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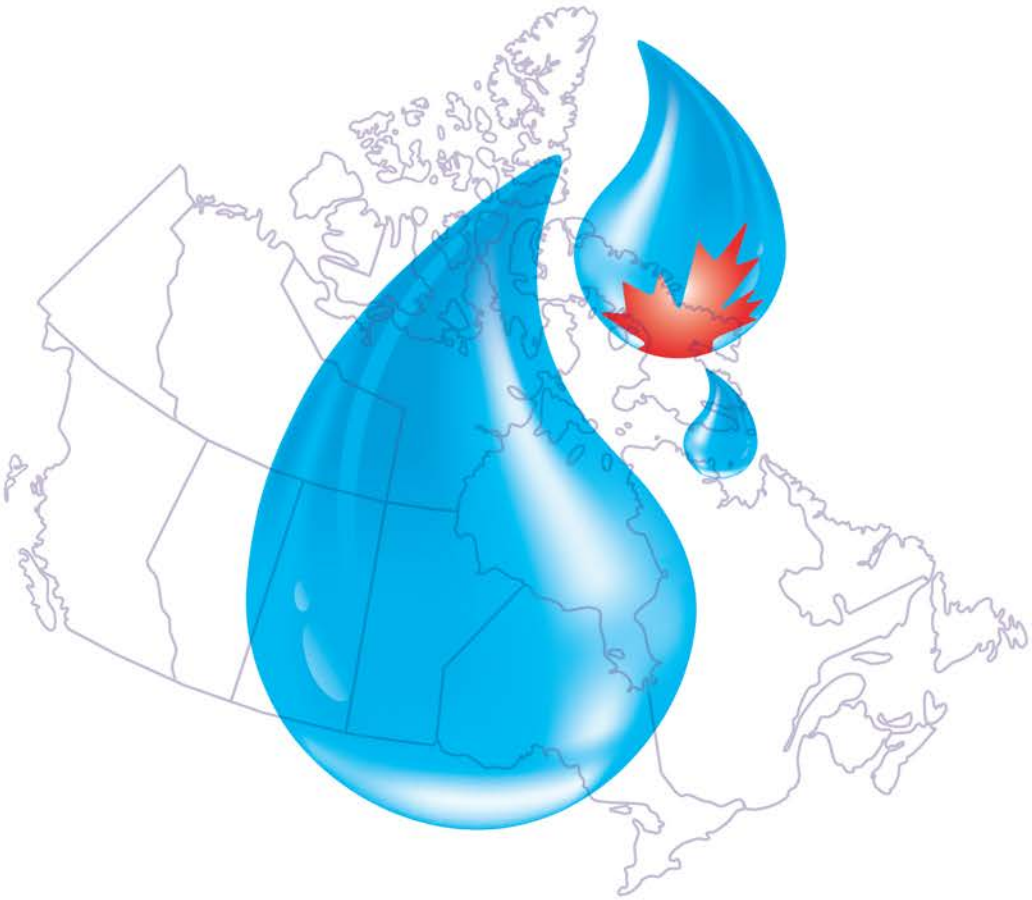
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Perfluorooctane Sulfonate (PFOS)



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Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Perfluorooctane Sulfonate (PFOS)

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Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Perfluorooctane Sulfonate (PFOS)

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Table of Contents

December 2018

Perfluorooctane Sulfonate

Part I. Overview and Application

1.0 Guideline

The maximum acceptable concentration (MAC) 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 concentrations to the corresponding MACs 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 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.

As PFOS and other perfluoroalkyl substances (PFAS) are increasingly being detected in the environment, more scientific studies on their health effects are being conducted in Canada and around the world. Health Canada continues to monitor new research and will work with provinces and territories to update the guideline, or develop new guidelines or other technical support material, as needed to reflect significant changes in the weight of evidence.

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 MAC for PFOS 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 PFOS remains in the human body longer than in does in rats, an approach that accounts for this difference was used in the derivation of the MAC for PFOS in drinking water.

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 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 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 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 guideline 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.

2.5 International considerations

The U.S. EPA has established a non-regulatory lifetime health advisory of 0.07 µg/L for PFOS, based on reproductive/developmental effects. It also specifies that when PFOA co-occurs with PFOS at the same time and location in a drinking water source, the health advisory should be applied to the sum of the concentrations of PFOS and PFOA. The Australia Department of Health has established a health-based drinking water quality value of 0.07 µg/L for use in site investigations, also based on reproductive/developmental effects. It also specifies that when PFOS co-occurs with perfluorohexane sulfonate (PFHxS), the drinking weater quality value should be applied to the sum of the concentration of PFOS and PFHxS. The World Health Organization and the European Union have not established a limit for PFOS in drinking water.

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.

PFOS and perfluorooctanoic acid (PFOA) 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, PFOS 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 PFAS including PFOS 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. PFOS migrates very slowly through the soil to groundwater.

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 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 characterization

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 conjunction 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 polyfluorinated precursors 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 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) (Health Canada, 2006). Regulations established under the *Canadian Environmental Protection*

Act, 1999 prohibit the manufacture, use, sale, offer for sale, or import of PFOS and its salts or compounds, unless designed for specific uses (Government of Canada, 2012).

4.1 Sources to water

A source of 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 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 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 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 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 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 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 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 (Berryman et

al., 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 (Berryman et al., 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 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 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 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 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 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

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. 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, PFOS was detected in all household dust samples analyzed for this compound (n = 132). The PFOS concentrations ranged from 1.5 to 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^{TM} 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 ng/mL; 95% CI: 10–12, 95th percentile: 31 ng/mL, n=1,376) are higher than in adult females (GM: 7.1 ng/mL; 95% CI: 6.3–7.9, 95th percentile: 20 ng/mL, n=1,504) (Health Canada, 2010). This effect persisted in Cycle 2 (2009-2011) of the study, 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 the skin is impermeable to 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 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 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 (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. 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 PFAS 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 PFAS 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 PFAS (C6-C12) from tap water. The recovery of the PFAS 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 PFAS 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 PFAS 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 PFAS 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 PFAS 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 were conducted with a direct injection (DI) of the water samples into 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 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 PFAS 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 PFAS, 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 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 PFAS 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 PFAS 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 PFAS 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 PFAS. 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 PFAS isomers (Berger et al., 2004; Jahnke and Berger, 2009).

The analysis of PFAS 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 PFAS 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 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 PFAS, 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 PFAS.

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 PFAS 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 PFAS and pre-existing treatment processes. If long-chain PFAS are detected in the drinking water sources, the utility may consider the implementation of treatments such as GAC. However, utilities that have shorter

chain PFAS in their raw water source may choose to implement RO. The treatment technologies need to be designed specifically for PFAS 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 PFAS 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 PFAS are present in the raw water year round, Rahman et al. (2014) suggested that GAC adsorption may be the preferred method for PFAS 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 PFAS 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 PFAS 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 PFAS 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 PFAS, 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 PFAS 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 PFAS 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 PFAS 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 PFAS 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 PFAS. 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 PFAS 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 PFAS 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 PFAS 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 PFAS (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 PFAS 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 PFAS due to competition for sorption sites with longer chain PFAS or NOM (i.e., DOC) may result in higher levels of shorter chain PFAS 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 PFAS 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 PFAS 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 PFAS since their pores sizes are larger than the effective diameter of the PFAS 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 PFAS 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 PFAS, 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 PFAS 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

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 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 PFAS. However, this system was not specifically designed for PFAS 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 PFAS 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 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 PFAS 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 PFAS (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 PFAS, and increases in concentration for other PFAS (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 PFAS.

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 PFAS 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 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, 2018):

- 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).

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. 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, 2017a) and that materials and components be certified to NSF/ANSI Standard 61 – Drinking Water System Components Health Effects (NSF/ANSI, 2017b) and NSF/ANSI Standard 372 – Drinking Water System Components Lead Content (NSF/ANSI, 2016). 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, 2017c) and reverse osmosis systems are covered in NSF/ANSI Standard 58: Reverse Osmosis Drinking Water Treatment Systems (NSF/ANSI, 2017d).

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 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). 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/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). Higher half-life values 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/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 on plasma predictions	Monkey[b]	2	2	3	2
	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 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 PFOS than 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 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.

I should be noted, however, that PFOS can be found as part of mixtures with other PFAS. Nonetheless, the vast majority of available studies on the toxicology of PFOS 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.

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 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).

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; 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., 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., 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., 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. 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) developed for chemical mixtures in source and drinking water (WHO, 2017). This section focuses on the evaluation of grouping PFOS and PFOA, which are the predominant PFAS detected in Canadian water samples, for the purpose of implementing an additive approach.

Considerations relevant to the grouping analysis are addressed within four over-arching questions (Meek et al., 2011; WHO, 2017):

1. The nature of exposure
2. The likelihood of co-exposure, taking into account the context
3. The likelihood of co-exposure within a relevant time-frame
4. 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 a grouping 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 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 co-exposure, taking into account the context

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 likelihood of co-exposure within a relevant time-frame

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 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 PFOA 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; WHO, 2017), 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:

$$TDI = \frac{0.028 \text{ mg/kg bw per day}}{25}$$

$$= \quad 0.0011 \text{ mg/kg bw per day}$$

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:

$$\text{HBV} = \frac{0.0011 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= \quad 0.010 \text{ mg/L (10 µg/L)}$$

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 9.1.2 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 ≥ 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 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.

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:

$$\text{HBV} = \frac{0.00006 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= 0.00056 \text{ mg/L}$$

$$\approx 0.0006 \text{ mg/L (0.6 µg/L)}$$

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 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; WHO, 2017), 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; WHO, 2017). 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; WHO, 2017), 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

$$\frac{\text{PFOS concentration in } \mu\text{g/L}}{0.6\ \mu\text{g/L}} + \frac{\text{PFOA concentration in } \mu\text{g/L}}{0.2\ \mu\text{g/L}} < 1$$

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 PFOS. This LHA was derived from a NOAEL of 0.1 mg/kg bw per day 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) 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.

The Australia Department of Health (2017) has established a health-based drinking water quality value of 0.07 µg/L (0.000 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 derived from a NOAEL of 0.1 mg/kg bw per day 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., 2005a). A TDI 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 HED (equivalent 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 intraspecies differences and 3 for interspecies toxicodynamic differences) was applied to the HED. 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 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 established for PFOS in drinking water. The 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. 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 supports the use of an additive approach for PFOS and PFOA, but it does not justify the use of this approach for other PFAS. 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 PFOS/PFOA removal data

Developed from table 3 in Rahman et al. (2014)

Water Source	Treatment Train[1]	Influent concentration[2] (ng/L)	Effluent concentration[2] (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	42	45	-7	Atkinson et al., 2008

Water Source	Treatment Train[1]	Influent concentration[2] (ng/L)	Effluent concentration[2] (ng/L)	% Removal of PFOS	Reference
	having 6 beds; 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] 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

[2] LOR = limit of reporting; ND = not detected

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