
  - Removed 50 million gallons from the Aquifer Storage and Recovery site.
  - Participated in interviews, forums and industry conferences to share our experience with regulators, utilities and the public.

Testing for PFAS in CFPUA Service Areas

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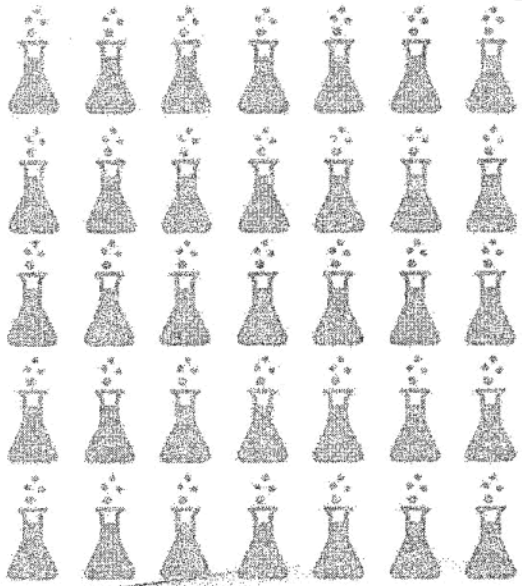


CFPUA regularly monitors for 45 different PFAS

8 PFAS do not have testing standards and results must be estimated

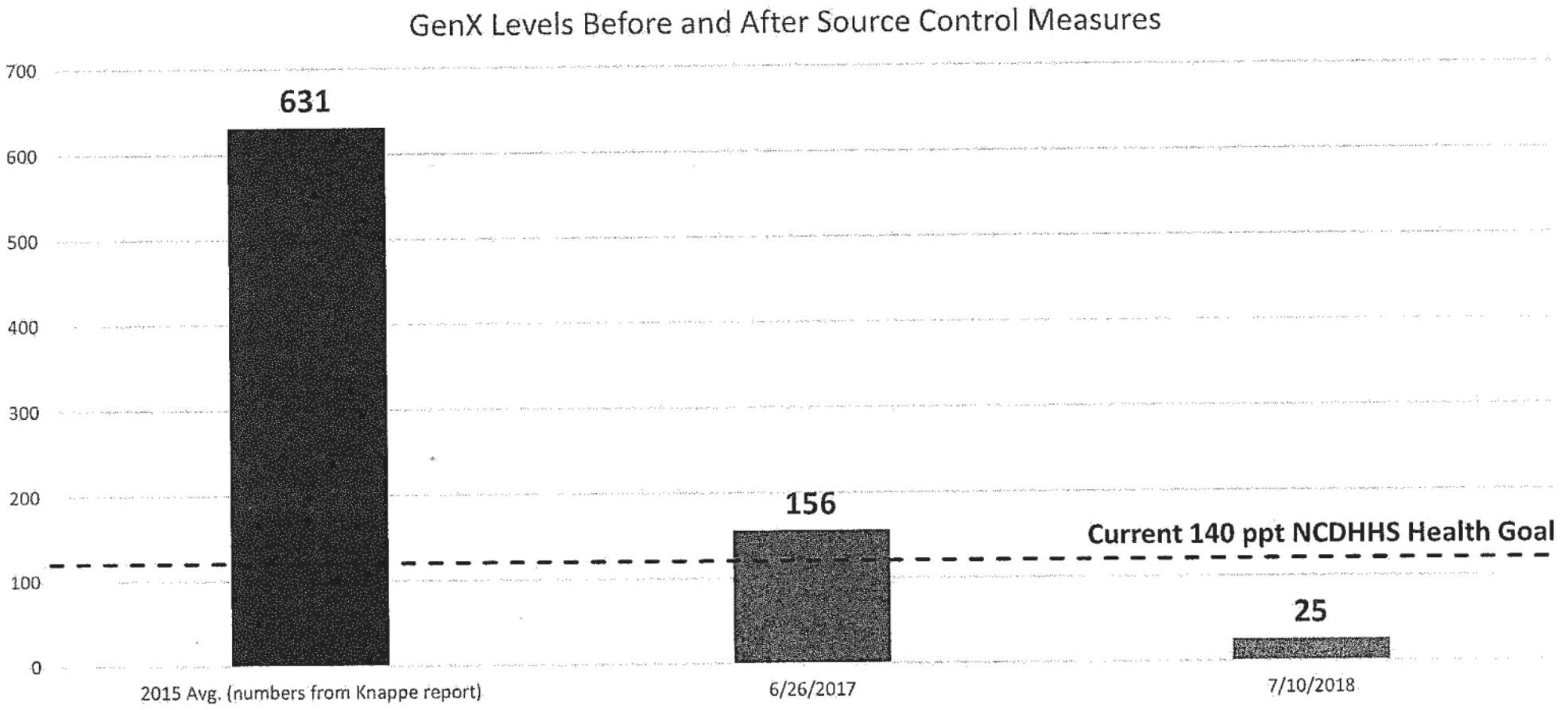
37 PFAS have testing standards

Of the **37** PFAS that have testing standards,

27 are typically at non-detectable limits and

10 are consistently detected

Source Control Shows Success with GenX



GenX Levels are Down, Other PFAS Remain: Is Remediation Needed?

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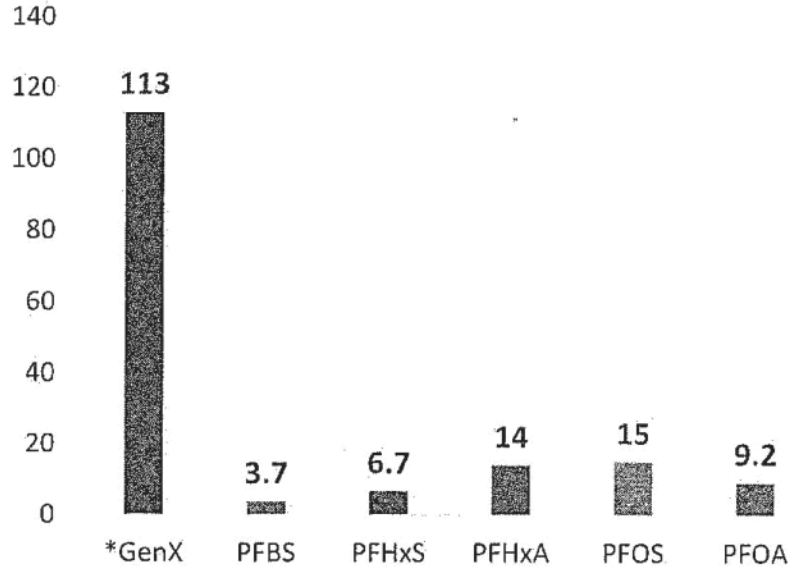
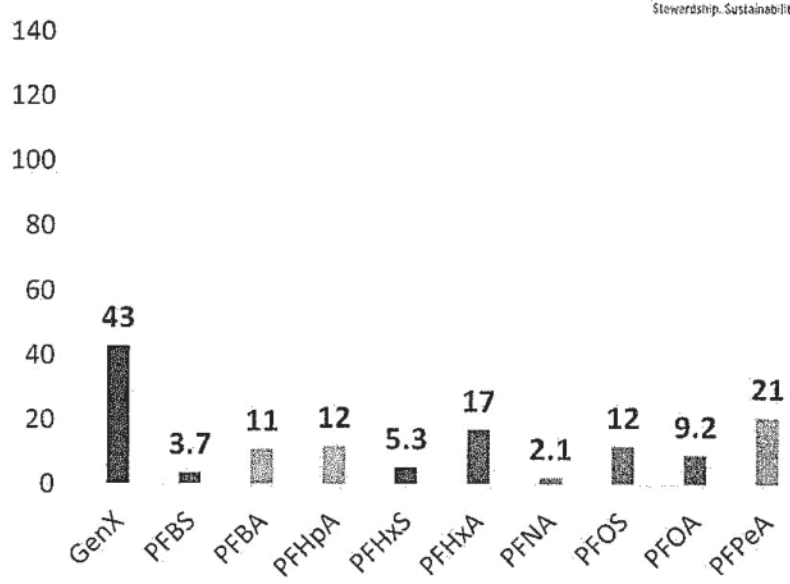


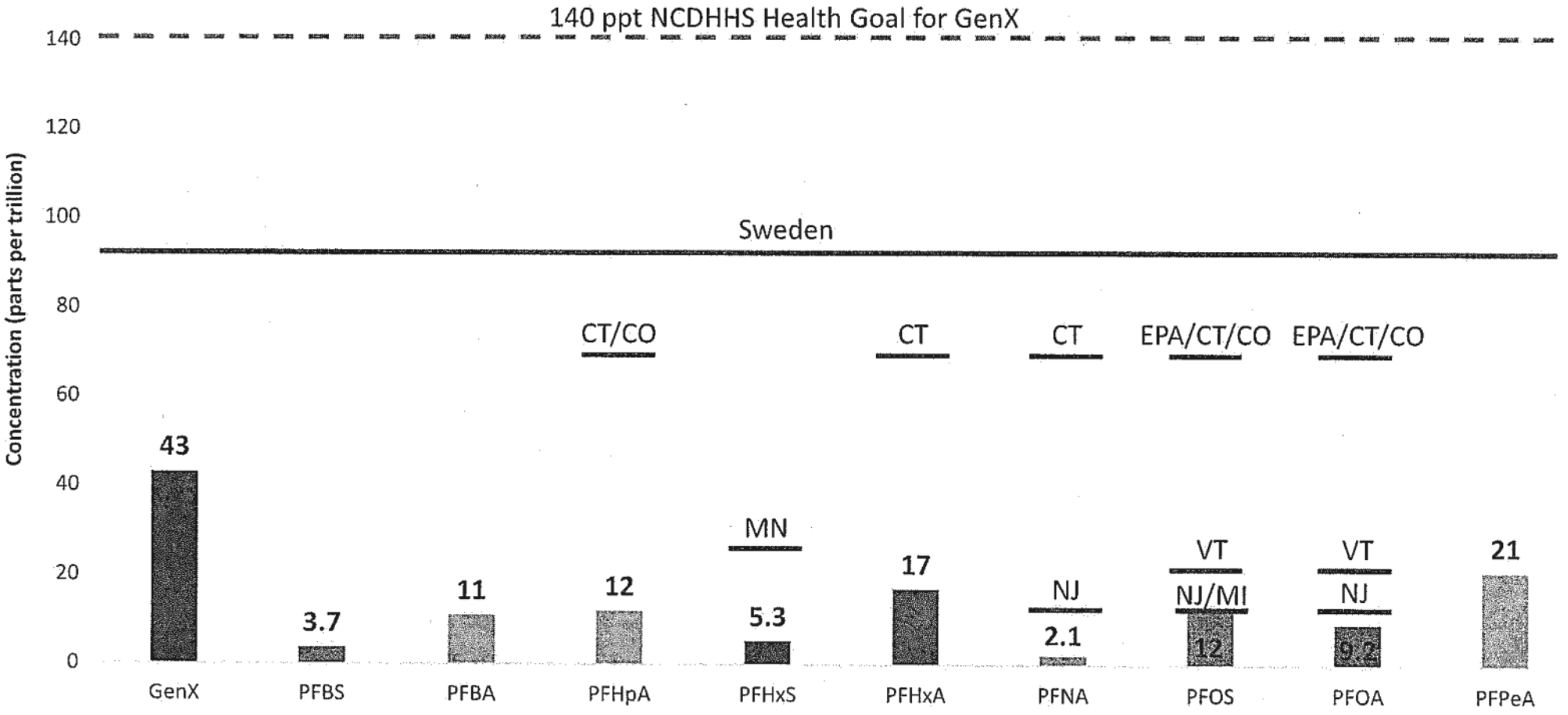
July 2017



June 2018

*Levels of compounds are measured in parts per trillion (ppt)

What Are the Existing Health Goals for PFAS?



Completed Pilot Testing to Select PFAS Treatment Options

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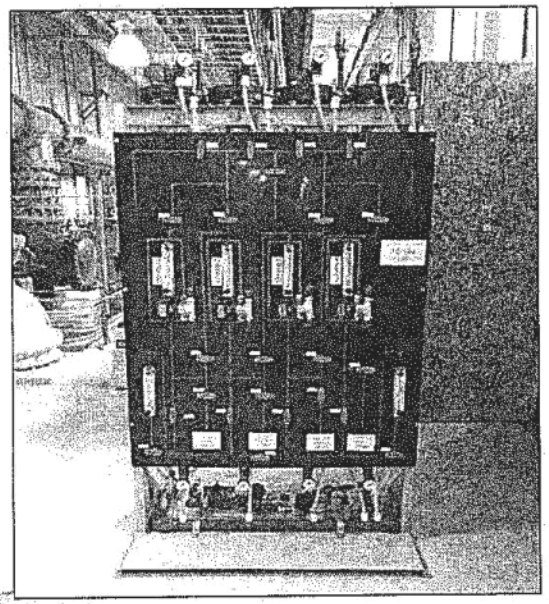

- Technologies Considered
  - Granular Activated Carbon
  - Ion Exchange
  - Reverse Osmosis
- Operational Strategies
- Criteria for Full Scale Design
- Considerations
  - Removal Rates
  - Environmental Impacts
  - Rate Impacts and Cost
- Secondary benefits if implemented for PFAS treatment

Life of GAC Media: When Do GenX and the "Connecticut Five" PFAS Begin to Breakthrough?

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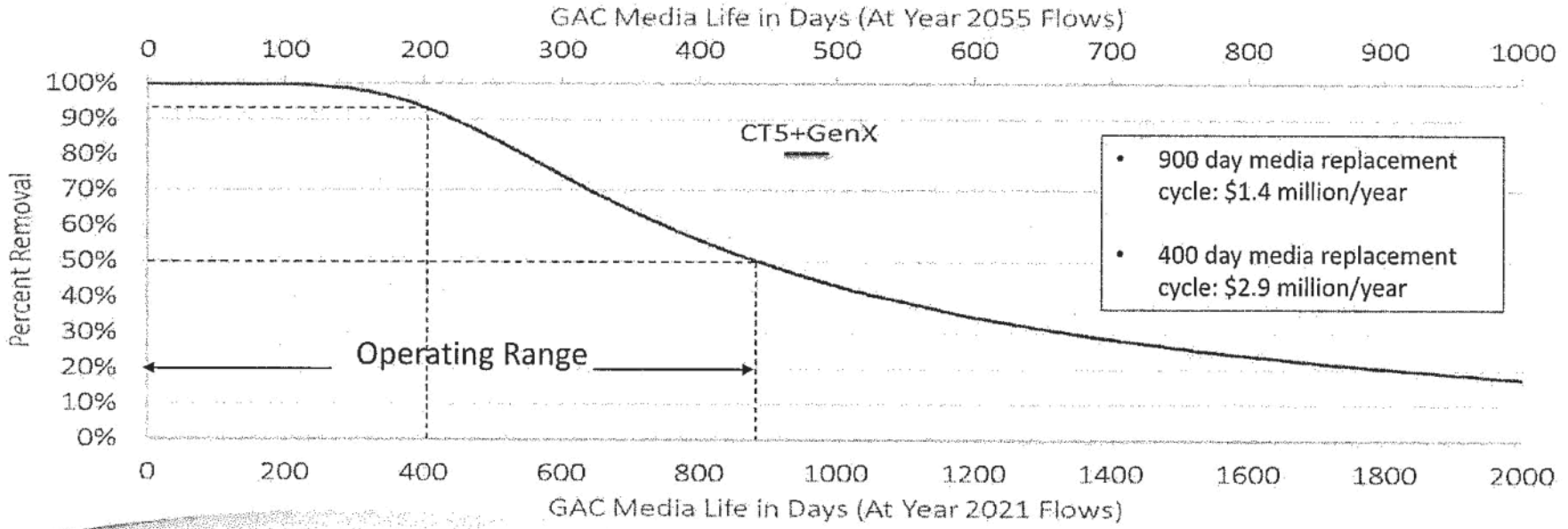
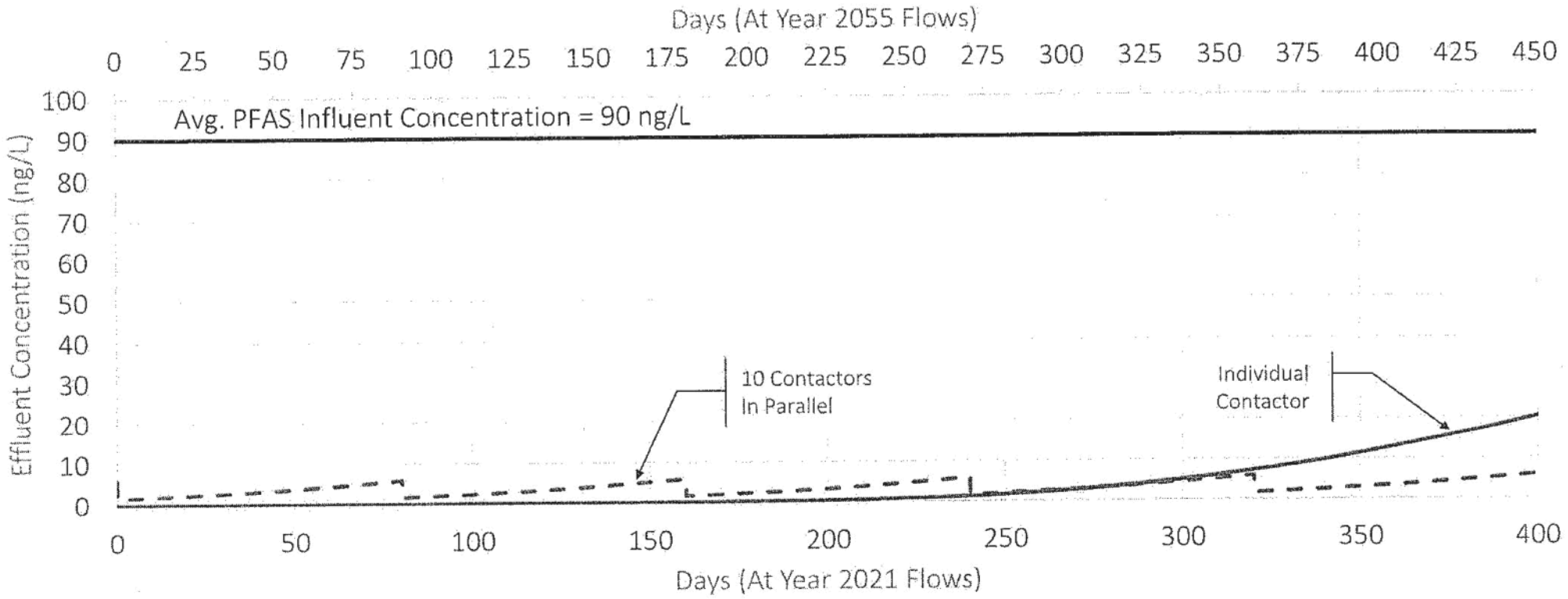


GAC Replacement Cycle at 400 Days Runtime



IX Performance

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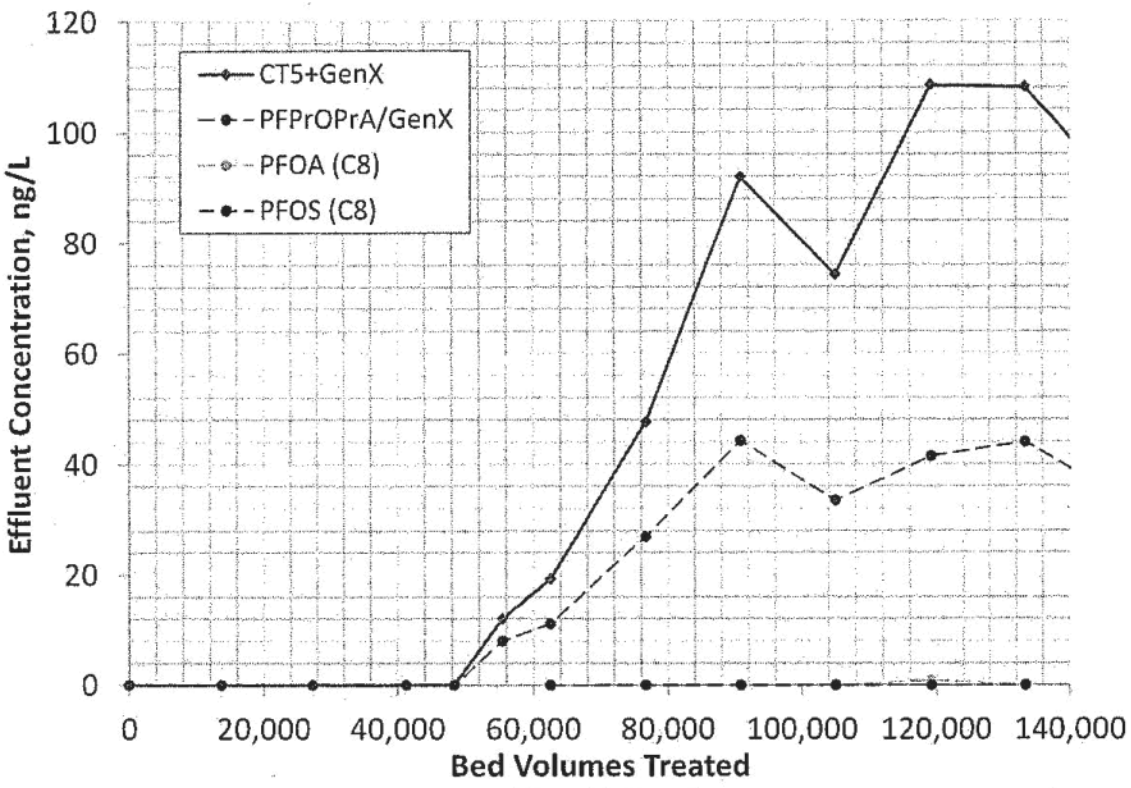

GAC is still the best treatment solution for the Sweeney WTP AND allows for transition to IX to address possible more stringent limits in the future.

Considerations for Selecting Treatment Process

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Consideration	Granular Activated Carbon	Ion Exchange	Reverse Osmosis
Treatment			
• PFAS removal	Effective towards PFAS reduction	Effective towards PFAS reduction	Provides broad removal of all varieties of PFAS
• Flexibility	Can be modified to adapt to changes in regulations	Limited flexibility.	Limited flexibility because RO provides broad removal
• Corrosion control	Consistent with existing corrosion control program	Consistent with existing corrosion control program	Requires additional treatment to prevent lead and copper corrosion
Environmental	Removes PFAS from the environment	Filter media must be disposed of, cannot be destructed like carbon	Creates waste stream with concentrated PFAS levels to Cape Fear River (NPDES Permit required)

Financial Comparison to Reduce PFAS at the Sweeney Water Treatment Plant

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	GAC	RO
Capital Costs	$46,000,000	$150,000,000
Annual Operating Costs	$2,900,000	$4,700,000
Lifecycle Net Present Value	$215,000,000	$504,000,000

Conceptual GAC Facility

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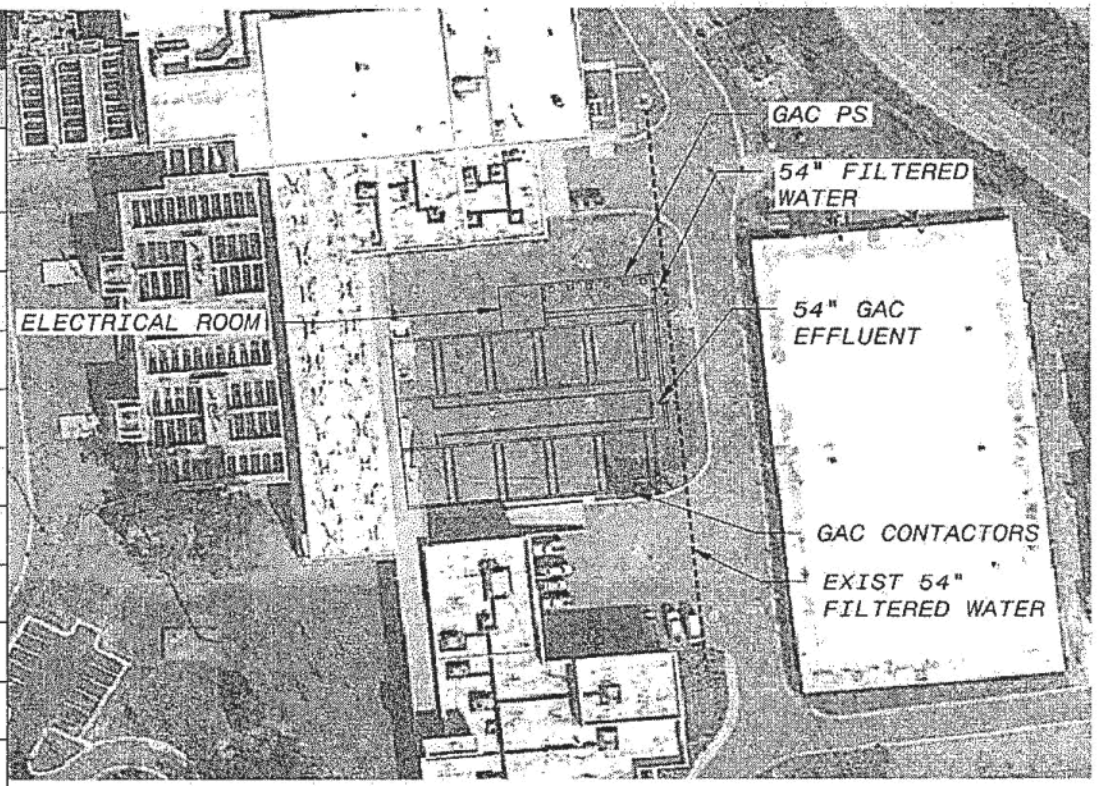
Deep Bed GAC Contactors Design Summary	
Contactors	
Quantity	10
Design Flow Rate, gpm (ea)	3,056
Type	Concrete Basin
Length (ea), ft	22
Width (ea), ft	37.6
Area (ea), sf	827
Media, per contactor	
Bed Depth, ft	10
Max Loading Rate, gpm/ft2	4.1
EBCT, min	20
Bed Volume, cf (ea)	8,272



Customer Survey: Significant Trends

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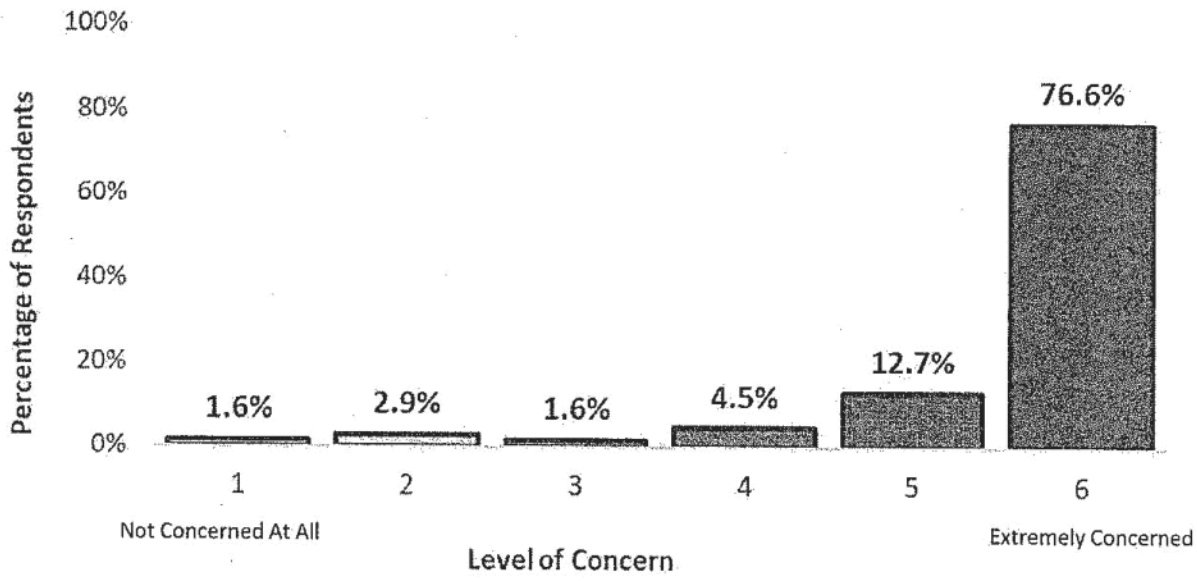
Question 4:

On a scale of one to six, rate your level of concern about GenX.

- 89.3% of respondents are concerned or extremely concerned about GenX.



Customer Survey: Significant Trends

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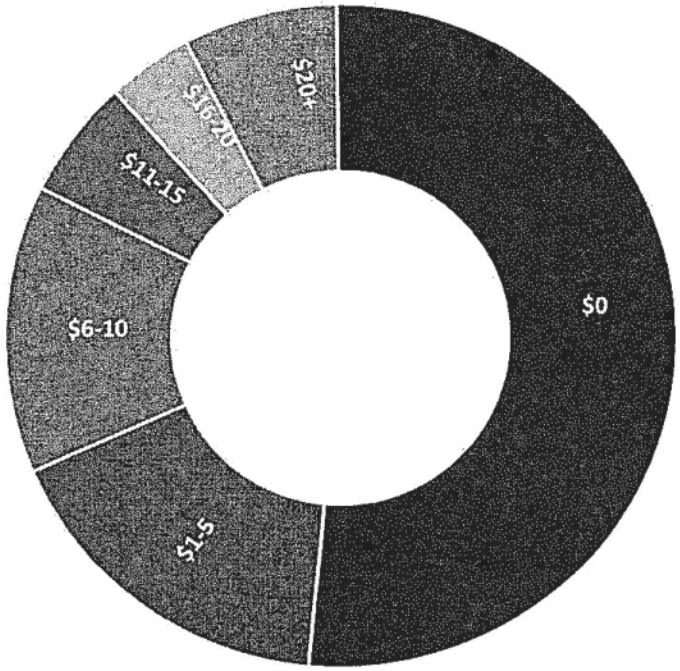
Question 6:

Select the most (per bimonthly bill) that you are willing to pay in addition to your current charges for the CFPUA plant upgrade.

- Of customers that responded "$0":
  - 83% responded that they were extremely concerned about GenX.
  - Many believe Chemours should be the organization that pays for an upgrade.
- 48.45% of respondents were willing to pay between $1-$20+ per bi-monthly bill for a Sweeney upgrade.



Customer Survey: What Are We Doing Well?

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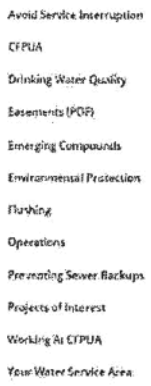
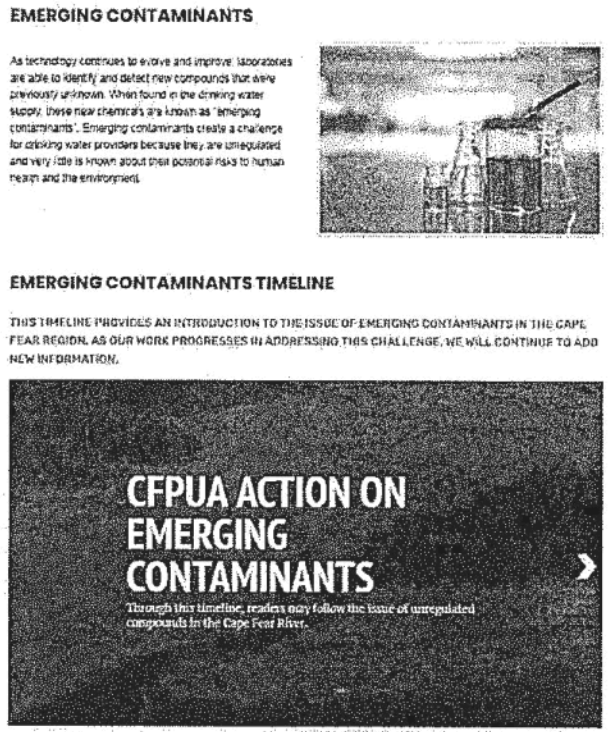
- **CFPUA website was listed as a popular source of information on this issue.**
  - Staff should continue to use the website, social media and our Notify Me! Program to release regular and accessible information to customers and the media regarding PFAS compounds and other water quality issues.

- **Customers overwhelmingly agree with our decision to take legal action.**
  - CFPUA should continue to update the public, when possible, on our litigation against Chemours





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Questions?

DEPARTMENT OF HEALTH



Minnesota Perspective on PFAS

David Rindal

Drinking Water Protection Section | Minnesota Department of Health

August 28, 2018

Overview

Topic

Background

Minnesota's PFAS Timeline

Heath-Based Values

Response

Lessons Learned

Minnesota Means Water



"Minnesota" is Dakota Sioux for "sky tinted water".

Minnesota has **90,000 miles** of shoreline, more than California, Florida, and Hawaii combined.

Minnesota Agency Water Roles

Quality

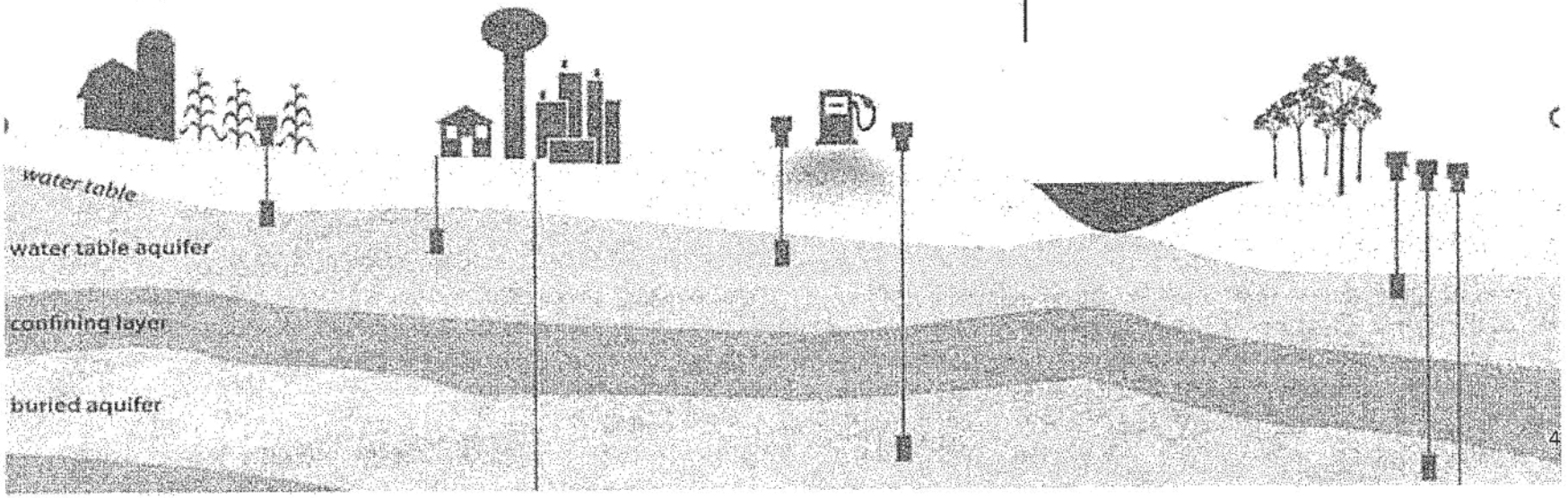
MDA
Pesticides
Fertilizer

MDH
Public water supply
Well construction
Health risk assessment

MPCA
Chemical releases
Industrial pollutants

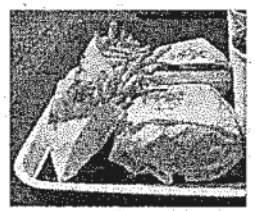
Quantity

DNR
Water supply/availability
Natural resource/ecosystem functions



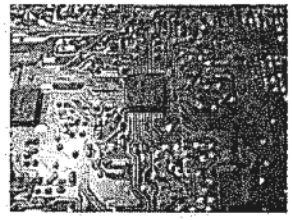
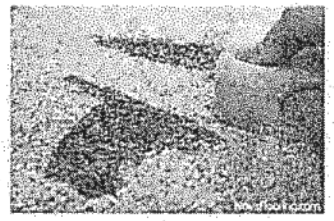
Per- and Polyfluoroalkyl Substances (PFAS)

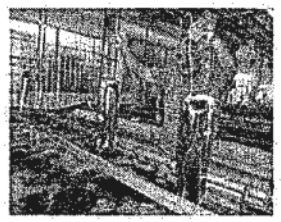
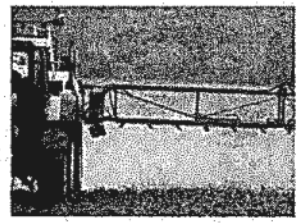
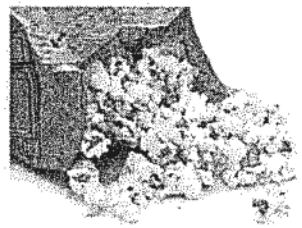





- Family of many synthetic chemicals
- Developed and used since the 1940s
  - resist heat, stains, water, oil, grease
  - "non-stick"
- Production increased rapidly in the 1970s
- Persist in the environment, found everywhere

Source: open access images – bing.com

Timeline of PFAS Activities in Minnesota

1950s – 1970s	• Disposal of PFAS occurred at sites in Washington County • No regulations at time of disposal
2000	• 3M began phase-out of PFOA/PFOS products
2002	• 3M informed State of MN of detections of PFOA/PFOS in production wells in Washington County • MDH releases first health-based guidance values

Timeline of PFAS Activities in Minnesota

2002 – 2004	• Groundwater monitoring revealed PFOA/PFOS contamination at additional sites
2007	• MPCA and 3M agree to consent order
2010	• MN Attorney General files natural resource damage lawsuit on behalf of state

Timeline of PFAS Activities in Minnesota

2014

- PFAS discovered at site in Bemidji, MN
  - UCMR3 monitoring
  - Source: firefighting foam (AFFF)

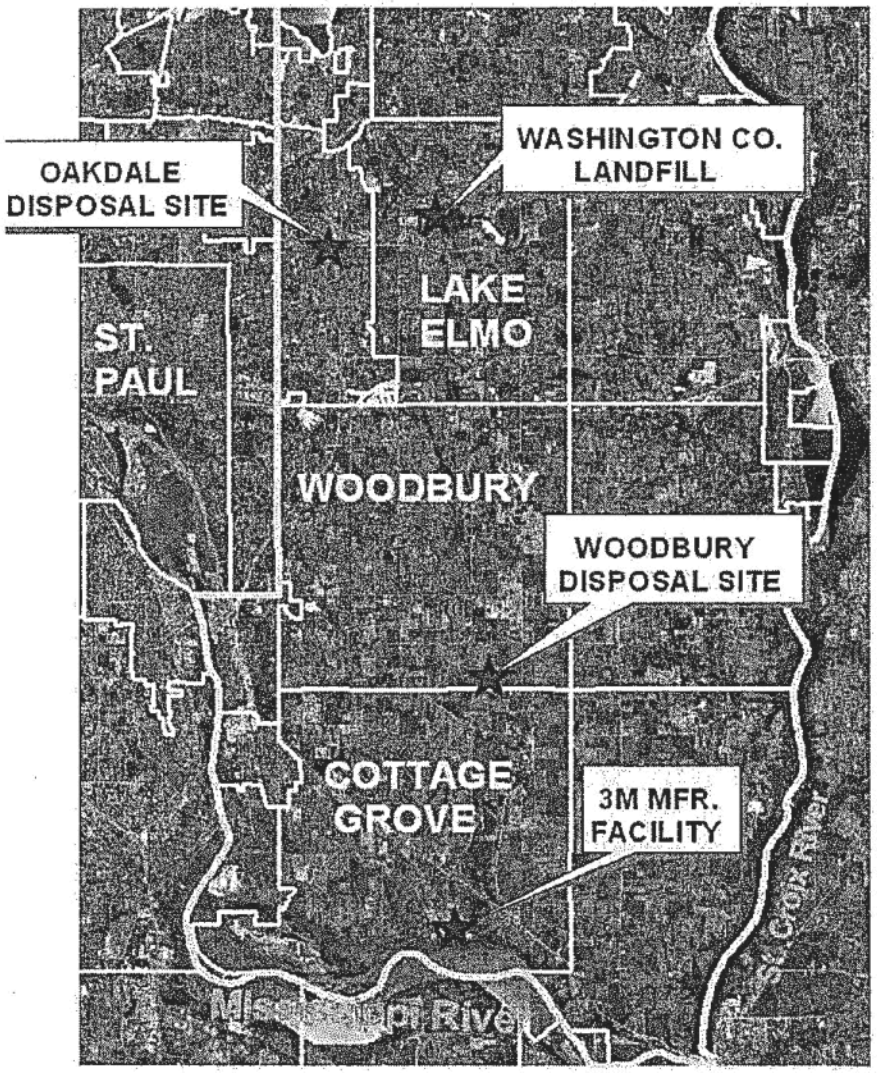
2018

- Settlement between 3M and State of Minnesota

2005 - present

- Public water system monitoring and treatment
- Private well monitoring and treatment

PFAS in Minnesota



LOCATION OF 3M SITES IN WASHINGTON CO., MINNESOTA

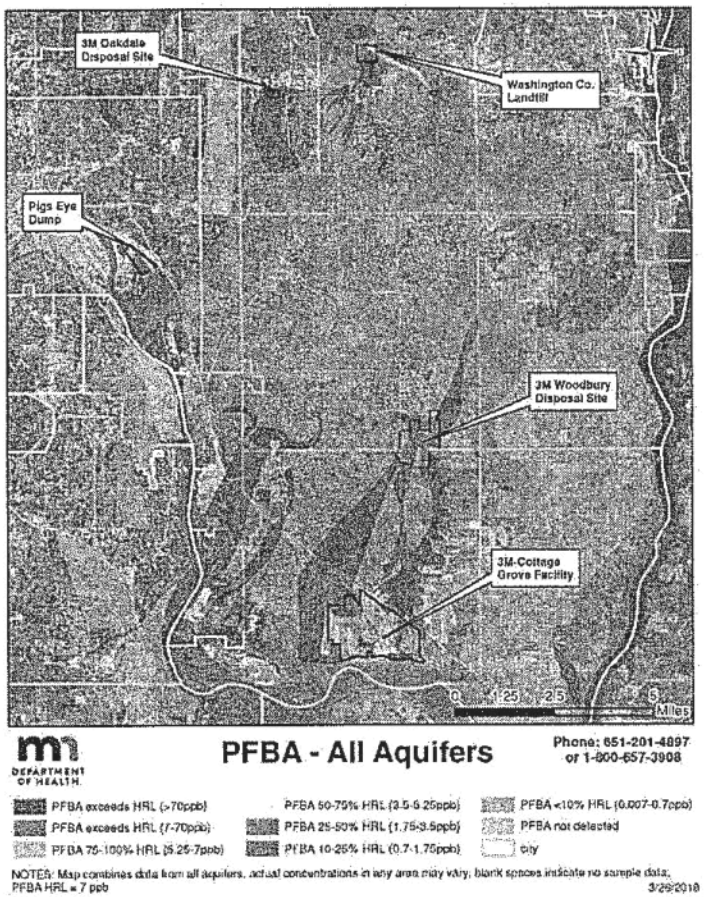


- 4 PFAS disposal sites in Washington County
  - 3M made PFAS at its Cottage Grove facility in the early 1950s
  - PFOA was a primary product; some PFOS, PFBA and other PFAS
- Additional site in Bemidji
  - Firefighting foam

9

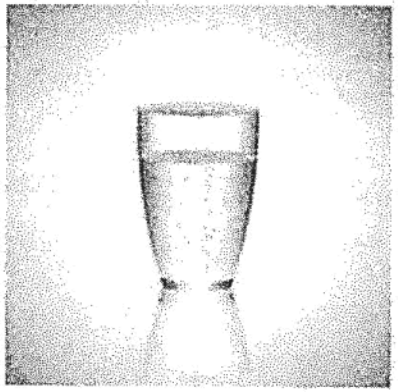
Extremely Large "Co-Mingled" Plumes

- Over 130 sq. mi. in Washington County
  - 4 major aquifers
  - 8 municipal systems & >1,800 private wells
  - Much larger than predicted by models
- PFBA most widespread
  - More PFBA in source areas
  - More mobile
- Movement of PFAS affected by several factors



MDH Health-Based Guidance Values

PFOS: 0.027 ppb	PFOA: 0.035 ppb
PFBA: 7 ppb	PFBS: 2/3 ppb



- The concentration of a chemical (or a mixture of chemicals) that is likely to pose little or no risk to human health
- Based on potential health impacts; do not consider cost and technology of prevention and/or treatment
- Non-regulatory
- Protective for susceptible & highly exposed populations
- Protective for tap water used for drinking, cooking, showering, and other uses
- Based on animal studies showing slight liver and thyroid effects (adults) and immune system and developmental effects (infants/children)

Health Risk Index

- MDH evaluates the combined effects of PFAS: Health Risk Index (HRI)
  - Allows us to account for differing levels of toxicity in similar chemicals
  - HRI > 1 indicates a possible health risk from given chemical group
- Cumulative – additivity assessment of chemicals with similar health endpoints (e.g. liver)

$$\frac{[\text{PFBA}]}{\text{PFBA HBG}} + \frac{[\text{PFBS}]}{\text{PFBS HBG}} + \frac{[\text{PFHxS}]}{\text{PFHxS HBG*}} + \frac{[\text{PFOA}]}{\text{PFOA HBG}} + \frac{[\text{PFOS}]}{\text{PFOS HBG}} = \text{Health Risk Index}$$

where [PFAS] = detected PFAS drinking water concentration in HBG units

*Currently using PFOS as an interim substitute

Risk Assessment and Water Guidance

PFAS	Health Endpoints
PFBA	Liver and thyroid
PFBS	Developmental, female reproductive system, kidney, and thyroid [blood system & liver no longer listed]
PFHxS	(see PFOS)
PFOA	Developmental, liver, immune system, and kidney
PFOS	Developmental, liver, immune system, and thyroid

	PFOA	PFOS	PFBA	PFBS	PFHxS
2002	7	1			
2006	1	0.6	1		
2007	0.5	0.3	7		
2009	0.3	0.3	7	7	
2013	0.3	0.3	7	7	0.3
2016	0.07	0.07	7	7	0.07
2017	0.035	0.027	7	3/2	0.027
2018-19		under review			under review

More information can be found at: *http://www.health.state.mn.us/divs/eh/risk/guidance/gw/table.html*

Response

DEPARTMENT OF HEALTH

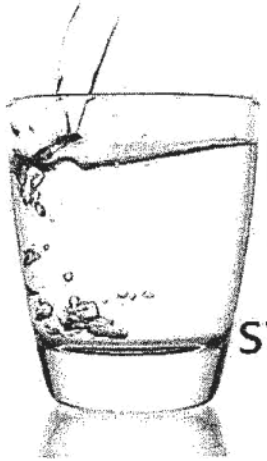
MINNESOTA POLLUTION CONTROL AGENCY

DEPARTMENT OF NATURAL RESOURCES

Washington County | MN

A great place to live, work, and play...today and tomorrow!

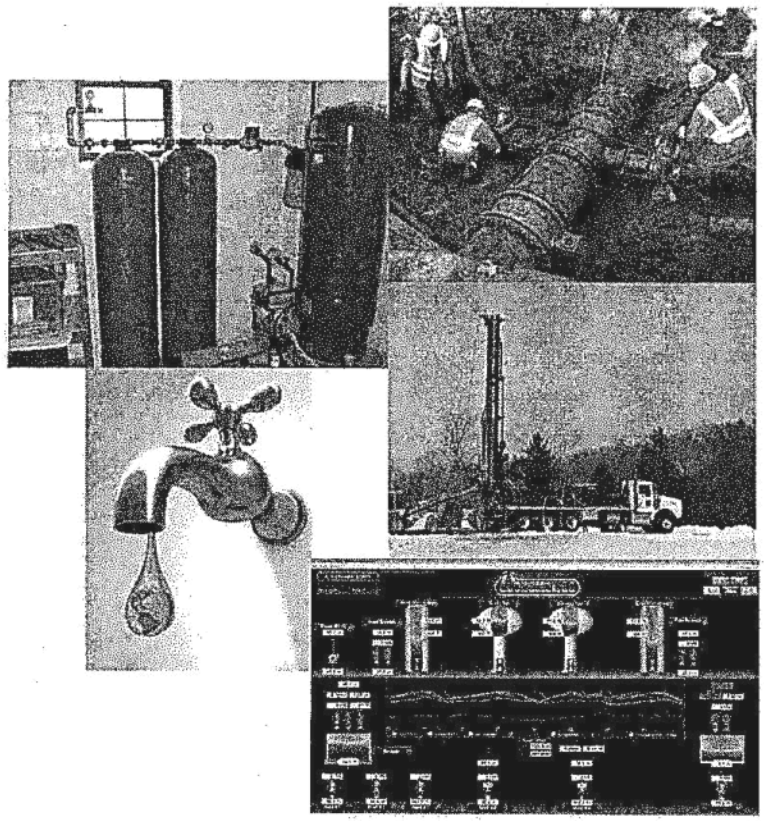
3M



Public water systems

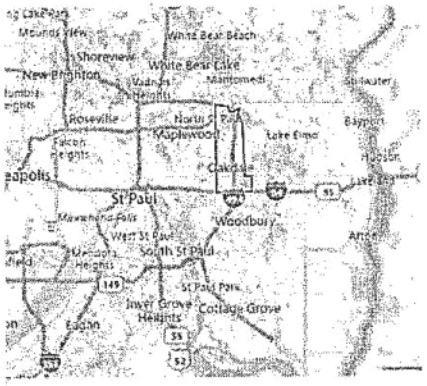
Response Options

- Regional interconnect
- New treatment facilities
- New wells
- Water conservation; limit use of contaminated wells
- Adapted blending scheme
- Others?



Oakdale (27,973)

- 9 wells; PFAS exceeds MDH health-based guidance value in 7 wells
- PFAS concentrations
  - highest in the state for community systems
  - PFOA: 0.440 ppb maximum
  - PFOS: 0.610 ppb maximum
- Treatment (GAC) installed in 2006 for 2 wells; carbon replaced annually
- Primarily rely on 2 treated wells and 2 "clean" wells for water supply
- Video: http://bit.ly/2rWs9z5

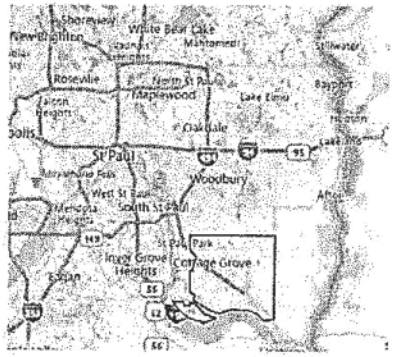


CITY OF OAKDALE MINNESOTA

16

Cottage Grove (36,492)

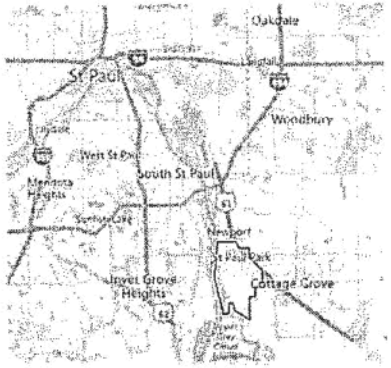
- 12 wells; PFAS exceeds MDH health-based guidance in 8 wells
- PFAS concentrations
  - PFOA: 0.066 ppb maximum
- Impacted when health-based guidance values lowered
- Installed GAC treatment on 2 wells in 2017
- Directly blend 7 wells to manage concentrations
- Temporary watering ban in 2017 after receiving health advisory letter from MDH and prior to treatment



Cottage Grove
Where Pride and Prosperity Meet

Saint Paul Park (5,519)

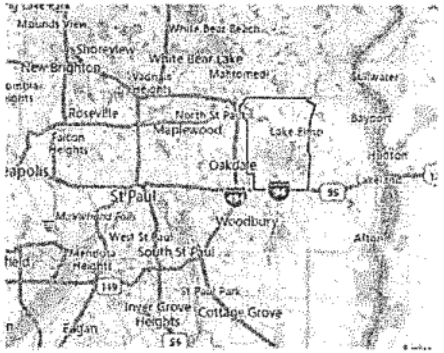
- 3 wells; PFAS exceeds MDH health-based guidance in 2 wells
- PFAS concentrations
  - PFOA: 0.043 ppb maximum
- Impacted when health-based guidance values lowered
- Want to install treatment on wells
- Managing pumping so clean well is used the most, and enforcing watering restrictions



City of Saint Paul Park
on the mississippi
Est. 1887

Lake Elmo (4,878 / 8,069)

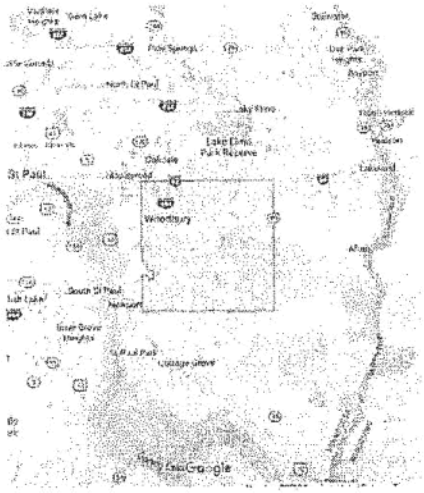
- Has 3 wells with 1 exceeding MDH health-based guidance values
- PFAS concentrations: no PFOS, 46 ppt PFOA
- Impacted when health-based guidance values lowered
- Many private wells in the city
- Options for new well limited by water quantity issues



THE CITY OF LAKE ELMO

Woodbury (69,245)

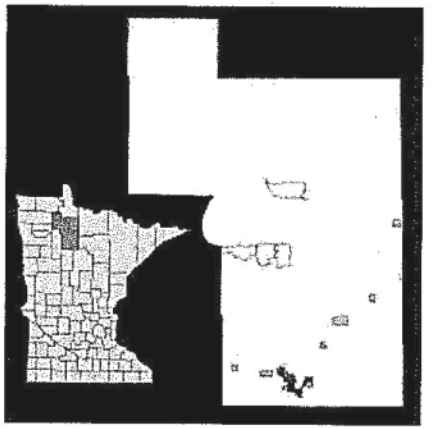
- 19 wells; PFAS exceeds MDH health-based guidance values in 5 wells
- PFAS concentrations
  - PFBA: 0.41 ppb maximum (all wells)
  - PFHxS: 0.07 ppb maximum (1 well)
  - PFOA: 0.049 ppb maximum (8 wells)
  - PFOS: 0.026 ppb maximum (3 wells)
- Primarily rely on wells that meet MDH health-based values for water supply. Others are used only seasonally to meet peak demand.



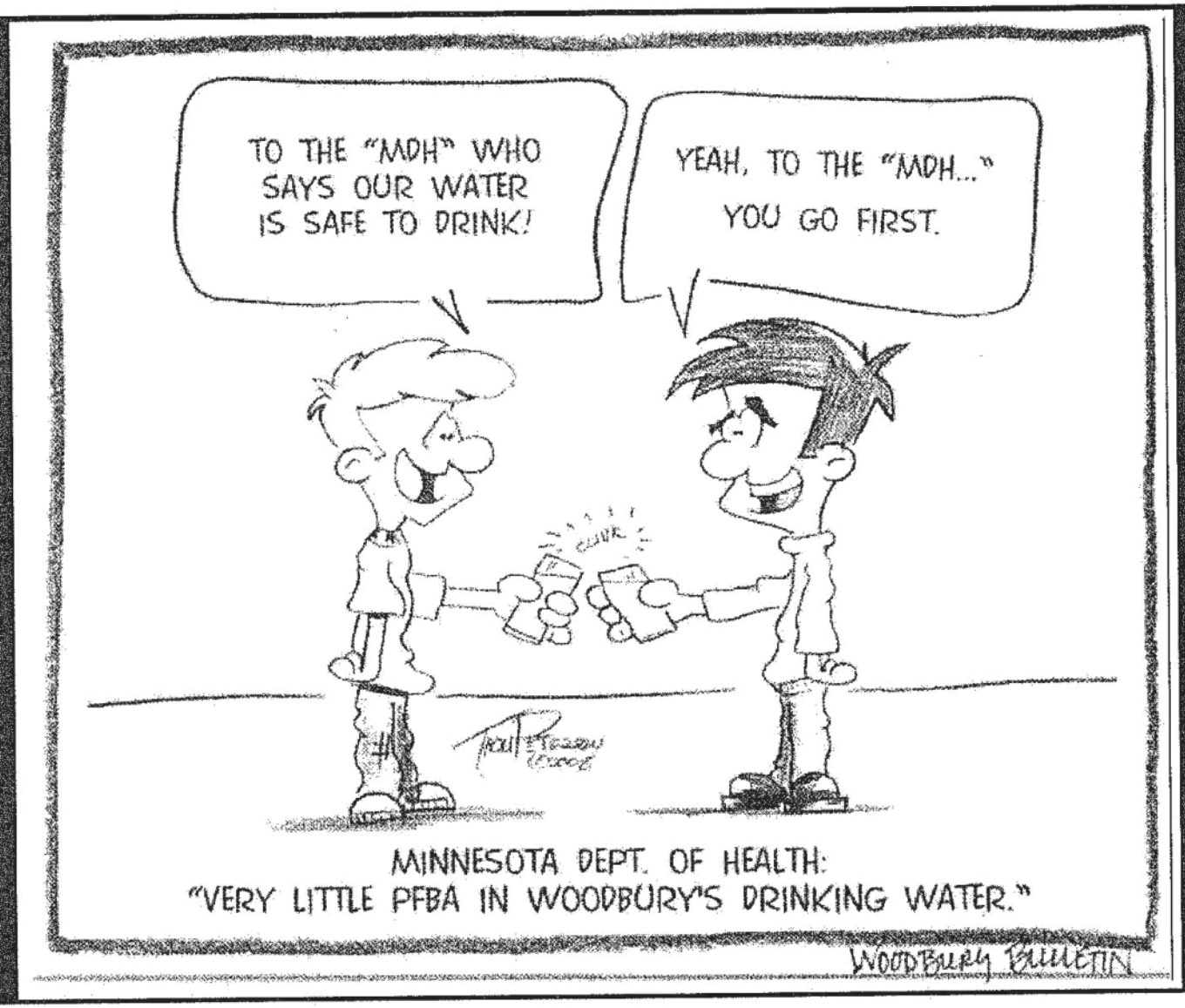
CITY OF Woodbury MINNESOTA

Bemidji (14,942)

- 5 wells; PFAS exceeds MDH health-based guidance values in 4 wells
- PFAS concentrations
  - PFOS: 0.37 ppb maximum
  - PFHxS: 0.57 ppb maximum
- Source: firefighting foam – city responsible party
- PFAS discovered through UCMR3 monitoring
- All affected wells within city's airport and go to combined discharge – currently using 2 by blending
- Evaluating options – wells, treatment, new well field



Bemidji
First City On The Mississippi


TO THE "MDH" WHO SAYS OUR WATER IS SAFE TO DRINK!
YEAH, TO THE "MDH..." YOU GO FIRST.
MINNESOTA DEPT. OF HEALTH:
"VERY LITTLE PFBA IN WOODBURY'S DRINKING WATER."
WOODBURY BULLETIN

Other PFAS Activities

- Private well sampling
  - >1,500 private wells sampled since 2003
  - >800 drinking water advisories issued
    - Homeowners provided in-home treatment funded by 3M
- Water filtration testing
  - GAC, RO, POU
- Fish consumption advice
  - Recommendations on how often to eat fish from certain waters



DEPARTMENT OF HEALTH

Water Treatment Using Carbon Filters (GAC)



ATTENTION ANGLERS

Avoid eating fish from this lake.

Lake Elmo, Washington County

High levels of contaminants (PFOS) have been found in fish. New information will be available within the next year and may change this advice.

May 2018

Questions or comments can be directed to:
MN Department of Health
(500) 657-3908

DNR AREA FISHERIES OFFICE
1200 Warner Road
St. Paul, MN 55106
(651) 259-5831

MINNESOTA
Department of Natural Resources
Department of Health

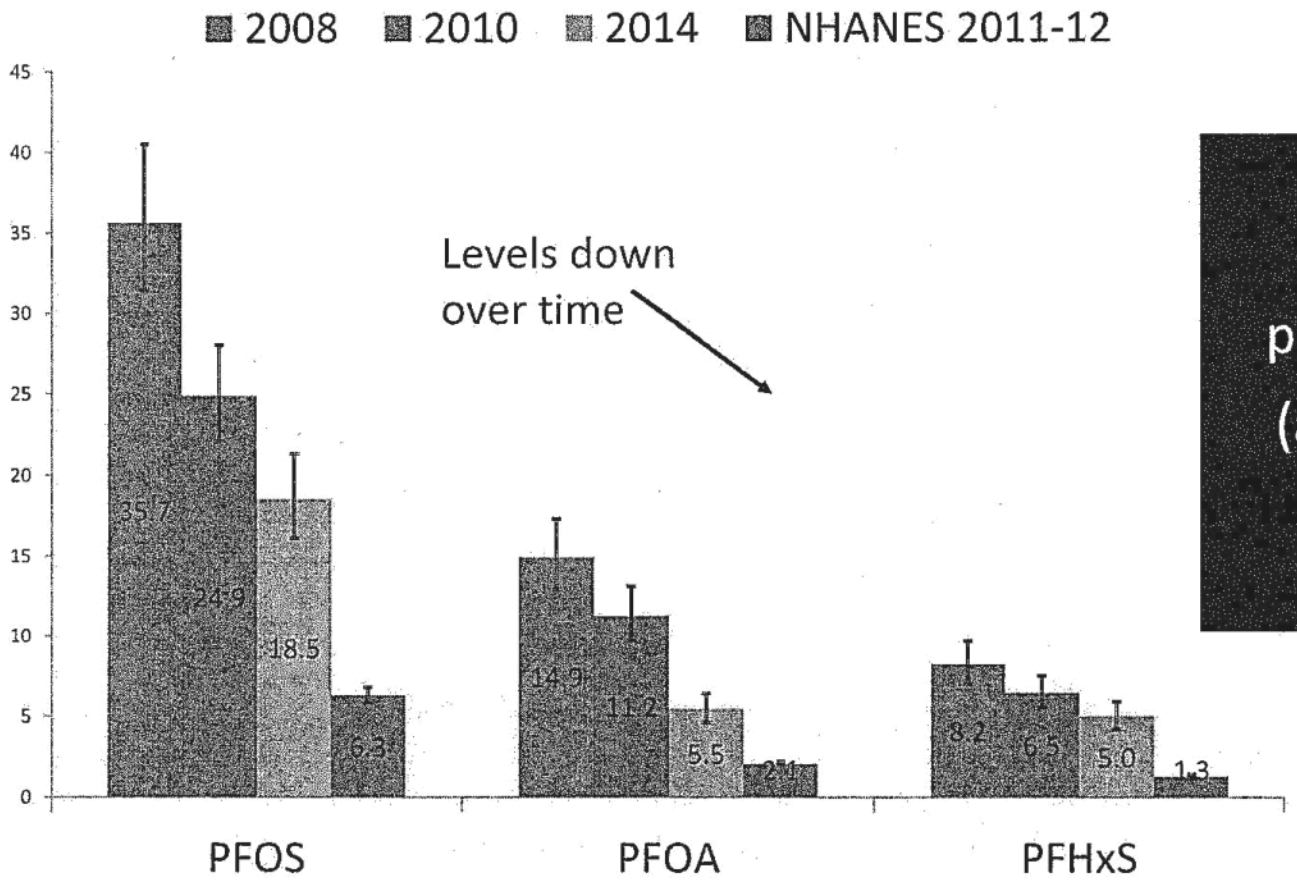
Other PFAS Activities

- PFAS in Homes and Gardens study (2010)
  - Tested water, soil, produce and dust at 20 homes with PFAS in water
  - PFBA found in 98% of produce
  - No health risks of concern when considering all exposures
- Biomonitoring
  - Measured blood levels of 8 PFAS chemicals in two groups of East Metro residents
  - Levels were highest in those who lived longest in the area before treatment was installed





Biomonitoring During Response



PFAS decreased in blood of people drinking treated water

(average concentrations still above national averages)

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2018 Minnesota 3M PFC Settlement

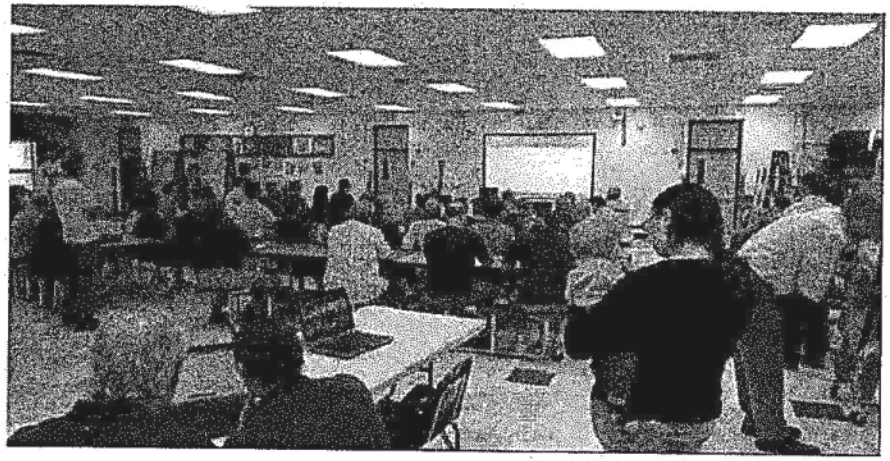
- $850 million grant to the state
- Trustees: Minnesota Pollution Control Agency and Minnesota Department of Natural Resources
- $720 million to provide long-term solutions for:
  - Clean and sustainable drinking water
  - Restoration and enhancement of natural resources
- Expectations for community participation
- Preserves 3M's obligations under the 2007 consent order

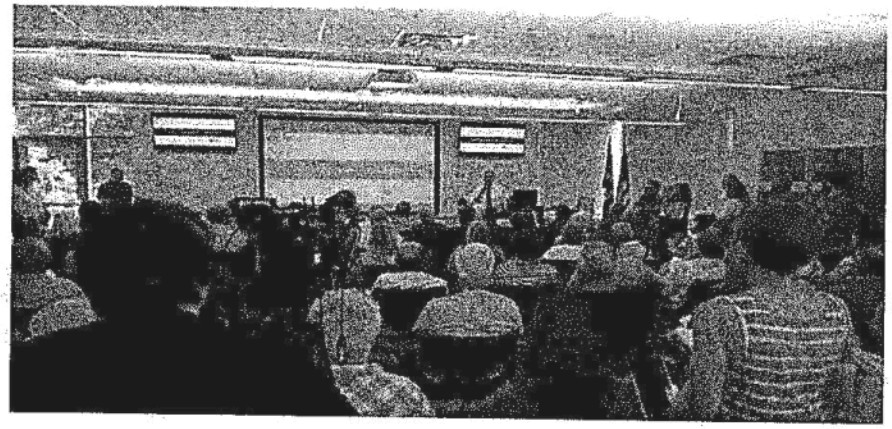


More information can be found at *https://3msettlement.state.mn.us*

Lessons Learned

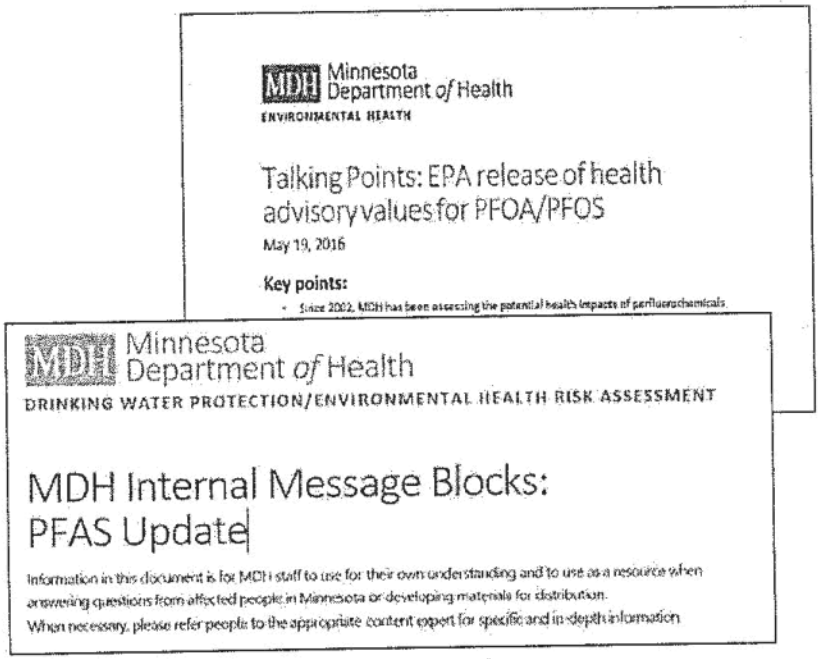
- Lack of federal maximum contaminant limit (MCL) means state has to decide how to act and regulate
- Collaboration is important
  - Different parties may have different priorities
- Politics can quickly change a timeline





Lessons Learned

- Communication is key
  - Must include the public, regulators, regulated parties, and elected officials
  - Not an emergency; PFAS health effects are based on a lifetime of exposure
  - State government regulators must give cities time to prepare a response
  - Unique risk communication challenges



MDH Minnesota Department of Health
ENVIRONMENTAL HEALTH

Talking Points: EPA release of health advisory values for PFOA/PFOS

May 19, 2016

Key points:

- Since 2002, MDH has been assessing the potential health impacts of perfluorochemicals

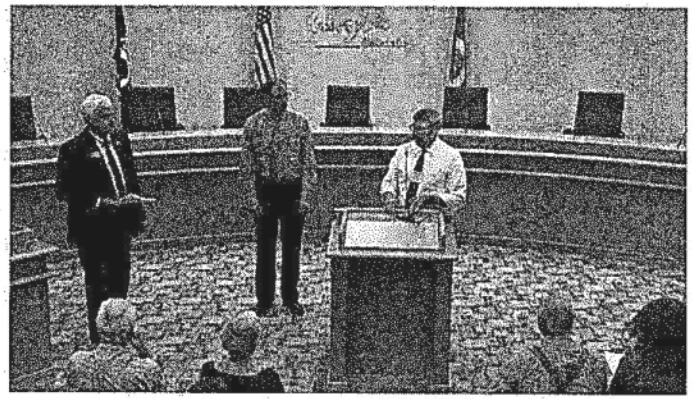
MDH Minnesota Department of Health
DRINKING WATER PROTECTION/ENVIRONMENTAL HEALTH RISK ASSESSMENT

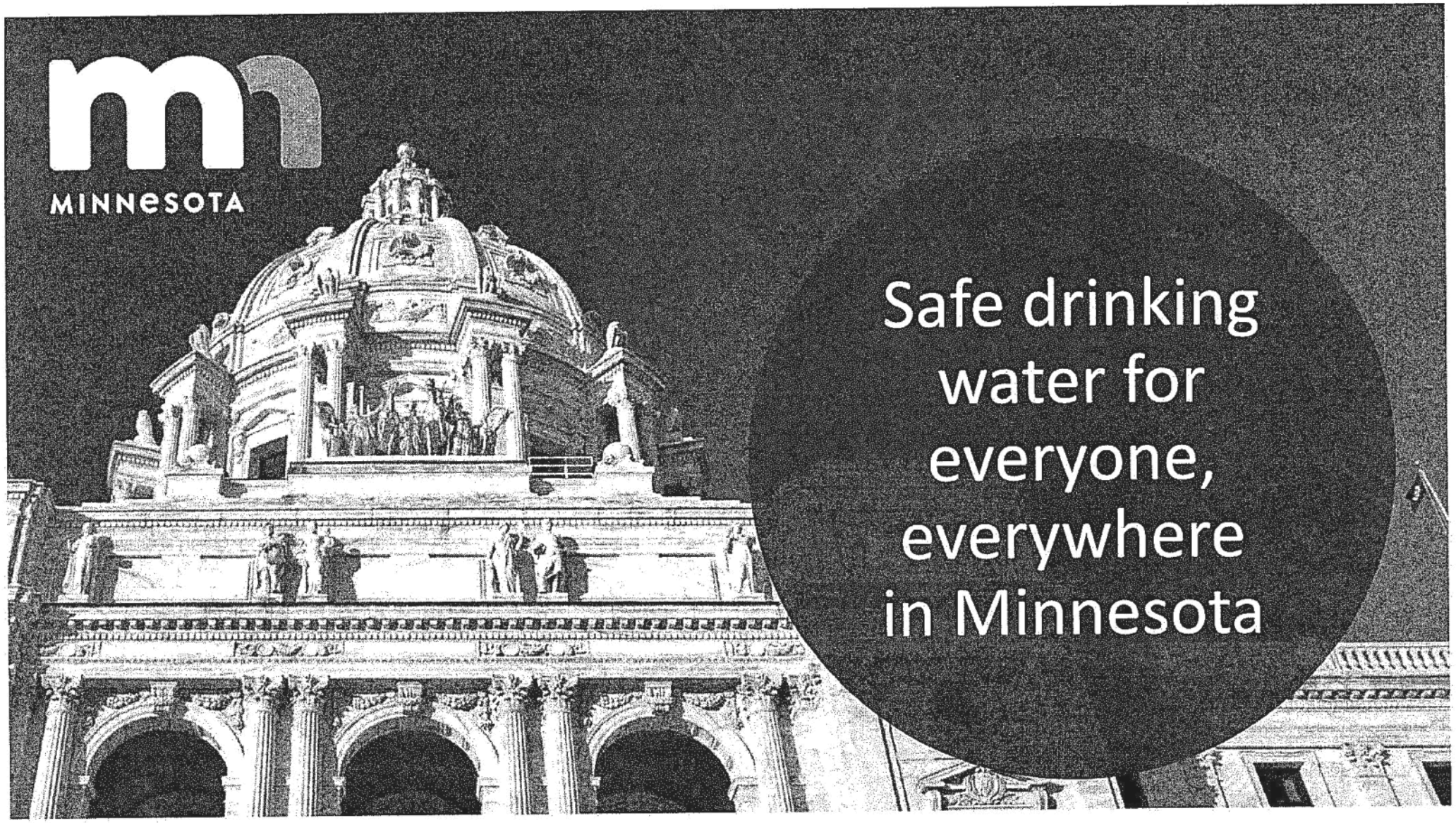
MDH Internal Message Blocks: PFAS Update

Information in this document is for MDH staff to use for their own understanding and to use as a resource when answering questions from affected people in Minnesota or developing materials for distribution.
When necessary, please refer people to the appropriate content expert for specific and in-depth information.

Going Forward

- Will continue to see changing health-based guidance values
- Will see broader analytical methods
  - Will be able to detect more PFAS chemicals (e.g. GenX)
- How to spend $720 million
  - Open houses and working groups to identify potential projects
  - Politicians and local municipalities may have "pet projects" they would like included – open checkbook mentality




MINNESOTA
Safe drinking water for everyone, everywhere in Minnesota

DEPARTMENT OF HEALTH

Questions?

David Rindal

david.rindal@state.mn.us

651-201-4660