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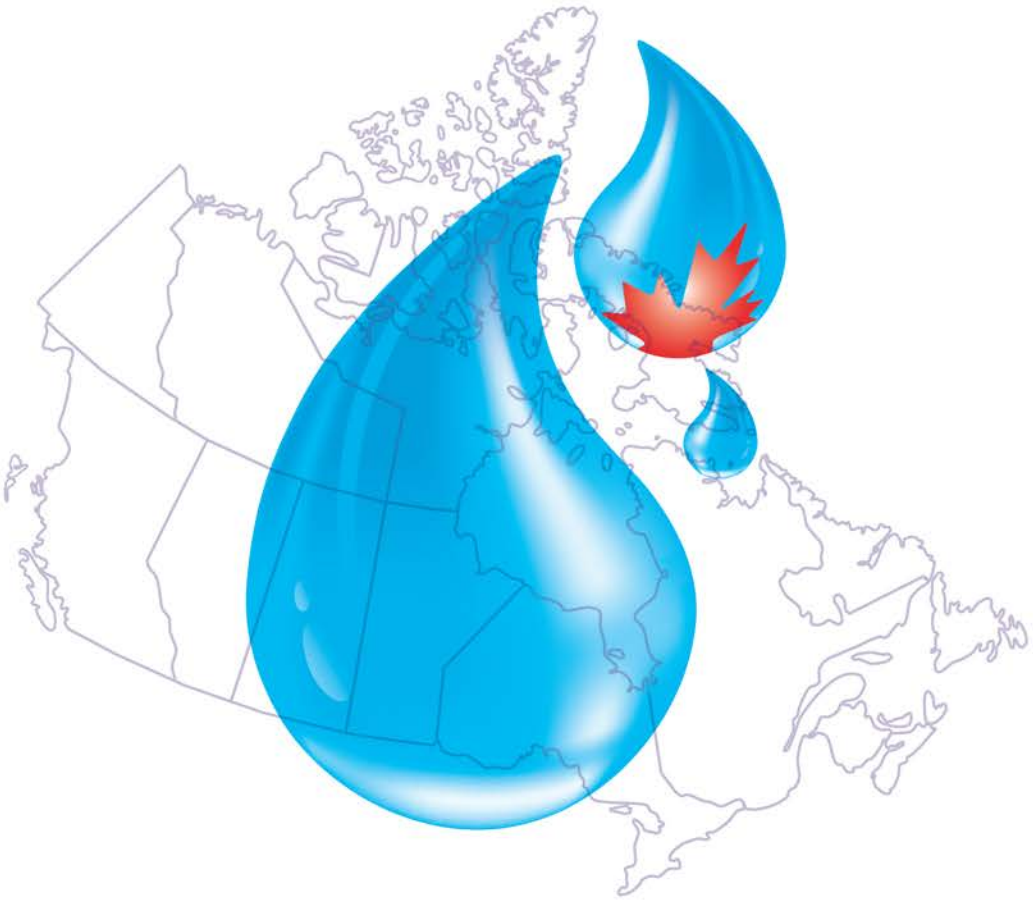
Guidelines for Canadian Drinking Water Quality

Guideline Technical Document

Perfluorooctanoic Acid (PFOA)



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Guidelines for Canadian Drinking Water Quality: Guideline Technical Document – Perfluorooctanoic Acid (PFOA)

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Guideline Technical Document

Perfluorooctanoic Acid (PFOA)

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Other Guideline Technical Documents for the Guidelines for Canadian Drinking Water Quality can be found on the following web page: www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/water-quality.html

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Perfluorooctanoic Acid

Part I. Overview and Application

1.0 Guideline

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

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

2.0 Executive summary

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

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

As PFOA 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

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

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

2.2 Exposure

Canadians can be exposed to PFOA in food, consumer products, dust, and drinking water. Exposure is mainly from food and consumer products, however, the proportion of exposure from

drinking water can increase in individuals living in areas with contaminated drinking water. PFOA is often found with other perfluoroalkyl substances, including PFOS. Although PFOA is not regularly monitored at water treatment plants in Canada, the analysis has been performed for a few locations. When detected in drinking water, it is usually found at levels below 0.003 µg/L.

2.3 Analysis and treatment

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

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

2.4 Additivity

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

2.5 International considerations

The U.S. EPA has established a non-regulatory lifetime health advisory of 0.07 µg/L for PFOA, based on 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 0.56 µg/L for use in site investigations, also based on reproductive/developmental effects. The World Health Organization and the European Union have not established a limit for PFOA 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.

PFOA and perfluorooctane sulfonate (PFOS) are typically found in groundwaters and surface waters impacted by aqueous film-forming foam (AFFF) (i.e., fire-fighting foams). They may also be found in groundwaters and surface waters contaminated by: discharges from

industrial facilities; effluents from wastewater treatment plants treating domestic or industrial waste; storm water runoff; or applications of biosolids from a municipal wastewater treatment plant to agricultural land. Like other groundwater contaminants, PFOA can reach drinking water wells through migration of a contaminated groundwater plume. It can also reach surface waters from air emissions of industrial facilities. Particle-bound volatile PFAS including PFOA may be carried from disposal sites by the wind and deposited on land or surface water, thus explaining their presence in remote locations and in waters not impacted by a point source. PFOA migrates very slowly through the soil to groundwater.

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

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

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

3.1 Monitoring

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

3.1.1 Source charcterization

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

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

3.1.2 Operational monitoring

Treatment systems should be specifically designed, operated and maintained for removal of PFOA and PFOS. The operational monitoring frequency will depend on the treatment technology the utility employs. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance. Utilities that use a GAC system for PFOA and PFOS removal may require quarterly monitoring of the treated water in order to assess the performance of the

GAC system and to determine the timing of the regeneration or replacement. Utilities should also be aware that ozone or advanced oxidation processes may oxidize polyfluorinated pecursors present in the source water, which could result in an increased concentration of PFOA in the finished water.

3.1.3 Compliance monitoring

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

Part II. Science and Technical Considerations

4.0 Identity, use and sources in the environment

Perfluorooctanoic acid (PFOA) is an anthropogenic compound with a chain length of eight carbons, of which seven are perfluorinated. It belongs to the class of chemicals known as perfluorocarboxylic acids (PFCAs), one of a broader class of chemicals known as perfluoroalkyls (PFAs) (Environment Canada and Health Canada, 2012), or perfluoroalkyl substances (PFAS). In this report, the term "PFOA" may refer to the free acid ($C_8HF_{15}O_2$; CAS number 335-67-1; 414.07 g/mol) or its conjugate base ($C_8F_{15}O_2^-$; CAS number 45285-51-6). The term APFO (ammonium perfluorooctanoate) refers to the ammonium salt ($C_8F_{15}O_2^- NH_4^+$; CAS number 3825-26-1), its principal salt, and K^+PFOA refers to the potassium salt (CAS number 2395-00-8). The main synonyms of PFOA are pentadecafluorooctanoic acid, perfluorooctanoate, C8, FC-143, pentadecafluoro1-octanoic acid, pentadecafluoro-n-octanoic acid, perfluorocaprylic acid, perfluoroctanoic acid, perfluoroheptanecarboxylic acid and octanoic acid.

PFOA is highly soluble in water, with estimates as high as 3,500 mg/L in neutral to alkaline pH and 9,500 mg/L in pure water, and as low as 0.7 mg/L at acidic pH (Kauck and Diesslin, 1951; Barton et al., 2007; Environment Canada and Health Canada, 2012). Solubility depends on the acid dissociation constant (pKa) of the acid form. Data for pKa indicate values ranging from –0.5 to 4 (Kissa, 1994; Burns et al., 2008; Goss, 2008; ATSDR, 2009; Goss and Arp, 2009; Environment Canada and Health Canada, 2012), and it was suggested that with such a low pKa value, the environmental partitioning of PFOA will be dominated by the anionic form (Goss, 2008).

PFOA has combined hydrophobic and hydrophilic properties over different portions of its molecule (Environment Canada and Health Canada, 2012). Due to this particularity, PFOA is thus expected to behave differently than traditional hydrophobic chemicals. The octanol:water partition coefficient (K_{ow}) cannot be determined directly (because multiple layers are formed in octanol/water) and the parameters usually estimated from the K_{ow} (e.g., K_{oc}, bioconcentration factor) cannot be calculated using this method (ATSDR, 2009; Environment Canada and Health Canada, 2012). The values of $LogK_{ow}$ estimated by modelling range from 3.62 to 6.30 (Arp et al., 2006; Jasinski et al., 2009; Environment Canada and Health Canada, 2012).

PFOA is essentially non-volatile, with a vapour pressure of 2.24×10^{-5} atm at 20°C (Barton et al., 2007; ATSDR, 2009; Environment Canada and Health Canada, 2012). Its Henry's law constant was estimated at 2.4×10^{-5} atm-m^3/mol (Barton et al., 2007).

Precursors of PFOA (polyfluoroakyl phosphate diesters, fluorotelomers, perfluorinated phosphonic acids) represent an indirect source of PFOA in the environment (Ellis et al., 2004; D'Eon et al., 2009; Lee, 2010).

The main producers of PFOA are located principally in the United States, Europe and Asia. Industrial information obtained in 2004 indicates no known manufacturers of perfluoroalkyl and fluoroalkyl substances in Canada; however, APFO was imported into Canada in quantities ranging between 100 and 100,000 kg (Environment Canada and Health Canada, 2012). Regulations established under the *Canadian Environmental Protection Act, 1999* prohibit the manufacture, use, sale, offer for sale, or import of PFOA or its salts, unless designed for specific uses (Government of Canada, 2012). APFO is mainly used as a commercial polymerization aid for fluoropolymer manufacturing. Fluoropolymers are used in the manufacture of stain/water-resistant coatings for textiles and carpets, hoses, cable and gaskets, non-stick coatings on cookware and personal care products. APFO is also used in aqueous fluoropolymer dispersions that are used in paints and in photographic film additives as well as within the aerospace industry

(e.g., it may be a component of aqueous film-forming foams [AFFFs] for firefighting; Environment Canada and Health Canada, 2012). Fluorochemicals (potential PFOA precursors) are also used in the treatment of food packaging materials (Environment Canada and Health Canada, 2012) such as microwaveable popcorn bags (Dolman and Pelzing, 2011). The term PFOA is not interchangeable with commercial mixtures containing PFOA, as these mixtures are often not well characterized and could include any product that contains even a small amount of PFOA (Environment Canada and Health Canada, 2012).

4.1 Sources to water

A source of PFAS in water is the discharge of AFFF for extinguishing fires. Discharge of AFFF was presumed to have resulted in increased levels of PFAS in water surrounding the Toronto International Airport, based on spatial and temporal trends of PFAS in water (Awad et al., 2011). Although the study focused on PFOS contamination, as this was the primary PFAS in the AFFF used at the location, PFOA-containing AFFFs could plausibly also result in similar increased concentrations of PFOA in water near discharge sites. Data supporting the possibility of contamination in the vicinity of firefighting training areas include measurements of elevated PFOA concentrations in groundwater near a Michigan air force base (Moody et al., 2003), at a firefighting training ground in Australia (Baduel et al., 2015), and in private drinking water wells proximate to an industrial site in Cologne, Germany (Weiß et al., 2012).

Elevated PFOA concentrations measured in surface water downstream from fluorochemical manufacturing plants have also been used as indications of the potential for industrial sources of PFOA in water (Hansen et al., 2002; Frisbee et al., 2009).

Mass balance studies of PFAS at wastewater treatment plants commonly report similar or higher PFOA concentrations in effluents in comparison to raw influents, suggesting that the degradation of other fluorinated organic compounds (i.e., fluoropolymers) into PFOA may take place during wastewater treatment (Clarke and Smith, 2011) and that conventional wastewater treatment plants are not effective in removing PFAS (Ahrens, 2011). PFOA was detected in effluent wastewater treatment facilities at concentrations ranging from 0.007 to 0.055 μg/L in Canada (Environment Canada and Health Canada, 2012) and at average concentrations ranging from 0.080 to 0.12 μg/L in effluents of seven different locations in the U.S. (Quinones and Snyder, 2009).

Although measures are in place in North America and Europe to restrict the production, use and/or the major exposure risks to PFAS (primarily PFOS, but to some extent PFOA), the ubiquitous use of PFAS within the built environment still causes their transfer to biosolids (sludge) (Clarke and Smith, 2011). The use of biosolids as fertilizers may thus represent a source of soil and water contamination with PFOA (Clarke and Smith, 2011). Elevated concentrations of PFOA were found in surface and well water in Decatur, Alabama, after biosolids from a municipal wastewater treatment plant (at which waste from local fluorochemical facilities were received) were applied in agricultural fields (Lindstrom et al., 2011).

4.2 Environmental fate

The elevated water solubility of PFOA and the negligible volatility of its ionized species suggest that PFOA species will partition primarily to the aquatic environment (Environment Canada and Health Canada, 2012).

PFOA may be found in air, surface water, sediment, groundwater and soil around the world (including the Arctic). Two long-range transport pathways have been proposed to explain this ubiquity (Post et al., 2012). The first pathway involves the atmospheric transport of volatile

precursors (e.g., fluorotelomer alcohol) and their oxidation to PFOA (and other PFAS) and further deposition onto land or water. The second pathway involves a long-range aqueous transport of the anionic forms of emitted perfluorinated carboxylates, such as PFOA, from the vicinity of industrial sources via the surface water currents (Butt et al., 2010; Post et al., 2012).

Experimental values of $LogK_{oc}$ vary between 1.2 and 4.5 (Dekleva, 2003; Higgins and Luthy, 2006; Prevedouros et al., 2006; ATSDR, 2009; Environment Canada and Health Canada, 2012; Zareitalabad et al., 2013). Data suggest that the sorption of PFOA can be described reasonably as a partitioning-like process with an average $LogK_{oc}$ of 2.8 (Zareitalabad et al., 2013).

PFOA may bioaccumulate in tissues of aquatic and terrestrial living organisms. Bioaccumulation data for different species of marine and terrestrial ecosystems indicate that PFOA has a low to moderate potential to accumulate in aquatic species (on a whole-body basis), while accumulation may be higher in certain organs/tissues (e.g., liver, blood) (Environment Canada and Health Canada, 2012). Briefly, the PFOA log bioaccumulation factors (BAFs) ranged from 0.02 to 0.63 for trout and from 9.6 to 19.4 for Pacific oysters. Log bioconcentration factors (BCFs) were estimated at 4.0 for the rainbow trout (carcass), 3.1–9.1 for carp, 1.8 for fathead minnows (whole body) and 0.8–3.0 for Pacific oysters. PFOA may also biomagnify in certain food webs (e.g., polar bears) (Environment Canada and Health Canada, 2012).

Under environmental conditions, PFOA does not hydrolyze, photolyze or biodegrade, and is considered extremely persistent in the environment (OECD, 2006; Environment Canada and Health Canada, 2012). PFOA is also resistant to microbial degradation (Liou et al., 2010). Moreover, biodegradation of precursor compounds could lead to increasing concentrations of PFOA in the environment (Ahrens, 2011; Clarke and Smith, 2011). Considering its empirical and physico-chemical properties, it was concluded that PFOA and its salts meet the persistence criteria in water, soil, sediment and air (half-lives of $\geq$ 182 days in soil and water, $\geq$ 365 days in sediment and $\geq$ 2 days in air) (Environment Canada and Health Canada, 2012).

The adsorption of PFAS onto natural sediments with varying organic carbon and iron oxide content, onto kaolinite, alumina and geothite was investigated in aqueous solution (Higgins and Luthy, 2006; Johnson et al., 2007; Pan and Yu, 2010; Tang et al., 2010; Wang et al., 2011; Xiao et al., 2011; 2015). Higgins and Luthy (2006) and Johnson et al. (2007) reported that the adsorption of PFAS on sediments collected from various riverines and lacustrine sites was influenced by the organic carbon, rather than the mineral content, of the sediment. Other studies demonstrated that the adsorption of PFOA/PFOS onto minerals was influenced by pH, ionic strength and the type of the cations present in the aqueous solution (Tang et al., 2010; Wang et al., 2011; Xiao et al., 2011).

5.0 Exposure

Canadians can be exposed to perfluorinated compounds present in food, consumer products, dust and drinking water. The major sources of perfluorinated compounds are expected to be food and consumer products, including solution-treated carpeting and treated apparel (Tittlemier et al., 2007); however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water.

The estimated total daily intake of PFAS (estimates not provided for individual PFAS) in Canadians was reported to be 410 ng/day for the general population of Canada (Tittlemier et al., 2007). Drinking water ingestion, estimated at 0.3 ng/day, contributed only a minor amount to the overall estimated exposure. Although some exposure data are available, they are considered

insufficient to justify modifying the default allocation factor for drinking water of 20%. This default allocation factor for drinking water is used as a "floor value" when drinking water is not a major source of exposure (Krishnan and Carrier, 2013); therefore, this value is applicable for PFOA, even though water is expected to be only a minor contributor to PFOA exposure for the general population.

5.1 Water

Although PFOA is not regularly monitored at water treatment plants in Canada, the analysis has been performed for a few locations. PFOA was not detected (method detection limit [MDL] of 0.51 ng/L) in raw or finished water from samples obtained in 2012 from two water treatment plants in Calgary (Alberta Environment and Water, 2013). In Quebec, raw and treated water samples were obtained monthly between April 2007 and March 2008 from seven sites (a total of 84 raw and treated water samples each). PFOA was detected in 75% of treated samples (MDL of 0.3–0.6 ng/L), with a median value of 2.5 ng/L and a maximum value of 98.0 ng/L. The detection rate and median concentrations were higher in treated water than in raw water, for which the detection rate and median were 55% and 2.0 ng/L, respectively (Berryman et al., 2012). The reported PFOA concentration in 5 tap water samples from Niagara-on-the-Lake, Ontario, was 2.1 ng/L (Mak et al., 2009). Lower concentrations of PFOA (0.2 ng/L) were reported in tap water from Calgary and Vancouver (Tanaka et al., 2006).

In a national survey of emerging contaminants in drinking water (including PFOA) performed by Health Canada, treated and raw water from groundwater and surface water sources (rivers and lakes) was monitored in winter and summer at 35 locations in 2009 and 30 locations in 2010. PFOA was detected (MDL of 0.023 ng/L) in 68% of raw water samples and 64% of treated water samples in summer 2009, with averages of 0.067 ng/L and 0.071 ng/L, respectively (median values of 0.050 and 0.060 ng/L, respectively). PFOA concentrations were slightly lower in winter 2009, with an average of 0.057 ng/L in detected raw samples (59% detection) and 0.056 ng/L in detected treated samples (55% detection). Detection rates for PFOA were lower in the 2010 locations, with detection rates in the summer of 18% in raw water (average of 0.066 ng/L and median of 0.030 ng/L) and 15% in treated water (average of 0.046 ng/L and median of 0.025 ng/L), and in winter of 33% in raw water (average of 0.055 ng/L and median of 0.040 ng/L) and 27% in treated water (average of 0.05 ng/L and median of 0.030 ng/L) (Health Canada, 2013a). Maximum levels of 0.220 ng/L and 0.180 ng/L were detected in raw and treated water samples, respectively.

PFOA levels in Etobicoke Creek, Ontario (a tributary of Lake Ontario) ranged from not detected (limit of quantification: 9 ng/L) to 11.3 µg/L following a fire alarm malfunction that released flame retardants containing PFAS (Moody et al., 2002). Interestingly, PFOA was also found upstream of the spill site at 0.02 µg/L.

5.1.1 Co-occurrence with other PFAS

Limited data show that PFOA is co-detected with other substances in several locations across Canada. In all of these studies, PFOS and PFOA were the predominant PFAS detected. PFOA is co-detected with:

- PFOS, perfluorohexane sulfonate (PFHxS), perfluoroethanesulfonate (PFEtS), perfluorooctanesulfonamide (PFOSA), perfluoroundecanoic acid (PFUDA), perfluorodecanoic acid (PFDA), perfluorononanoic acid (PFNA), perfluoroheptanoic acid (PFHpA), perfluorohexanoate (PFHxA), perfluoro-n-pentanoic acid (PFPeA), and

perfluorobutanoate (PFBA) in tap water in Niagara-on-the-Lake, Ontario (Mak et al., 2009);

- PFOS, PFNA and PFUDA in treated and raw water in Québec (Berryman et al., 2012);
- PFOS, PFBA, PFPeA, PFHxA, PFHpA, PFNA, PFBS, and PFHxS in groundwater at former fire-fighting training areas in British Columbia, Alberta, Nova Scotia, and Ontario (Paterson et al., 2008; Environmental Sciences Group, 2015);
- PFOS and PFDA in Nova Scotia and Ontario, and PFUDA, PFDoA, and PFOSA in Nova Scotia (Environmental Sciences Group, 2015).

5.1.2 Leaching from drinking water materials

Polymers and elastomers used as joining and sealing materials in water distribution systems may contain trace amount of PFOA. PFOA salts are used as a processing aid in the production of fluoropolymers such as polytetrafluoroethylene (e.g.,Teflon®) and in fluoroelastomers (e.g., Viton®). An important consideration for reducing exposure to PFOA is to address leaching from these materials by specifying that they meet health-based standards. NSF/ANSI Standard 61 (Drinking Water System Components—Health Effects) limits the leaching of PFOA into drinking water. The standard ensures that materials meet health-based leaching requirements and are safe for use in potable water applications by specifying the single product allowable concentration (SPAC) for contaminants. Although the current SPAC for PFOA is 0.0003 mg/L (NSF/ANSI, 2017a), it is presently under review by NSF International to reflect up-to-date science. Polymers and elastomers used as joining and sealing materials in water distribution systems that meet NSF/ANSI Standard 61 would be expected to leach very low concentrations of PFOA into drinking water.

5.2 Food

Food is generally considered to be the main source of exposure to PFOA for the majority of the Canadian population, but exposure from food is still well below what is considered unsafe to humans. PFOA was measured in a selection of Canadian food composite samples (samples from the Canadian Total Diet Study [TDS]) conducted in 2004 and additional samples collected within 1992 and 2001) to estimate the dietary intake. PFOA was detected in 3 out of 54 food composites. The detected PFOA concentrations (on a w.w. basis) were 0.74 ng/g (pizza; the sample was above the limit of detection but below the limit of quantitation), 2.6 ng/g (roast beef) and 3.6 ng/g (microwave popcorn). Values were used to estimate the average dietary daily exposure of Canadians; food was estimated to contribute 250 ng/day of perfluorinated compounds, of which approximately 70 ng was attributed to PFOA (Tittlemier et al., 2007).

Store-bought and restaurant foods commonly consumed by Canadians were collected in Whitehorse (Yukon Territory, Canada) in 1998 and analyzed for PFAS. PFOA was detected in several composite samples (0.36–0.77 ng/g w.w. for cookies, processed cheese, peppers, canned lunchmeats, and pizza), but all measurements were below the limits of quantification (0.65–1.52 ng/g w.w.) (Ostertag et al., 2009a).

The concentrations of PFAS in the traditional foods of Inuit in Northern Canada was measured to estimate their dietary exposure. PFOA was infrequently detected (9% out of 68 samples) in the traditional foods collected from Chesterfield Inlet, Igloolik, Pond Inlet and Qiqiktarjuak in Nunavut, between 1997 and 1999. PFOA was detected in ringed seal (liver: 0.3 ng/g; blood: 0.1 ng/g), eider duck (whole body: 0.4 ng/g), caribou liver (baked: 0.7 ng/g; raw: 0.1 ng/g) and caribou stomach (raw: 0.8 ng/g); the other concentrations were below the detection limit (<0.1 to <0.6 ng/g) (Ostertag et al., 2009b).

PFOA is a processing aid in the manufacture of polytetrafluoroethylene (PTFE), which is used for many purposes, including non-stick cookware. Residual PFOA was detected in PTFE cookware and film (Begley et al., 2005); however, only minor transfer of PFOA from these products was observed in investigations on the migration into watery and fatty simulated foodstuff (Begley et al., 2005; Powley et al., 2005; Washburn et al., 2005; Sinclair et al., 2007). PFOA has also been detected in microwave popcorn bags (Begley et al., 2005; Sinclair et al., 2007; Dolman and Pelzing, 2011), and found in food contact papers treated with polyfluoroalkyl phosphate surfactant (PAPs) or di-perfluoro-alkyloxy-amino-acid (PAA) (Xu et al., 2013). The migration rates of PFOA from food contact papers treated with these compounds ranged from 7% to 92% for five different food simulants (Xu et al., 2013).

5.3 Air

The inhalation intake of PFOA for Canadians was considered negligible due to its low volatility (Tittlemier et al., 2007).

The levels of PFAS in outdoor air were determined in a Canadian study conducted in 2007 in Vancouver (Shoeib et al., 2011). PFOA samples were collected using outdoor passive samplers deployed in residential yards for approximately 3 months. PFOA was detected in 4 out of 6 samples (<0.47–9.2 pg/m^3; mean: 1.4 pg/m^3) (Shoeib et al., 2011). Similar concentrations were measured in the Canadian Arctic (Resolute Bay, Cornwallis Island, Nunavut) in 2004, with a mean concentration (gas and particulate phase of atmospheric air) of 1.4 pg/m^3 (Stock et al., 2007).

In indoor air, the levels of PFOA primarily depend on its concentration in air particulates and are thus related to the levels in indoor dust, as well as the number, type and age of the potential sources (e.g., carpeting, furniture and paint) (Fraser et al., 2012). To date, data on indoor air concentrations of PFOA are limited to those reported in the aforementioned residential study (Shoeib et al., 2011). The authors collected PFOA in indoor air using passive samplers deployed for approximately 4 weeks in bedrooms of 59 participants. PFOA was the dominant ionic PFAS, with a geometric mean concentration of 28 pg/m^3 (arithmetic mean: 113 pg/m^3, median: 21 pg/m^3, range: 3.4–2,570 pg/m^3).

5.4 Consumer products

Owing its use patterns, human exposure to PFOA would likely result from contact with, or the use of, certain consumer products (Health Canada, 2006). Estimates of the contribution of solution-treated carpeting and treated apparel to Canadians' daily intakes of total perfluorinated compounds were 120 ng/day and 12 ng/day, respectively (Tittlemier et al., 2007). As no Canadian data were available on exposure to PFOA in consumer products, data from other countries are summarized below.

PFOA has been measured in a variety of consumer products, including waterproofing agents, fluorotelomer-treated textiles, apparel and carpeting, aqueous firefighting foams, non-stick ware, industrial floor waxes and wax removers, latex paint, home and office cleaners, PTFE-coated dental floss and dental tape, and PTFE film/sealant tape (Begley et al., 2005; Washburn et al., 2005; Herzke et al., 2012). PFOA has also been measured in ski waxing blocks and glider powders, with occupational exposure to airborne PFAS measured during professional ski waxing (Freberg et al., 2010).

5.5 Soil and household dusts

The estimated contribution of dust to Canadians' daily intakes of total perfluorinated compounds was 28 ng/day (Tittlemier et al., 2007). The study did not estimate the total daily contribution of soil to perfluorinated compound exposure.

PFOA concentrations in dust from Canadian houses were reported to vary from <2.3 to 1,234 ng/g with a median value of 19.7 ng/g (mean: 106 ng/g). House age and fraction of floor covering were reported to be significantly correlated with the concentration of PFAS in dust—older houses and those with smaller fractions of the floor covered with carpet were characterized by lower concentrations of PFAS (Kubwabo et al., 2005).

In another Canadian study conducted in Vancouver, BC, PFOA was detected in all house dust samples analyzed for this compound (n = 132). The PFOA concentrations ranged from 1.9 to 1390 ng/g (median: 30 ng/g, mean: 97 ng/g) (Shoeib et al., 2011). PFOA levels in dust collected from homes in Toronto, Ontario (n=19) ranged from <0.98 ng/g to 4000 ng/g (median: 69 ng/g, mean: 270 ng/g) (Goosey and Harrad, 2011). Another Canadian study investigating PFAS levels in household dust in a family home in Edmonton, Alberta found PFOA in the housedust (550.0 ng/g) and carpets (16.0 – 153.0 ng/g) (Beesoon et al., 2012). The authors attributed the high levels of PFOS to carpet treatment with Scotchgard carpet protector.

No study reporting background PFOA levels in soils was located. Some data are available in soil surrounding perfluorochemical industrial facilities (as reviewed by ATSDR, 2009).

5.6 Human biomonitoring data

Human PFOA blood levels have been shown to be influenced by gender and age. The Canadian Health Measures Survey (CHMS), Cycle 1 (2007–2009) indicates that PFOA plasma levels in adult males (geometric mean [GM]: 2.9 ng/mL; 95% CI: 2.7–3.2, 95th percentile: 6.0 ng/mL, n=1376) are higher than in adult females (GM: 2.2 ng/mL; 95% CI: 2.0–2.4, 95th percentile: 5.0 ng/ml, n=1504) (Health Canada, 2010). This effect persisted in Cycle 2 (2009-2011) of the study (Males—GM: 2.6 ng/mL, 95% CI: 2.4–2.9, 95th percentile: 6.0, n=511; Females—GM: 2.0 ng/mL, 95% CI: 1.8–2.2, 95th percentile: 4.4 ng/mL, n=506) (Health Canada, 2013b).

5.7 Multi-route exposure through drinking water

The multi-route exposure assessment process is not applicable for PFOA, due to the compound's high molecular weight and low volatility (Krishnan and Carrier, 2008); therefore, the relative contributions of exposure to PFOA from both inhalation and dermal routes during showering and bathing were not estimated. Based on the high molecular weight of 414.07 g/mol and the ionic properties of PFOA at pH levels typical in drinking water, volatility and dermal penetration are expected to be low. Moreover, dermal permeability coefficients measured in *in vitro* studies predict that PFOA is impermeable to skin under typical conditions (Fasano et al., 2005; Franko et al., 2012). Consequently, exposure to PFOA via inhalation and dermal routes during showering or bathing is expected to be negligible.

6.0 Analytical methods

To date, the United States Environmental Protection Agency has not approved any analytical methods for the analysis of PFOA in drinking water. There are some methods that can be used to measure PFOA in drinking water at levels well below the MAC. However, they require good quality control procedures to produce accurate results.

6.1 Available methods

EPA Method 537 ver. 1.1, International Standard Organization (ISO) Method, 25101 and 3M Method ETS-8-154.3 can all be used for the analysis of PFOA in drinking water (3M, 2008; ISO, 2009; U.S. EPA, 2009a). All methods use a solid phase extraction (SPE) technique followed by a liquid chromatograph (LC) coupled to electrospray ionization (ESI) tandem mass spectrometry (MS/MS) operated in negative ion mode. For the purpose of trace quantitation of PFOA in drinking water, the chromatographic conditions are selected such that all isomers (linear and branched) are co-eluted together.

In the EPA method, a water sample is fortified with labelled internal standards and passed through a SPE cartridge to extract target analytes in addition to their corresponding internal standards. The compounds are eluted from the SPE cartridge, concentrated and injected into a LC-MS/MS. The mass spectra and retention times of the analytes are identified by comparison to internal standards. The MDL for PFOA is 1.7 ng/L (0.0017 µg/L) and the Lowest Concentration Minimum Reporting Level (LCMRL) is 5.1 ng/L (0.0051 µg/L) (U.S. EPA, 2009a). PFOA has been included in the third Unregulated Contaminant Monitoring Rule (UCMR3), which stipulates that using Method 537 ver. 1.1, an MRL of 20 ng/L (0.02 µg/L) for PFOA must be achieved and reported by the utilities during monitoring (U.S. EPA, 2012b).

The results of an inter-laboratory trial (Taniyasu et al., 2013), conducted in 2006, were used to establish whether ISO Method 25101 was reliable for the analysis of PFOA and PFOS in environmental water samples, including drinking water. The intra- and inter laboratory precisions were in the range of 3–7% and 15–22%, respectively for PFOA for all environmental water samples analyzed. The recovery of the internal standards for PFOA ranged from 91 to 98%. These results confirmed that this analytical method was reliable and can be used for the analysis of PFOA in environmental water samples. The method uses SPE, LC-MS/MS and is applicable for the quantification of the linear and branched isomers of PFOA and PFOS. The branched isomers can be separated from the linear isomers by using specific chromatographic column and optimized conditions. ISO Method 25101 was found to be appropriate for determination of PFOA levels in unfiltered samples of drinking water, groundwater and surface water with concentrations in the range of 10 – 10,000 ng/L (0.01 – 10 µg/L) (ISO, 2009).

Method (ETS-8-154.3) was developed and validated by 3M for PFOA analysis in drinking water, groundwater and surface water samples. The analytical steps are similar to EPA Method 537 Ver 1.1 and the method has a limit of quantitation (LOQ) of 25 ng/L (0.025 µg/L) for PFOA (3M, 2008).

6.2 Analytical challenges

In spite of the significant improvements in analytical methods for the determination of PFAS in environmental water samples, challenges, uncertainties and drawbacks still remain. Major challenges associated with the trace quantitation of PFAS included matrix effects and a background contamination in the analytical blanks. In order to generate accurate data, quality control procedures (i.e., matrix spikes, duplicates, spike-recovery experiments, surrogate recovery checks) are critical. In addition, the use of isotope-labelled internal standards is a standard practice and must be used in the analysis of PFAS. In addition, PFOA analyses should be conducted by an accredited laboratory or by a laboratory with a stringent quality assurance/quality control (QA/QC) program in place to ensure data quality.

6.2.1 Matrix effect

Although LC-MS/MS is a highly selective and sensitive technique, it is susceptible to matrix effects which is one of the major uncertainties in the trace quantitation of PFOA in environmental water samples (Martin et al., 2004; Yamashita et al., 2004; Taniyasu et al., 2005; van Leeuwen et al., 2006; Arsenault et al., 2008). Matrix effects result from the co-extracted components from the sample, which affect the signal intensity of the target analyte and either suppress or enhance the spectral signal. The extent of the matrix interference varies, depending on the nature of the samples. Although the matrix interferences are negligible for drinking water and groundwater (ISO, 2009), the PFOA quantification requires efficient extraction and clean-up procedures. The aim of these procedures is to separate the compounds in the sample by their chemical and physical properties, to concentrate the target analyte and to purify the extract prior to the instrumental determination. The most frequently used technique for the extraction of PFASs from drinking water samples includes SPE cartridges with different packing material such as reverse phase (C18) cartridge (Loewen et al., 2005; Wolf and Reagen, 2011; Zainuddin et al., 2012), mixed hydrophobic/polar (Oasis HLB) cartridges (Yamashita et al., 2004; Taniyasu et al., 2005; Villaverde-de-Saa et al., 2015) and a weak anion exchange (WAX) cartridges (Taniyasy et al., 2005; 2013). Several studies conducted a liquid-liquid extraction (LLE) technique to extract and concentrate PFASs in different environmental aqueous matrices prior to LC-MS/MS (Gonzales-Barreiro et al., 2006; Szostek et al., 2006; Backe et al., 2013). A laboratory study (Gonzales-Barreiro et al., 2006) used an LLE to extract PFASs (C6-C12) from tap water. The recovery of the PFASs with a carbon chain greater than C8 was in the range 80-93%. The authors indicated that the method was less efficient in extracting short-chained PFASs when compared to the SPE technique (Gonzales-Barreiro et al., 2006).

The clean-up procedures involved a washing step after the sample enrichment on the SPE cartridge and a filtration to remove solids from the final extract (Yamashita et al., 2004; Larsen and Kaiser, 2007; van Leeuwen and Boer, 2007). Care should be taken to avoid contamination of the extract or losses of PFASs during the clean-up procedures. Prior to a SPE, a sample pre-treatment (filtration) may be required to facilitate extraction or to remove matrix constituent that will interfere with analyses (van Leeuwen and Boer, 2007; Ding et al., 2012).

The most suitable approach to assist in the quantification of PFASs is to use of isotopically-labelled internal standards (isotope dilution). It is important that the appropriate isotope-labelled internal standards are used for the quantitation of the corresponding native compound. Isotope-labelled internal standards will have the same retention time as the target analytes (excluding isomeric separation) and the monitoring of their signals will determine whether the analytes signal are suppressed or enhanced. The application of surrogates or isotopically-labelled internal standards early in the sampling or the sample preparation steps will compensate for the inefficiency/losses in the extraction and other sample preparation steps (Martin et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007). Wolf and Reagen (2011) reported that an addition of isotope-labelled internal standards prior to sample collection simplified the sample preparation procedures. The method demonstrated an accuracy of 105% and a precision of 12% for PFOA in laboratory Milli-Q water samples (Wolf and Reagen, 2012).

If isotope-labelled internal standards are not available, a standard addition quantitation, which involves spiking known quantities of a standard into the sample, is an alternative to use when matrix effects are unavoidable (Weremiuk et al., 2006; Furdui et al., 2007; van Leeuwen et al., 2009).

The use of MS/MS for analysis of PFOA enables the detection of product (daughter) ions. The transitions from m/z ratio 413 (parent ion $C_7H_{15}COO^-$) to m/z ratio 369 and 169 (daughter ions) are used for PFOA quantification (ISO, 2009; U.S. EPA, 2009a).

6.2.2 Background contamination in the analytical blanks

A known source of background contamination is the presence of fluoropolymers, such as polytetrafluoroethylene (PTFE) and perfluoroalkoxy compounds in various laboratory consumables. Ammonium perfluorooctanoate and ammonium perfluorononanoate are used as fluoropolymer processing aids and are common components in the laboratory products. These fluoropolymers may lead to quantifiable background levels in the analytical blanks especially when quantifying trace levels in water samples. Contacts with such laboratory materials and products during analysis of PFOA should be avoided (Martin et al., 2004; Yamashita et al., 2004; ISO, 2009).

Yamashita et al. (2004) studied the sources of background contamination at various analytical steps, including sample collection, extraction and sample clean up prior to the instrumental analysis. Polypropylene bottles used for sample collection and storage, in addition to different types of SPE cartridges and purified reagent water, were found to be sources of PFASs contamination in the analytical blanks. Taniyasu et al. (2005) and Berger et al. (2011) found that the polypropylene containers are unsuitable for collection and storage of water samples intended for analysis of long-chain PFCAs such as perfluoroundecanoic and perfluorododecanoic acids, because of the adsorption of the compounds on the containers' surface. The authors recommended the use of high density polyethylene or glass containers. However, ISO method 25101 and EPA Method 537 recommended against the use of glassware for sampling due to the potential adsorption of PFOA on the walls (ISO, 2009; U.S. EPA, 2009a). The storage and sample preservation steps prior to the instrumental analysis should prevent changes in composition of the sample matrix and the concentration of the analyte (van Leeuwen et al., 2007).

SPE cartridges can also be a source of contamination and the U.S. EPA (2009a) recommends that SPE devices be tested prior to using them for analysis to ensure that there is no contamination of the sample. Several studies were conducted with a direct injection (DI) of the water samples into liquid chromatograph column. The method avoids the use of additional materials and sample preparation processes, which may limit possible contamination and target compound losses (Schultz et al., 2006; Furdui et al., 2008; Dickenson and Higgins, 2013).

HPLC tubing, nylon filters, auto-sampler vial caps made of Teflon or Viton fluoropolymers, valve seals and degassers were identified as the potential sources of contamination of the instrumental blanks with PFOA (Yamashita et al., 2004; Taniyasu et al., 2005; Schultz et al., 2006; Larsen and Kaiser, 2007) and to lesser extent with PFOS (Yamashita et al., 2004). The instrumental background contamination can be reduced by replacing or bypassing the fluoropolymers parts such as a degasser (Arbuckle et.al, 2013) with offline degassing of mobile phases; replacing fluoropolymer components with stainless steel, polyetheretherketone (PEEK) tubing, installing an upstream guard column, extensively flushing of the LC system or reducing the LC-column equilibration time (Martin et al., 2004; Yamashita et al., 2004; Villagrassa et al., 2006; Larsen and Kaiser, 2007; Nakayama et al., 2007; Shoemaker et al., 2009; Arbuckle et.al, 2013).

6.3 Analytical performance

Recent analytical improvements have been realized through the availability and use of high quality standards and stable isotope internal standards to compensate for the matrix effect

and for inefficiencies in the extraction procedure and/or other sample preparation steps (Yamashita et al., 2004; Lowen et al., 2005; Taniyasu et al., 2005; Nakayama et al., 2007; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). There are currently, a number of high quality analytical-grade standards that are commercially available and the list of these standards continues to expand (van Leeuwen et al., 2009, Berger et al., 2011).

In the early 2000s, quantification of PFASs was biased by the lack of proper analytical standards, isotopically labelled surrogates and reference material and there was a significant analytical variability between laboratories. Two inter-laboratory studies were conducted to analyze PFASs, including PFOA and PFOS, in environmental water samples and found a varying degree of accuracy. In the first study (van Leeuwen et al., 2006), conducted in 2004/2005, factors resulting in poor agreement between participating laboratories, were determined to be low PFOA/PFOS concentrations (below 20 ng/L) in water samples; the use of low purity standards, high matrix effect, and a high background contamination in the analytical blanks. The relative standard deviation (RSD) reported in the study was 118% for PFOA (van Leeuwen et al., 2006). In the second inter-laboratory study, the performance of the participating laboratories improved due to the minimization of the matrix effects; the use of higher quality (purity and isomeric composition) shared standards (provided by a single source), and the use of mass-labelled internal standards. The reported RSD value in this study was 32% for PFOA.

Methods using SPE and DI procedures followed by LC/ESI/MS/MS have been reported in the literature for the determination of PFAS, including PFOS in water samples (Yamashita et al., 2004; 2005; Taniyasu et al., 2005; 2013; Furdui et al., 2008; Hansen et al., 2010; Berryman et al., 2012; Zainuddin et al., 2012; Villaverde-de-Saa et al., 2015). Details regarding the preconditioning procedures of the SPE cartridges, eluent, clean-up procedures, MS quantification parameters and QC procedures specific to each method are available in the cited reference.

A study reported a limit of detection (LOD) (signal-to-noise [S/N] = 3:1) of 0.28 ng/L and an LOQ (S/N= 10:1) of 0.94 ng/L using an SPE followed by LC-MS/MS for analyzing PFOA in surface water. A water sample of 500 mL was loaded on the Oasis WAX cartridge, a target fraction was eluted, dried under nitrogen gas and before the analysis the samples were filtered. The recovery value of 115±6% for PFOA was calculated by isotopically-labelled internal standards calibration (Sun et al., 2011; Li et al., 2011).

Villaverde-de-Saa et al. (2015), using an SPE followed by LC–MS/MS, developed a method for the determination of seven PFCAs (C6–C12) and PFOS in environmental waters samples. A water sample of 1.0 liter, fortified with internal standards, was loaded on the Oasis HLB cartridge. The method reported a LOD of 0.03 ng/L and a LOQ of 0.11 ng/L for PFOA, (LOD and LOQ were calculated as 3 and 10 times the standard deviation, respectively). The recovery value of 89±4% for PFOA was calculated by isotopically-labelled internal standards calibration.

Furdui et al. (2008) investigated the concentration of PFASs in water samples from the Great Lakes. The analysis of nine target contaminants including PFOA, were performed by directly injecting the samples into LC-MS/MS. Quantification was performed using internal standard correction and standard addition. An isotope dilution provides the most accurate and precise results. The method had a LOQ (signal-to-noise [S/N] =10:1) of 0.5 ng/L for PFOA (Furdui et al., 2008).

The province of Québec reported results of the monitoring PFASs at 16 sites, including seven drinking water treatment plants. A total of 226 water samples (84 raw, 84 treated and 58 surface water samples) were analyzed. Both raw and treated water were sampled monthly for a period of one year. Sampling of the surface water was limited through the year. The samples were

analyzed using C18 cartridges and LC-MS/MS in positive ionization mode. Reported DLs ranged from 0.5 to1.0 ng/L and 0.3 to 0.6 ng/L for untreated (250 mL analysed sample) and finished water (500 mL sample), respectively. In order to compensate and correct the instrumental variations and the matrix effect, isotopically-labelled internal standards were added prior to the LC (Berryman et al., 2012). Although the photoionization technique is less sensitive than the electrospray ionization, it is less prone to matrix effect (Martin et al., 2004).

Berger et al. (2004) compared different mass spectrometric techniques (time-of-flight [TOF] high resolution MS, triple-quadrupole tandem MS, and IT-MS) coupled with a high performance liquid chromatography (HPLC) for analysis of PFASs including PFOA. The instrument parameters such as vaporizer temperature, collision energy, and cone voltage fragmentation were optimized for each mass spectrometry technique. Negative electrospray ionization was selected as the ionization mode for all instruments. The study indicated that both TOF high resolution MS and triple-quadrupole tandem MS methods had higher sensitivities than IT-MS for all tested PFASs. Although IT-MS had a higher DL and smaller linear range, it provided the best results for tentative structure elucidation and qualitative analysis of branched PFASs isomers (Berger et al., 2004; Jahnke and Berger, 2009).

The analysis of 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 PFASs and fluorotelomer alcohols. PFAS are derivatized in order to be amenable for GC analysis. However, the use of the derivatization techniques is limited for PFOS analysis due to the instability of the PFOS's derivatives (Moody et al., 2001; Villagrassa et al., 2006).

7.0 Treatment technology

The available data and calculated pKa (2.8) values indicate that PFOA is a strong acid which predominantly dissociates to a negatively charged form (anion) at environmentally relevant pH values (U.S. EPA, 2005; Lange et al., 2006; Prevedouros et al., 2006). Based on the physical-chemical properties of the ionized form (a negligible vapor pressure, a high solubility in water and moderate sorption to solids), Prevedouros et al. (2006) suggested that PFOA would accumulate in surface water. Given the hydrophobic and oleophobic nature of the fluorinated alkyl chain and the hydrophilic nature of the carboxylate group, hydrophobic and electrostatic effects likely influence PFOA adsorption (Higgins and Luthy, 2006; Xiao et al., 2011). The nature of the chemical structure of PFOA (i.e., strong carbon - fluorine (C-F) bonds) makes it resistant to hydrolysis and biodegradation as well as to several chemical treatment processes (Lange et al., 2006; ATSDR, 2009).

7.1 Municipal scale

Dickenson and Higgins (2013) evaluated the ability of wide range of full-scale treatment techniques to remove PFASs, including PFOA and PFOS, from raw water or potable water reuse plants. The treatment trains varied, but generally consisted of coagulation followed by physical separation, aeration, chemical oxidation, UV irradiation, and disinfection. Regardless of the treatment train applied, there was little or no decrease in PFOA and PFOS concentrations and the authors concluded that these treatment methods are not effective in removing PFASs.

GAC adsorption and membrane filtration techniques appear promising for removal of PFOA in drinking water, achieving treated water concentrations below 0.2 µg/L (Tang et al., 2006; Lampert et al., 2007; Wilhem et al., 2008; Deng et al., 2010; Takagi et al., 2011; Appleman et al., 2014). In order to achieve a PFOA concentration below 0.2 µg/L, the GAC system must be specifically designed and appropriately operated for PFOA removal in drinking water. The presence of natural organic matter (NOM) in the source water may deteriorate GAC performance by directly competing for adsorption sites and preloading (fouling) the GAC beds. Therefore, the effectiveness of GAC to remove PFOA in drinking water appears to be dependent on the regeneration frequency and/or replacement of the carbon (Kolstad 2010; Takagi et al., 2011; Appleman et al., 2014). Membrane filtration such as reverse osmosis (RO) and bench-scale nanofiltration (NF) studies demonstrated effective removal of all tested short-and long-chain PFASs including PFOA in drinking water. Although the RO process is effective, it is likely to be an expensive treatment method (Steinle-Darling et al., 2008); Quinones and Snyder, 2009; Appleman et al., 2013; Flores et al., 2013). Anion exchange resins may also be effective in removal of PFOA. However full-scale evaluation of this technology has not been conducted specifically for PFOA removal in drinking water.

The selection and effectiveness of each treatment strategy is driven by several factors, including source water chemistry, concentration of PFOA and/or other PFASs and pre-existing treatment processes. If long-chain PFASs are detected in the drinking water sources, the utility may consider the implementation of treatments such as GAC. However, utilities that have shorter chain PFASs in their raw water source may choose to implement RO or NF. The treatment technologies need to be designed specifically for PFASs removal and operated appropriately in order to achieve contaminants removal objectives in drinking water (Dickenson and Higgins, 2013).

The ability of various drinking water treatment processes and treatment trains to remove PFOS have been summarized by Dickenson and Higgins (2013) and Rahman et al. (2014). Appendix A summarizes the percentage removal of PFOA in full-scale plants where both raw and finished water concentrations were reported (Rahman et al., 2014). Data show that the treatment technologies employed by these plants (with the exception of GAC, RO and NF) did not appreciably remove PFOA. They also show that in some cases concentrations in the finished water were higher than in the raw water, likely due to the breakdown of precursor compounds to form PFOA during the treatment (Takagi et al., 2008; Shivakoti et al., 2010). Takagi et al. (2011) also postulated that these higher finished water levels may result from desorption from GAC filters used for long periods of time without reactivation and the leaching of these compounds from Teflon-coated treatment equipment.

7.1.1 Conventional treatment

Conventional drinking water treatment processes generally incorporate coagulation, flocculation, sedimentation, and filtration, followed by primary and secondary disinfection. Common coagulants used in drinking water include aluminum sulfate (alum), ferric hydroxide, ferric chloride, polyaluminum chloride and coagulant aid polymers. Filtration media can consist of sand (single media); sand and anthracite (dual media); or sand, anthracite, and garnet (multi or mixed garnet media). GAC may also be used as the filter media.

Conventional full-scale drinking water treatment techniques have been found ineffective in removing PFOA from source waters. Samples collected from several full scale conventional treatment plants indicated essentially no difference in the PFOA concentrations between plant influent and concentrations in water following the coagulation, sedimentation, and sand filtration

steps (Loos et al., 2007; Shivakoti et al., 2009; Takagi et al., 2011; Thompson et al., 2011). Similarly, Eschauzier et al. (2012) reported that slow- and rapid- sand filtrations were ineffective for PFOS and PFOA removal. The inability of conventional water treatment to remove PFOA and PFOS may be due to their extremely low concentrations in water and their hydrophilicity which renders them unamenable to removal by conventional treatment processes (Rahman et al., 2014). These findings are in agreement with recently conducted bench-scale studies of the removal of PFOA from water (Deng et al., 2011; Xiao et al., 2013).

Jar tests (Xiao et al., 2013) achieved an approximately 3% removal of an influent concentration of 0.083 µg/L (83 ng/L) of PFOA, with an alum dose of 30 mg/L and pH of 7.9. A removal efficiency below 10% was reported under a range of alum doses ranging from 10 to 60 mg/L and pH levels ranging from 6.5 to 8.0. Removal rates of approximately 25% were observed using enhanced coagulation with alum doses greater than 60 mg/L and pH 4.5 – 6.5. In general, the removal efficiencies were below 35% under the examined coagulation conditions (alum doses 3-110 mg/L and pH 4.5-8.0). Ferric chloride coagulation exhibited similar results. The authors indicated that removal rates were lower for PFOA than PFOS in both conventional and enhanced coagulation conditions, possibly due to PFOA having a lower molecular size and a potential for being less hydrophobic.

However, Deng et al. (2011) demonstrated that the addition of powdered activated carbon (PAC) before the coagulation process was capable of enhancing the removal efficiency of PFOA in water after the coagulation. In the experiments, an initial PFOA concentration of 21.2 µg/L was decreased to 5.8 µg/L with a polyaluminium chloride (PACl) dose of 10 mg/L. A concentration below 1.0 µg/L was measured in the finished water after the addition of 10 mg/L of PACl and PAC doses up to 16 mg/L, to the initial PFOA concentrations in the range of 0.5-3.0 mg/L. The study found that the concentration of PFOA in the finished water decreased with increasing initial turbidity and PACl dose, and increased with increasing pH or temperature

7.1.2 Adsorption

Adsorbents typically used in drinking water treatment include activated carbon, activated alumina, zeolites, clays, metal oxides, hydroxides, and carbonates (AWWA, 2011; U.S. EPA, 2012). GAC is used in a fixed bed, while PAC is generally added directly to the raw water as a powder or mixed with water to form a slurry.

Several laboratory studies of PFOA and PFOS adsorption kinetics indicate that PAC reached sorption equilibrium in 4 hours while GAC reached equilibrium in 168 hours, (Yu et al., 2009) and that PFASs removal percentages were generally higher for PAC than for GAC (60–90% versus 20–40%, respectively) for 10 minutes adsorption time (Hansen et al., 2010). These results may be due to PAC's smaller particle size, and higher specific surface area per volume of carbon when compared to GAC (Yu et al., 2009; Hansen et al., 2010). If PFASs are present in the raw water year round, Rahman et al. (2014) suggested that GAC adsorption may be the preferred method for PFASs removal, while PAC may be more appropriate for short-term spill response remediation.

7.1.2.1 Granular activated carbon

Full-scale evaluations of the effectiveness of GAC adsorption for the removal of PFOA in drinking water sources have been mixed. Several full-scale studies, specifically designed and operated for PFASs removal in drinking water, observed successful removal of PFOA by GAC with a long empty bed contact time (EBCT) and an appropriate regeneration regime (MDH, 2008a; Wilhem et al., 2008; Rumsby et al., 2009; Little Hocking Water Association, 2010;

Appleman et al., 2014). Other water treatment plants found similar levels of PFOA in both source and finished water, suggesting that GAC treatment only partially removes this contaminant, if at all. These treatment plants were not specifically designed for PFASs removal in drinking water. As the GAC had been in place for a variable period of time, it was likely that the preloading by NOM had deteriorated the GAC performance leading to similar PFOA levels in the influent and treated water (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012, Flores et al., 2013).

A full-scale GAC treatment system with a flow rate of 1.5 m^3/minute was specifically designed for PFASs removal in groundwater. The system used two GAC contactors in a lead/lag configuration with an EBCT of 13 minutes each. The lead vessel operated for approximately 10 months and treated 30,129 BVs before the concentration of PFOA exceeded 0.05 µg/L. The GAC unit was capable of reducing an influent PFOA concentration in the range of 0.45–0.83 µg/L to below 0.05 µg/L, in the treated water from the lag vessel, for 72,775 BVs (approximately 22 months). At that point, the lead vessel water reached 0.25 µg/L PFOA, its carbon was replaced with virgin media and the vessel was put in the lag position (Appleman et al., 2014). Another full-scale 400 gpm (1.5 m^3/minute) GAC treatment system proved effective for the removal of PFOA in surface water, with an influent concentration decreasing from 0.9 µg/L to below the DL of 0.01 µg/L in the treated water. An increase in PFOA concentration in the treated water was observed after approximately 3 months with levels exceeding the treated water goal of 0.1 µg/L after 5 months of operation (Wilhelm et al., 2008; Rumsby et al., 2009).

The behaviour and fate of PFASs, including PFOA and PFOS, was assessed by analyzing influent and treated water from several drinking water treatment plants that included GAC in the treatment train. These plants were not specifically designed for PFASs removal in drinking water. The hydraulic retention time of individual treatment steps was considered when the efficiency of each these steps was assessed (Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013). The studies found that only the GAC step was capable of removing PFASs in drinking water. Removal of approximately 50% of PFOA was reported when a GAC process was included in the treatment train (Eschauzier et al., 2012; Flores et al., 2013). The paragraphs below provide more details on some of these studies.

A full-scale 5 million gallons per day (MG/D) treatment plant, designed to remove trace levels (ng/L) of organic contaminants in surface water, consisted of river bank filtration, softening, UV/H_2O_2, biologically-active GAC filtration and six GAC contactors. The GAC system operated in parallel mode with an EBCT of 10.5 minutes. Water samples analyzed before and after the GAC system demonstrated reduction of an influent PFOA concentration of 9.7 ng/L to below 5 ng/L (Appleman et al., 2014).

Eschauzier et al. (2012) monitored the concentrations of PFOA and PFOS in a drinking water treatment train consisting of coagulation, rapid sand filtration, dune passage, softening, ozonation and GAC treatment. Only the GAC step was effective for PFASs removal. The system used two-stage GAC contactors in a lead/lag configuration. Of the 40 filters, 20 were used in parallel mode as a first stage and the other 20 were used as a second stage filter. Each GAC filter operated at a flow rate of 348 m^3/hour and an EBCT of 20 minutes, resulting in a total EBCT of 40 minutes. Each virgin GAC filter was installed as a second stage filter and was switched to the first stage after 15 months of operation. After another 15 months, the carbon was reactivated and put back in service as a second stage filter. The GAC system achieved approximately 50% reduction on the average influent PFOA concentration of 8.8 ng/L in the feed water to the first GAC stage (Eschauzier et al., 2012). Flores et al. (2013) reported similar results for the removal

of PFOA (45%) in a water treatment plant, which had 24 GAC contactors installed and that were regenerated approximately once a year.

Takagi et al. (2008, 2011) investigated the behaviour, fate and removal efficiency of PFOA and PFOS in drinking water treatment processes from several drinking water treatment plants that included GAC in the treatment train. The removal efficiency of PFOA and PFOS were less than 50% in many of the water treatment plants. A negative removal rate in certain plants suggested that desorption from GAC filters, used for long periods of time without reactivation, may be responsible for these observations. The negative removal rates could also result from the formation of PFOA and PFOS from the degradation of the precursor compounds found in the raw water (Takagi et al., 2011). However, greater than 90% removal of PFOA was observed for 4 months in a 1.5 MLD water treatment plant after the replacement of its activated carbon in the GAC unit. The treatment train consisted of coagulation/sedimentation, rapid sand filtration and two GAC contactors (coal and coconut-shell carbon) in parallel mode. Both GAC contactors were capable of reducing the PFOA concentrations in the range of 25–44 ng/L to below the LOQ of 0.7 ng/L for 4 months. The concentration of the GAC filtered water gradually increased to13 ng/L at the end of the 8 month study period (Takagi et al., 2011).

Rapid small-scale column tests (RSSCTs) are a common bench scale test used to evaluate GAC. Using RSSCTs, Appleman et al. (2013) compared the effectiveness of three different types of GAC for removal of several PFASs including PFOA and PFOS. The column experiments were conducted with an EBCT of 0.38 minutes using deionized water and surface water [dissolved organic carbon (DOC) of 1.7 mg/L], both spiked with 1.0 µg/L of each PFASs. The tests were run for a total of 125,000 BVs (approximately 33 days). Carbon performance varied based on the type of carbon and water chemistry, with GAC being more effective at removing PFASs in deionized water. Of the three carbons, F300 achieved the best results. In the experiments conducted with deionized water, a concentration greater than 0.02 µg/L PFOA (2% of influent concentration C_0) was observed at approximately 30,000 BVs (8 days) and a filtered water concentration of 0.05 µg/L (5% of C_0) was measured after 56,000 BVs. However, the filtered water concentration reached 0.2 µg/L (20% of C_0) after 11,000 BVs (3 days) and full (100%) breakthrough was observed at a run length of 26,000 BVs in spiked surface water. Although RSSCTs are not suitable for evaluating the effect of preloading/fouling of GAC columns by DOC, the observed rapid breakthrough in the spiked natural water demonstrated that the presence of DOC affects the GAC performance in the removal of PFASs by directly competing for adsorption (Appleman et al., 2013).

The efficiency of PFOA removal by GAC adsorption is impacted by NOM in source water which competes for the carbon adsorption site and will adsorb irreversible, causing the carbon's capacity for the target compound to be reduced. When the adsorption capacity of the GAC is exhausted, it must be removed from the contactor and replaced with fresh or reactivated carbon. GAC is used in a fixed bed reactor, as a substitute for existing filtration media (i.e., sand) in a conventional filter, as a layer in a multi-media rapid filter, or in a separate contactor. The reactor can be located at the beginning of the treatment train in a dual-media or sand-replacement mode, or later in the treatment train as a second-stage contactor. The rate of GAC exhaustion will vary substantially for the same water source depending in which configuration GAC will be employed. A dual media (GAC and sand) is used when turbidity removal and the adsorption/removal of the contaminants are combined in a single unit process. The dual media filter (typically located after sedimentation) is likely to be exposed to higher DOC concentrations, and this filter will be exhausted faster. A GAC contactor located at the end of a treatment train will likely experience slower preloading/fouling, since the treatment steps prior to a GAC contactor will reduce the

DOC influent concentrations. GAC contactors in lead/lag configuration have also been shown to achieve a PFOA concentration below 0.2 µg/L in treated water (Appleman et al., 2014; Little Hocking Water Association, 2010). This treatment strategy will assist in completely utilizing the entire GAC capacity and reducing operating cost (i.e., carbon replacement cost) (Crittenden et al., 2012).

Close monitoring of PFOA breakthrough (treatment objective) is necessary for efficient operation of GAC unit. Studies indicated that PFOA was successfully removed from drinking water when a frequent regeneration or replacement (3 to 6 months) of the GAC was performed (e.g., Wilhelm et al., 2008; Rumsby et al., 2009; Takagi et al., 2011). Takagi et al. (2011) observed that GAC regenerated over periods greater than one year were not effective in removing PFOA and PFOS and suggested regenerating the carbon 2 to 3 times per year. A GAC replacement at approximately every 3 months was needed to achieve PFOA removal to below 0.004 µg/L in a system where the influent PFOA concentrations ranged from 1.9 to 15 µg/L (Little Hocking Water Association, 2010). A full-scale 2,500 gpm GAC treatment plant, using two GAC contactors in series observed breakthrough of PFOA and PFOS after 286 days and 550 days, respectively. With the replacement of the GAC at the earliest time of PFOA breakthrough, the system was able to treat 1.9 million gallons of water for 23 months (MDH, 2008a; Kolstad, 2010).

Eschauzier et al. (2012) observed that the removal efficiencies of PFASs by GAC increased with increasing carbon chain length and that sulfonate compounds were removed for a longer period of time than the carboxylate compounds. Shorter-chained PFASs (especially perfluorobutanoic acid [PFBA] and perfluorobutane sulfonate [PFBS]) were not removed by GAC. These findings were in agreement with previous batch experiments showing that the sorption of PFASs on activated carbon decreased with decreasing the carbon chain-length and perfluorosulfonates adsorbed stronger than perfluorocarboxylates with the same carbon chain length (Ochoa-Herrera and Sierra-Alvarez, 2008; Hansen et al., 2010; Dudley et al., 2012; Appleman et al., 2014). Branched isomers of PFOS and PFOA were found to be less sorbable to GAC than linear isomers. Desorption of shorter chain PFASs due to competition for sorption sites with longer chain PFASs or NOM (i.e., DOC) may result in higher levels of shorter chain PFASs in the treated water (Eschauzier et al. (2012).

7.1.2.2 Powdered activated carbon

No full-scale data were reported on the efficacy of PFOA removal by PAC. Most published studies on the efficacy of PAC were conducted at the bench-scale. PFOA concentrations in some of these bench-scale studies were order of magnitude higher than the concentration observed in natural waters. However, trends observed for PAC in terms of preferential adsorption (chain-length dependence) and competition with NOM were similar to that documented for GAC (Hansen et al., 2010; Dudley et al., 2012).

Dudley et al. (2012) evaluated the adsorbability of ten PFASs with different carbon chain lengths (from C4 - C10) on commercially available PACs (coconut shell, lignite, wood, and bituminous coal) and superfine PACs (S-PACs) obtained by wet-milling the commercially obtained PACs. Sulfonate substances were found to be more adsorbable than carboxylate substances and sorption kinetics were faster with S-PACs when compared to PACs. The removal efficiencies of PFAS increased with increasing carbon chain length (i.e., negligible removal of C4 compounds but greater than 90% removal for C7-C10 compounds). The presence of NOM was found to decrease the effectiveness of PFAS removal by PAC in batch studies. The authors also

concluded that significant removal of smaller chain PFASs may not be achievable at practical PAC dosages (Dudley et al., 2012).

Yu et al. (2009) investigated the sorption kinetics and isotherms of PFOA and PFOS on PAC, GAC and an anion-exchange resin. The anion exchange resin had the highest sorption capacity for PFOA while PAC was found to be the adsorbent of choice for PFOS. Another laboratory experiment found 88% and 25% removal of PFOA by PAC and GAC, respectively, based on an initial concentration of 1.4 µg/L in groundwater. The study also observed that PFOS sorption on PAC was faster than on GAC, suggesting that the sorption kinetics were influenced by the size of the activated carbon (Hansen et al., 2010). Qu et al. (2009) inferred that PAC could be used as an effective adsorbent for the removal of PFOA from water because the removal efficiency increased from 51.1% to 99.9% when the PAC doses were increased from 0.1 g/L to 10 g/L (initial PFOA concentration of 20 mg/L).

7.1.3 Membrane filtration

There are four main types of membrane filtration processes in drinking water treatment applications: microfiltration (MF), ultrafiltration (UF), nanofiltration, and reverse osmosis. Low pressure membranes such as MF and UF are not capable of rejecting PFASs since their pores sizes are larger than the effective diameter of the PFASs molecules (~1 nm) (Tsai et al., 2010; Rahman et al., 2014). Bench-scale studies indicated that the membrane molecular weight cut-off (MWCO) of NF/RO is probably the most important factor for removal of PFASs for these technologies. In general, NF membranes have a lower rejection (95%) than RO (greater than 99%), which is consistent with the fact that NF membranes have larger pores (Tang et al., 2006, 2007; Steinle-Darling and Reinhard, 2008; Lipp et al., 2010; Appleman et al., 2013; Rahman et al., 2014).

The available scientific information on the removal of PFOA and PFOS from drinking water supplies by membrane filtration is limited to one full-scale RO drinking water utility (Flores et al., 2013) and several indirect potable water reuse plants (Quinones and Snyder, 2009; Appleman et al., 2014). Due to the physical location of these indirect potable water reuse plants, they were considered to be major potential contributors to the drinking water facilities' source water in the conducted studies (Quinones and Snyder, 2009).

Although a full-scale conventional treatment was reported as being ineffective for PFOA removal in surface water; 92% removal of PFOA was achieved when RO followed the conventional treatment train (Flores et al., 2013). The RO system's feed water was filtered by the conventional treatment process and blended with untreated groundwater. Feed water PFOA concentration ranged from 15 to 26 ng/L (average 21 ng/L) and the RO system was capable of reducing these PFOA concentrations to an average of 2.1 ng/L (Flores et al., 2013).

Two indirect potable water reuse plants with RO units in their treatment trains were capable of reducing a PFOA concentration to below 55 ng/L in the RO treated water. Both RO systems had a flux rate of 12 gallons per square foot per day (gfd) (20 $L/m^2/h$) and water recovery in the range 80-85%. The feed PFOA concentrations to the RO units ranged from 9.5 to 200 ng/L (Dickenson and Higgins, 2013; Appleman et al., 2014). A survey of several drinking water utilities and indirect potable water reuse plants showed that the PFOA concentrations in the treated water were comparable to the levels found in the raw water samples in almost every case. However, removal was only observed in one planned potable reuse facility when an integrated membrane treatment consisting of MF and RO was employed. The membrane system was capable of rejecting a feed PFOS concentration of 15 ng/L to below 5 ng/L (Quinones and Snyder, 2009).

Bench-scale experiments evaluated the rejection behaviour of unfouled and fouled NF membranes on the removal of PFASs, including PFOA (Appleman et al., 2013). The study found that a polyamide thin film composite flat-sheet NF membrane was capable of rejecting all of tested compounds in the range of 93 to 99%. Greater than 97% rejection of an average influent PFOA concentration of 664 ng/L (LOQ of 20 ng/L) was observed in all experiments using virgin membranes and spiked de-ionized water; virgin membranes and spiked groundwater; and fouled membranes and spiked groundwater. The fouling layer on the NF membrane showed no negative effect on PFOA rejection (Appleman et al., 2013). Another bench-scale study was conducted on one RO (MWCO of 100 Da) and three NF (MWCO range of 200 – 360 Da) membranes for the removal of PFOA. The RO membrane achieved a 99.9% rejection of PFOA from the feed water concentration of 3500 ng/L with a permeate PFOA concentration in the range of 3–6 ng/L. The RO system was operated with a flux rate of 30–40 L/m^2/h and a feed pressure of 8 bars (116 psi). All tested NF membranes achieved a rejection in the range of 95.5–99.8% of an average feed PFOA concentration of 3000 ng/L, with a flux rate of up to 70 L/m^2/h and an operating pressure in the range of 4–7 bars (58-101 psi) (Lipp et al., 2010).

Although there is limited information on full-scale RO and only bench-scale NF treatment information, both technologies are considered effective for PFOA removal from drinking water (Appleman et al., 2014). The results of the NF studies are promising since NF is a less energy intensive process than RO. Testing of the selected NF membrane for PFOA removal at both pilot- and full-scale is an important step for utilities when considering this treatment process. Since the size exclusion is an important mechanism for PFASs rejection by NF membranes, consideration should be taken to select membranes with MWCO smaller than the size of PFOA.

Considerations when using RO treatment include disposal of the reject water and the potential for increased corrosivity of the treated water. RO rejects a significant portion of the influent water as contaminant-rich brine, and the concentrate discharge must be disposed of appropriately. The removal of contaminants can cause mineral imbalances that could increase the corrosive nature of the treated water. In most cases, post-treatment corrosion control measures need to be taken.

7.1.4 Ion exchange

PFOA is in an anionic form at ambient water pH values and therefore is expected to be amenable to removal by anion exchange resins (Senevirathna et al., 2010). Two primary mechanisms, hydrophobic and electrostatic interactions, were proposed for the removal of PFOA by ion exchange resins (Carter et al., 2010; Deng et al., 2010; Xiao et al., 2012).

Appleman et al. (2014) reported results for the only one known full scale application of ion exchange for the removal of PFASs. However, this system was not specifically designed for PFASs removal in drinking water. A 350 gpm full-scale ion exchange plant reduced the concentrations of PFOA in the range of 68–120 ng/L to an average concentration 24 ng/L in groundwater. A strong base anion resin impregnated with iron oxide used for arsenic removal was assessed for PFOA removal after the resin had been in use for 5 and 9 months. The highly porous strong base anion exchange resin, achieved greater than 75% removal of PFOA, partial removal of perfluoroheptanoic acid (PFHpA) (46%), and high removal of both PFOS (>92%) and perfluorohexanesulfonate (PFHxS) (97%). Shorter carbon chain compounds such as PFBA, and perfluorohexanoic acid (PFHxA) exhibited little to no removal. Results also indicated that perfluorosulfonic acids were preferably removed by anion exchange resin over the perfluorocarboxylic acids.

Exchange resins exhibit a degree of selectivity for various ions, depending on the concentration of ions in solution and the type of resin selected. Laboratory-scale evaluations of different types of resins (i.e., ion exchange resins, non-ion exchange resins) for removal of PFASs in water have been reported in the literature (Lampert et al., 2007; Carter et al., 2010; Deng et al., 2010; Senevirathna et al., 2011; Xiao et al., 2012; Chularueangaksorn et al., 2013). Batch kinetic tests conducted with a high initial PFOA concentration (mg/L) demonstrated a greater than 99% removal of PFOA in 25 hours of contact time using a commercial anion exchange resin, while another anion resin achieved only 37% removal. The study also observed that PFOS anions were preferably removed over PFOA anions in the ion exchange process (Lampert et al., 2007). In laboratory experiments, anion exchange resins demonstrated greater capacity for PFASs removal than non-ion exchange resins (Chularueangaksorn et al., 2013, 2014). Laboratory-scale fix-bed columns compared the performance of anion exchange and non-ion exchange resins. The tests were conducted with an influent concentration of 5 µg/L PFOA for 120 days of operation. The breakthrough goal of 0.5 µg/L was observed with run lengths of 119,880 BVs (111 days) and 68,040 BVs (60 days) by the anion exchange and non-ion exchange resins, respectively (Chularueangaksorn et al., 2013).

While findings showed that anionic resins had a higher capacity for PFOA than non-ion exchange resins (Deng et al., 2010; Chularueangaksorn et al., 2013, 2014), it was also observed that moderately polar non-ionic resins performed better than non-polar non-ionic resins for removal of PFOA from water (Xiao et al., 2012).

Studies indicate that the ion-exchange process is a promising technology (Dickenson and Higgins, 2013) for the removal of PFAS, including PFOA, from drinking water. However, additional studies on the, selectivity of the resins, kinetic limitations, the impact of DOC, regeneration rates, and the presence of competing ions such as sulfate and nitrate on removal efficiency are needed (Dickenson and Higgins, 2013; Rahman et al., 2013).

7.1.5 Oxidation, UV irradiation and advanced oxidation processes

Advanced oxidation processes (AOPs) have been developed for removal of contaminants that are resistant to more typical chemical oxidation treatment processes. They include the use of appropriate combinations of ultraviolet (UV) light, chemical oxidants and catalysts (e.g., ozone, hydrogen peroxide, titanium dioxide) to generate highly reactive radicals, such as hydroxyl radicals, which are strong oxidants and react rapidly and non-selectively with organic contaminants.

Rahman et al. (2014) summarized studies that have demonstrated that PFAS like PFOA will likely be resistant to oxidation, even by molecular ozone and hydroxyl radicals. Due to the low reactivity of PFOA with ozone and AOPs, chlorine–based oxidation processes will likely not oxidize PFOA under typical drinking water conditions. The resistance of PFOA to oxidation is due to the shielding effect of the fluorine atoms and the strength of the carbon-fluorine bonds (3M, 1999; ATSDR, 2009). These conclusions have been confirmed in surveys of full-scale treatment plants (Quinones and Snyder, 2009; Shivakoti et al., 2010; Takagi et al., 2011; Eschauzier et al., 2012; Flores et al., 2013) described below.

In a survey of several drinking water utilities, Quinones and Snyder (2009) observed that PFOA was resistant to chlorination, chloramination and ozonation even in a combination with other treatment processes such as coagulation/flocculation, deep bed filtration and UV irradiation. Results from drinking water treatment plants in Japan reported similar concentrations of PFOA in samples of water treated with an ozonation process and in the raw water samples (Shivakoti et al., 2010; Takagi et al., 2011). Ozone doses in the range 0.37–0.85 mg/L and contact time as high as

120 minutes showed that the ozonation process was ineffective to degrade PFOA at four utilities (Takagi et al., 2011). Thompson et al. (2011) observed that an ozone dose of 5 mg/L with a contact time of 15 minutes in reclaimed water was not effective at reducing PFOA concentrations in the range of 7.1–12.4 ng/L.

A full scale treatment plant employing two UV reactors, each capable of treating 3 MG/D groundwater with a UV dose of 80 mJ/cm^2 and UV transmittance of 95%, were not capable of reducing an influent PFOA concentration in the range of 11–15 ng/L. Another full scale 5 MG/D treatment plant reported that a UV dose of 500 MJ/cm^2 in combination with a dose of 4 mg/L H_2O_2 was also ineffective at degrading 19 ng/L PFOA in surface water (Appleman et al., 2014). Oxidation/AOPs and UV irradiation appear ineffective for PFOA removal in drinking water. However, ozone or AOPs may be able to oxidize polyfluorinated precursor chemicals that may be present in raw water, resulting in the potential for increasing the concentration of PFOA and PFOS in the finished water (Rahman et al., 2014).

7.1.6 Aeration/air stripping

The removal of compounds using air stripping is based on the equilibrium partitioning of chemicals between air and water, which is affected by the contact surface area between the air and the water, as well as temperature, vapour pressure and the pH of the water.

Dickenson and Higgins (2013) evaluated 23 PFASs (including PFOA and PFOS) in raw and finished drinking water and at various steps along the treatment train. They found that aeration was ineffective at removing PFOA and PFOS (10% removal).

7.1.7 River bank filtration (soil aquifer treatment)

River bank filtration (RBF) is a drinking water treatment method where surface water flows through the subsurface sand and gravel layers of the bank or bed of a river to extraction wells and contaminants are removed through the processes of filtration, sorption, dilution and biodegradation.

A drinking water utility utilizing RBF with a hydraulic residence time of approximately 10 days observed approximately 30% removal for PFOA, variable removal of some PFASs, and increases in concentration for other PFASs (Appleman et al., 2014). The authors concluded that this variation was possibly due to the variability in the influent concentrations from wastewater effluents impacted the drinking water sources and/or due to breakdown of precursor compounds through the river bank. Dickenson and Higgins (2013) concluded that RBF was not likely to result in significant removal of PFASs.

7.1.8 Emerging technologies

Other potential treatment technologies for removal of PFOA and PFOS have promise, but are still being researched actively. They have not yet all been evaluated on drinking waters by laboratory, pilot, or full-scale studies, but have been mentioned in reviews of bench scale studies of some PFASs removal from drinking water and wastewater (Vecitis et al., 2009; Eschauzier et al., 2012).

7.1.8.1 Nanomaterials and nanotechnologies

Nanomaterials are being developed for drinking water treatment applications, including ion exchange, sorption and oxidation processes, and abiotic reduction (e.g., nanozerovalent iron) (Boyd et al., 2013). Different nanomaterials/nanotechnologies show promise for removal of PFOS including carbon nanotubes (CNTs), chitosan-based molecularly imprinted polymers (MIPs),

electrospun nanofibrous membranes (ENFMs), and titanium dioxide (TiO_2) assisted photocatalysis (Yu et al., 2008; Deng et al., 2012; Dai et al., 2013). CNTs are carbon molecules composed of carbon lattices that can take the form of tubes. Chitosan is a natural polysaccharide based on the shells of crustaceans. It may be prepared as a nanoparticle or electrospun in nanofibers (Sonia and Sharma, 2011; Zhao et al., 2011a; Boyd et al., 2013). Molecular imprinting is a technique where specific sites for target compounds are constructed on a polymer so that specific adsorbates are recognized in the sorption process. ENFMs are prepared by electrospinning nanofibers of polymer or polymer composite materials to create membranes of non-woven fibers with diameters ranging from several hundreds to tens of nanometers (Greiner and Wendorff, 2007; Dai et al., 2013; Boyd et al., 2013).

Deng et al. (2012) have demonstrated the effectiveness of CNTs for removal of perfluorinated contaminants, including PFOA and PFOS, from aquatic environments when the hydrophobic interactions were involved in the sorption of perfluorinated contaminants onto the CNTs. The sorption of the perfluorinated contaminants was increased with increasing carbon-fluorine chain length with the same functional group.

7.1.8.2 Photolysis and photochemical degradation

Although a full-scale UV treatment process was reported ineffective in removal of PFOA in drinking water, several laboratory-scale evaluations of synthetic waters, wastewaters and industrial waters have reported that UV-visible light, UV in the presence of persulfate, UV in the presence of TiO_2 and perchlorate, UV in the presence of iodide and UV irradiation using carbonate radical ions may degrade PFOA concentrations (Hori et al., 2004a, 2005; Chen and Zhang, 2006; Chen et al., 2007; Fujii et al., 2007; Giri et al., 2011, 2012, 2013; Dillert et al., 2007; Panchangam et al., 2009; Qu et al., 2010).

A laboratory-study reported 87% degradation and defluorination of an initial PFOA concentration of 25 mg/L under 185 nm UV light irradiation in the presence of persulfate. When compared to direct photolysis the photochemical reaction enhanced PFOA degradation. The study observed a formation of short-chain PFCAs (Chen and Zhang, 2006). Another laboratory-study reported on the effectiveness of sulfate radical anion ($SO_4^{\cdot -}$) to decomposed PFOA in a photochemical reaction. The authors reported that PFOA concentration of 1.35mmol was completely decomposed by the photochemical system using $SO_4^{\cdot -}$ and 4 hours of UV visible light irradiation. The study also reported on the formation of shorter-chain PFCAs in a stepwise manner (Hori et al., 2005). After UV-visible light irradiation was applied under 0.48 MPa of oxygen, 89.5% of an initial PFOA concentration of 1.35 mmol was decomposed and the formation of CO_2, F^- and short-chain PFCAs was observed. The authors also reported that heteropolyacids due to their high stability are attractive photocatalysts in the degradation reactions of PFCAs. In the presence of heteropolyacid, 7.44 µmol PFOA in aqueous solution were completely degraded after 24 hours of UV irradiation. The photocatalyst enhanced the PFOA degradation and suppressed the formation of the short-chain PFCAs (Hori et al., 2004a). Tang et al. (2012) studied the effectiveness of the UV–Fenton technique for PFOA removal in water and found almost complete degradation and defluorination of PFOA within several hours, while PFOA was hardly degraded by a conventional Fenton system alone.

7.2 Residential scale

Generally, it is not recommended that drinking water treatment devices be used to provide additional treatment to municipally treated water. In cases where an individual household obtains

its drinking water from a private well, a private residential drinking water treatment device may be an option for reducing PFOA concentrations in drinking water.

Although there are no certified residential treatment devices for the reduction of PFOA from drinking water, available data suggests that residential activated carbon and reverse osmosis can achieve treated PFOA concentrations of 0.2 µg/L and below 0.05 µg/L, respectively. In addition, treatment devices using anion exchange may be effective for the reduction of PFOA.

The Minnesota Department of Health (MDH, 2008b) completed a study of the effectiveness of point-of-use (POU) water treatment devices for PFOA, PFOS and PFBA removal and demonstrated that RO and activated carbon filters were capable of reducing PFOA concentrations typically found in drinking water. Laboratory screening tests and field evaluation of devices installed in municipal water systems were undertaken. In the laboratory tests, the challenge waters had a PFOA concentration of 3.0 µg/L and the target goals for performance was 0.2 µg/L. The field testing involved monitoring and sampling of four activated carbon and seven RO point-of-use devices installed at two municipal wells. One of the wells had concentrations of 0.6 µg/L PFOA, 0.9 µg/L PFOS, and 1.4 µg/L PFBA, while only PFBA was present (1.5 µg/L) at the second well. All RO devices were equipped with an activated carbon pre-filter (before the RO membrane) and a post-treatment (after the RO membrane) activated carbon polishing filter. Results indicated that all activated carbon and RO devices were effective in removing PFOA to below the quantification limit of 0.2 µg/L and below the detection limit of 0.05 µg/L, respectively. Based on these results, activated carbon and RO are expected to be effective at reducing the level of PFOA in drinking water to levels below the MAC of 0.2 µg/L.

Health Canada does not recommend specific brands of drinking water treatment devices, but it strongly recommends that consumers use devices that have been certified by an accredited certification body as meeting the appropriate NSF International (NSF)/American National Standards Institute (ANSI) drinking water treatment unit standards. These standards have been designed to safeguard drinking water by helping to ensure the material safety and performance of products that come into contact with drinking water. Certification organizations provide assurance that a product conforms to applicable standards and must be accredited by the Standards Council of Canada (SCC). In Canada, the following organizations have been accredited by the SCC to certify drinking water devices and materials as meeting NSF/ANSI standards (SCC, 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 PFOA removal in residential scale applications. Ion exchange treatment devices is typically designed and constructed for residential use by drinking water treatment system providers or dealer. If an ion exchange system is used, the water may need to be filtered through a GAC filter to remove any chlorine or chloramine (if connected to a treated water supply) from the water before it reaches the resin.

Health Canada strongly recommends that chemicals used in treatment systems be certified to NSF/ANSI Standard 60 – Drinking Water Treatment Chemicals Health Effects (NSF/ANSI, 2017b) and that materials and components be certified to NSF/ANSI Standard 61 – Drinking Water System Components Health Effects (NSF/ANSI, 2017a) 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 PFOA. Periodic testing by an accredited laboratory should be conducted on both the water entering the treatment device and the finished water to verify that the treatment device is effective. Devices can lose removal capacity through use and time and need to be maintained and/or replaced.

8.0 Kinetics and metabolism

PFOA is considered chemically unreactive, and it is not metabolized. The oral absorption of PFOA is rapid and complete (Kemper, 2003; Hundley et al., 2006; Lau et al., 2007). Once absorbed, PFOA is primarily restricted to plasma and extracellular fluid (Butenhoff et al., 2004a; Han et al., 2012) and excreted in urine.

8.1 Absorption

PFOA is rapidly and nearly completely absorbed in the GI tract. In rats, studies consistently estimated the oral absorption rates of PFOA at >93% after a single dose (0.1 to 25 mg/kg bw) by gavage (Johnson and Ober, 1979, 1999; Kemper, 2003; Cui et al., 2010). Hundley et al. (2006) derived similar absorption rates for mice, rats, hamsters and rabbits after a single oral bolus of PFOA at 10 mg/kg bw. The estimated absorbed fractions were generally higher in males (rats: 89%, mice: 82%, hamsters: 92%) than in females (rats: 76%, mice: 61%, hamsters: 75%) except for rabbits (88% in both sexes). Fasted rats exhibited PFOA plasma concentrations approximately 2–3 times higher after a single oral bolus at 10 mg/kg bw (Hinderliter et al., 2006).

No controlled study data regarding the oral absorption of PFOA in humans are available; however, studies of residents living in areas with contaminated drinking water (Emmett et al., 2006a; Wilhelm et al., 2008) provide evidence of elevated serum PFOA concentrations. Emmett et al. (2006a) correlated the number of glasses of tap water ingested per day with blood concentrations, indicating this was the primary exposure route for populations with elevated PFOA concentrations in drinking water.

Limited inhalation or dermal studies have reported PFOA kinetics; however, the physicochemical properties of the compound suggest that these routes of exposure are not important when PFOA is found in drinking water (see Section 5.7).

8.2 Distribution

PFOA is mainly present in serum/plasma (Johnson and Ober, 1999; Kudo et al., 2007). The volume of distribution, which is similar across species (approximately 170 mL/kg bw), suggests extracellular distribution (Butenhoff et al., 2004a; Han et al. 2012). PFOA is tightly bound to serum protein, which plays an important role in distribution in blood and to tissues (Han et al., 2005). Binding in blood is primarily to serum albumin, with >90% of PFOA in serum expected to be bound to albumin in rats and humans (Han et al., 2003). To a lesser extent, PFOA can also bind to plasma γ-globulin, α-globulin, α-2-macroglobulin, transferrin and β-lipoproteins (Kerstner-Wood et al., 2003; Butenhoff et al., 2012a). Protein binding also occurs in organs and tissues. Luebker and coworkers (2002) reported *in vitro* binding of PFOA to rat liver fatty acid binding protein (L-FABP). PFOA has also been shown to bind to rat kidney and urine α2μ-globulin; however, dissociation constants were low compared to other ligands known to induce hyaline droplet nephropathy (Han et al., 2004). Linear PFOA isoform preparations bound more tightly to human serum albumin compared to branched isoforms, although the binding affinities were similar to one another (within one order of magnitude) (Beesoon and Martin, 2015).

PFOA kinetics are non-linear at high doses, which is hypothesized to be due to the saturation of organic ion transporters (OATs) responsible for renal reabsorption at high doses (e.g., 20 mg/kg bw per day administered in capsules), resulting in a higher excretion rate at high doses than at low doses (e.g., 0.1 mg/kg bw per day) (Andersen et al., 2006). Serum levels did not increase proportionally with increasing dose, except at lower doses in some studies and steady-state was reached more rapidly than expected at high doses with classical kinetics (4–5 half-lives). However, at lower gavage doses closer to those relevant to human environmental exposures, kinetics are consistent with linear first order processes, and serum levels are proportional to administered dose (Loveless et al., 2006; Lou et al., 2009). This non-linearity can affect PFOA distribution; for example, after a single intravenous dose in male rats, a lower proportion of the dose was distributed to the liver (27%) at 17 mg/kg bw compared to 52% at 0.4 mg/kg bw (Kudo et al., 2007).

Few data have been gathered on the human tissues to which PFOA is typically distributed. However, the tissue distribution is well documented in experimental animals, including monkeys, rats, and mice. In monkeys, PFOA distribution to the liver has been documented following administration of oral capsules containing PFOA (Butenhoff et al., 2002; 2004a). PFOA levels in other organs were not investigated. In orally exposed rats, PFOA has been detected most frequently and at the highest levels in the liver (Ylinen et al., 1990; Kemper, 2003; Martin et al., 2007). Additional primary tissues of distribution include the testes, spleen, lung, kidney, brain, skin, muscle, bone gastrointestinal tract and adipose tissue (Ylinen et al., 1990; Kemper, 2003). In orally exposed mice, PFOA has been detected in the liver, kidney, and bile (Lou et al., 2009; Minata et al., 2010).

In humans, PFOA was detected in approximately one half of the analyzed liver samples (in 6 males and 6 females from Catalonia, Spain; aged 27–79 years), and was significantly higher in males than in females (Kärrman et al., 2010), but was below the limits of quantification in livers in cadavers with environmental exposure (Olsen et al., 2003a). Neither cerebrospinal fluid

(Harada et al., 2007) nor thyroid (Pirali et al., 2009) have been observed to be relevant partitioning sites for PFOA.

In rats, PFOA concentrations were consistently higher in males than in females after single or repeated exposures (Ylinen et al., 1990; Kemper, 2003). The differences have been attributed to more rapid elimination of PFOA in females than males. In mice and non-human primates, there do not appear to be sex differences in PFOA concentrations (Griffith and Long, 1980; Butenhoff et al., 2004a; Lou et al., 2009). Lou et al. (2009) reported similar serum, liver and kidney PFOA concentration time-courses in male and female CD-1 mice after a single oral gavage of 1 or 10 mg/kg bw; however, the 95% confidence intervals on the mean half-lives do not overlap, indicative of possible sex differences in mice. Sex differences in PFOA concentrations have also been noted in human biomonitoring studies (see Section 5.6). As previously described in Section 5.6, serum PFOA levels in humans appeared to be influenced by age and gender in CHMS. The effect was also observed in U.S. studies, such as the National Health and Nutrition Examination Survey (NHANES) 1999–2008 (Kato et al., 2011) and other reference populations (Harada et al., 2004; Hölzer et al., 2008; Ingelido et al. 2010). As age increases, PFOA concentration has been shown to decrease in males and increase in females (Kato et al. 2011). Plausible explanations are menstrual bleeding, especially in nulliparous women (Ingelido et al., 2010), pregnancy and lactation. Supporting this hypothesis is the observation of higher serum PFOA levels in primiparous women than multiparous women (Kim et al., 2011), as well as the significant decrease in serum PFOA levels with duration of lactation (2–7 weeks vs. 3–4 months after delivery) (von Ehrenstein, 2009; Monroy et al., 2008).

PFOA exposure can occur transplacentally and lactationally. Fetal transfer via the placenta has been demonstrated in rats (Hinderliter et al., 2005) and mice (Fenton et al., 2009). In humans, concentrations of PFOA in cord blood of newborns are similar to maternal blood concentrations (Tittlemier et al., 2004; Midasch et al., 2007; Monroy et al., 2008; Beesoon et al., 2011; Needham et al., 2011; Gützkow et al., 2012). Moreover, serum concentrations in young children have been noted to be higher than serum concentrations in their mothers in a reference (i.e., not PFOA-contaminated) area (Hölzer et al., 2008) and in an area with elevated environmental PFOA levels (Mondal et al., 2012); however, serum concentrations were similar between children and mothers in an area with elevated PFOA levels in drinking water (Hölzer et al., 2008). Lactational transfer of PFOA has been measured in various mammal species, including humans, rats, mice, and sheep (Hinderliter et al., 2005; Fenton et al., 2009; Kim et al., 2011; Needham et al., 2011). Concentrations of PFOA in milk are consistently lower than in maternal plasma (Hinderliter et al., 2005; Fenton et al., 2009; Liu et al., 2011); Milk PFOA levels were approximately 10% and 25% of maternal plasma levels in rats and mice, respectively. In humans, a review of milk and maternal serum concentrations found the maternal milk:serum ratios across several studies to be approximately 0.11–0.12 (Liu et al., 2011). PFOA levels in human milk decrease significantly throughout the lactation period (Thomsen et al., 2010), and with increasing number of infants breastfed (Tao et al., 2008; Kadar et al., 2011). In a community with PFOA-contaminated water, infants breastfed for ≥ 12 months had significantly higher serum PFOA concentrations than infants who were not breastfed (Mondal et al., 2014); however, the authors noted that the estimates may be imprecise as they are based on only 8 infants in the long-duration group. Similarly, a study of Faroese infants with serum PFOA data at birth and at 11, 18, and 60 months estimated an increase in serum PFOA concentrations of about 28% per month during the period of exclusive breastfeeding and of about 4% per month during periods of partial breastfeeding (Mogensen et al., 2015a). In this study, serum PFOA levels measured up to five years of age did

not decline to serum PFOA levels at birth, which the authors attributed to ongoing dietary exposure to PFOA (in particular through traditional intake of pilot whale meat).

8.3 Metabolism

The available data indicate that PFOA is not metabolized. Studies conducted in rodents and non-human primates did not reveal quantitatively significant metabolism of PFOA, and PFOA was not metabolized when incubated with microsomal fractions of human or rat intestine, kidney or liver homogenates (Kemper and Nabb, 2005; EFSA, 2008; ATSDR, 2009).

8.4 Excretion

Remarkable species-dependent differences in elimination half-life have been observed, with PFOA remaining in human bodies for a much longer duration than other species, including non-human primates, rats and mice (Post et al., 2012). Elimination half-lives from serum in humans are significantly longer than in non-human primates and rats. Species- and sex-related differences are primarily attributed to elimination kinetics where, at higher doses, the kinetics of PFOA in rodents and primates do not follow one-compartment or simple first-order models (Andersen et al., 2006). Half-life values for serum elimination of PFOA in humans were derived from data obtained in retired workers from a 3M Company factory in Alabama, U.S.A (arithmetic mean of PFOA serum half-life = 3.8 years; range = 1.5–9.1 years; 95% CI = 3.1–4.4 years; Olsen et al., 2007) and current workers in a fluorochemical plant in China (geometric mean of PFOA serum half-life = 4.1 years; range = 0.44–3663 years; no 95% CI reported; Fu et al., 2016). In populations exposed environmentally through the consumption of PFOA-contaminated drinking water, half-life values could be estimated using measured declines in serum or plasma PFOA levels after exposures ceased due to filtration of drinking water. The geometric average half-life in Germany was reported as 3.26 years (range = 1.03–14.67; no 95% CI reported; Brede et al., 2010), and the average value for Mid-Ohio Valley was 2.3 years (95% CI = 2.1–2.4 years; no range provided; Bartell et al., 2010). An additional cross-sectional study in the Mid-Ohio Valley (with estimated, rather than measured, initial serum concentrations) identified average half-life values of 2.9–10.1 years (with values varying depending on the average serum concentrations in the community and duration since cessation of exposure) (Seals et al., 2011). The arithmetic mean of the elimination half-life was estimated as 2.1 years (95% CI = 1.8–2.4 years; range = 0.19–5.2 years) in young females and 2.6 years (95% CI = 2.2–3.0 years; range = 0.06–14 years) in males and older females in healthy adult volunteers in China (Zhang et al., 2013). In a study of Faroese children followed from birth to 5 years, the biological half-life of the serum-PFOA concentration was estimated as 4.2 years (Mogensen et al., 2015a). The authors cautioned against drawing conclusions regarding differences in elimination kinetics between children and adults based on this data because the cohort is not representative of the general population and the half-lives were calculated assuming negligible subsequent exposures following peak exposure levels. The half-life of PFOA in animals varies depending on experimental protocols, but is on the order of days to weeks in rodents and monkeys (see Table 1).

Table 1: Serum half-life estimates in humans and experimental animals

Species	Dosing regime	Mean half-life (days)	Reference
Rat	Single oral dose of 0.1 mg/kg bw; followed for 22 days (M) or 5 days (F)	8.41 ± 1.56[a] (M) 0.13 ± 0.04[a] (F)	Kemper, 2003
	Single oral dose of 0.1 mg/kg bw;	11.55 ± 2.36[a] (M)	

Species	Dosing regime	Mean half-life (days)	Reference
	followed until PFOA < quantitation limits	0.14 ± 0.05[a] (F)	
	Single oral dose of 1 mg/kg bw; followed for 22 days (M) or 5 days (F)	5.76 ± 1.33[a] (M) 0.14 ± 0.05[a] (F)	
	Single oral dose of 5 mg/kg bw; followed for 22 days (M) or 5 days (F)	7.26 ± 1.21[a] (M) 0.19 ± 0.03[a] (F)	
	Single oral dose of 25 mg/kg bw; followed for 22 days (M) or 5 days (F)	6.56 ± 1.60[a] (M) 0.68 ± 0.41[a] (F)	
	Single i.v. dose of 1 mg/kg bw; followed for 22 days (M) or 5 days (F)	7.73 ± 0.815[a] (M) 0.12 ± 0.02[a] (F)	
Mouse	Single oral dose of 1 or 10 mg/kg bw; followed for up to 80 days	21.7 (19.5–24.1)[b] (M) 15.6 (14.7–16.5)[b] (F)	Lou et al., 2009
Monkey	Single i.v. dose of 10 mg/kg bw; followed for 123 days	20.9 ± 12.5 (M) 32.6 ± 8 (F)	Butenhoff et al., 2004b
	Daily oral dose of 10 mg/kg bw for 6 months; followed for up to 147 days post-dosing	19.5[c] (M)	
	Daily oral dose of 20 mg/kg bw for 6 months; followed for up to 147 days post-dosing	20.8[c] (M)	
Human	26 former workers with an average of 31 years of work and 2.6 years retired; external exposure data not provided	1387 (1132–1606)[b]	Olsen et al., 2007
	138 adults and children, 2 years after reduction of PFOA concentrations in drinking water; doses not provided (Arnsberg, Germany)	1190[c]	Brede et al., 2010
	200 adults, ~1–2 years after reduction of PFOA concentrations in drinking water; doses not provided (Mid-Ohio Valley)	840 (767–876)[b]	Bartell et al., 2010
	86 adults; external exposure data not provided	767 (657-876)[b] (F) 949 (803-1095)[b] (M & F)	Zhang et al., 2013
	81 children; prenatal exposure assessed from mother's serum-PFOA at pregnancy week 32; external exposure data not provided	1533[c] (M & F)	Mogensen et al., 2015a
	302 workers before and after PFOS was restricted in 2009; years of service not reported; external exposure data not provided	1497[d] (M & F) 1716[d] (M) 1132[d] (F)	Fu et al., 2016

[a] ± Standard deviation
[b] 95% confidence interval
[c] No standard deviation or confidence interval was provided by authors
[d] Geometric mean since authors did not provide arithmetic mean

Urinary excretion is the major route of elimination in rats (particularly females, which have much greater urinary elimination rates than males) (Vanden Heuvel et al., 1991; Kudo et al., 2001) and monkeys (Butenhoff et al., 2002, 2004a). The urinary excretion process involves glomerular filtration, secretion into the tubular fluid, and reabsorption from tubular fluid. Glomerular filtration of PFOA is limited by extensive binding of PFOA to plasma proteins. Renal reabsorption of PFOA is thought to be driven by OAT proteins residing on membranes of proximal tubular cells (Yang et al., 2010; Han et al., 2012), and contribute to rat sex-related differences in renal clearance (Yang et al., 2009a). Unlike the rat, no gender differences in PFOA urinary elimination are apparent in the mouse (ATSDR 2009) or monkey (Butenhoff et al., 2004a). A dose-dependent (non-linear) upward trend for urinary excretion of PFOA was observed in male rats after dosing with capsules containing PFOA (Butenhoff et al., 2004b). Consistent with observations in animals given low doses, the relationship between external dose and internal dose (serum level) is linear in humans with environmental exposures to PFOA (Clewell, 2009); however, non-linear kinetics—as seen in animals at higher doses—might occur at higher human exposures. The relevance of urinary clearance in humans has been questioned, as renal clearance of PFOA was substantially lower than in animals (Harada et al., 2005). It is important to note that the non-linear toxicokinetics of PFOA have only been investigated in experimental animals following bolus oral exposures to PFOA, therefore, it is not clear if non-linear toxicokinetics are applicable to other modes of administration.

Biliary and fecal excretion also contributes to the elimination of PFOA, which may be subject to extensive enterohepatic recirculation (Vanden Heuvel et al., 1991; Kudo et al., 2001; Harada et al., 2007; Kudo et al., 2007). The relative importance of fecal excretion of PFOA depends on the urinary clearance. Fecal excretion is less important than urinary excretion in rats (Harada et al., 2007) and monkeys (Butenhoff et al., 2004a); however, data in rats indicate that the proportion of excretion occurring from this route becomes greater as doses and exposure durations increase (Cui et al., 2010). The relevance of this excretion route in humans is unclear. Harada et al. (2007) reported that the biliary excretion rate in four humans was significantly higher than serum clearance via urine and concluded that biliary excretion may represent a major excretion route in human; however, these data are not consistent with a case history that reported detection of PFOA in urine but not feces in a man with elevated serum PFOA levels (Genius et al., 2010).

In females, lactation can be a significant route of excretion, as shown in mice (Abbott et al. 2007) and in women (von Ehrenstein, 2009; Kim et al., 2011; Mondal et al., 2014; Mogensen et al., 2015a). Menstrual bleeding may be a significant route of excretion for women (Harada and Koizumi, 2009) and could potentially contribute to differences in serum levels measured between genders in humans.

8.5 Physiologically-based pharmacokinetic (PBPK) models

Several models with varying complexities have been developed to describe the kinetics of PFOA in both experimental animals and humans (Andersen et al., 2006; Tan et al., 2008; Loccisano et al., 2011, 2012a, 2012b, 2013). Due to the non-linear nature of PFOA pharmacokinetics, where faster clearance is seen with high bolus oral dosing, physiological models can provide an improved means of assessing cross-route and cross-species dosimetry for risk assessment.

The first model developed for PFOA was a biologically-motivated compartmental pharmacokinetic (PK) model for monkeys, which included saturable renal resorption of filtered

PFOA (Andersen et al., 2006). Subsequent work to refine the model included the addition of a liver compartment and of time-dependent functions for protein binding and volume of distribution to fit high-dose monkey and rat oral and intravenous plasma, urine and feces kinetic data (Tan et al. 2008). PFOA PBPK models for adult rats (Loccisano et al., 2012a), monkeys (Loccisano et al., 2011) and humans (Loccisano et al., 2011) built upon the compartmental models. Further models for lactation and pregnancy were developed for rats (Loccisano et al., 2012b) and humans (Loccisano et al., 2013). No models have been developed for mice, and no pregnancy and lactation models have been developed for monkeys. The basic structure of the PBPK model was the same for all three species, with only time-dependent changes in physiology included to describe pregnancy and lactation along with the time-dependency for plasma and tissue binding. The models included tissue compartments for gut (for oral/dietary dosing), skin (human and monkey model only; for dermal dosing), liver, fat, and kidney, with remaining body tissues grouped together (and not divided into richly and poorly perfused compartments). Biliary excretion and fecal elimination of the unabsorbed bolus oral dose or dietary exposure was added to the rat model; moreover, the rat version did not include a fat compartment (which became lumped with the rest of the body) or physiological gut, which was described as a one compartment non-physiological compartment. The PBPK model assumes only the free plasma fraction of PFOA is available for uptake into tissue, excretion or resorption. Elimination from plasma is described as glomerular filtration of the free fraction into a filtrate compartment. The filtered PFOA can either be eliminated in urine or resorbed into the kidney where it can return to systemic circulation. The models were relatively good at reproducing controlled dosing data for rats (dietary, oral gavage, and IV routes of exposure; Loccisano et al., 2012a), and monkeys (IV and oral gavage routes of exposure; Loccisano et al., 2011). Although no controlled dosing data were available for humans, biomonitoring data (for typically only a single timepoint) were within similar ranges as model simulations (using measured water concentrations for the biomonitored populations, along with assumptions on ingestion patterns; Loccisano et al., 2011).

The Loccisano models for humans (2011), monkeys (2011) and rats (2012a) were considered for use in the current assessment (see Section 10). Additionally, a mouse model that was scaled from the rat model was used, but it could not be validated. Further specifics of the models used for this assessment, including the values used for each of the physiological and chemical-specific parameters, are described in Campbell and Clewell (2013). Exposure was described as a constant intake of PFOA in humans (ingesting 1.5 L of water per day) and the model was allowed to reach steady state conditions prior to determining the predicted drinking water concentration consistent with the internal dose metric. To be conservative, the longest regularly reported half-life (3.8 years) was used, as this would result in the lowest predicted water concentration. The human was simulated as a 70 kg adult.

The Andersen et al. (2006) pharmacokinetic model was modified by Wambaugh and colleagues (2013) by adding a gut compartment for oral absorption and specifying an upper limit on tissue distribution. The authors used the model to translate dose regimes and available LOEL, NOEL, and benchmark dose (BMD) values from 9 *in vivo* studies of PFOA into internal dose metrics (area under the curve, average, and maximum serum concentrations). The data were modelled for cynomolgus monkeys, male and female Sprague-Dawley rats, and CD-1 and C57Bl/6 mice. A Bayesian approach was employed to model ranges of various physiological parameters. Wambaugh et al. (2013) identified relatively good concordance between predicted and measured (at study termination) serum concentrations, with few outliers, and identified that mean and maximum serum concentrations were most consistent among the various adverse endpoints. Dose metrics for points-of-departure (PODs) tended to be similar, indicating

consistency between species and adverse outcomes. However, this model could not be fully validated based on existing human pharmacokinetic data.

Dermal and inhalation routes from contact with drinking water were not included in as potential routes of exposure in this effort, as their contribution to exposure is considered to be negligible (see Section 5.7).

8.6 Animal-to-human extrapolation

Although animal-to-human extrapolations are typically discussed after the selection of potential PODs, consideration has been given to this extrapolation earlier in the PFOA assessment, as the large variability between species can affect POD selection. The large differences in PFOA clearance between humans and other species must be accounted for when using animal studies as a basis for human risk assessments. The application of default approaches for animal-to-human extrapolation—such as the use of an interspecies uncertainty factor of 10 or allometric scaling—might not be sufficiently protective of humans, who receive longer internal exposures to target tissues. For this reason, chemical-specific approaches that can account for pharmacokinetic differences between species and nonlinear behavior of PFOA were considered for the risk assessment. These approaches include the application of chemical-specific adjustment factors (CSAFs) and PBPK modelling. A discussion and application of each of these approaches is outlined below, and further details can be found in a report prepared for Health Canada by Summit Toxicology (2015).

8.6.1 Derivation of CSAFs

A major advantage of the application of CSAFs over default uncertainty or allometric scaling factors is that the approach incorporates both species- and chemical-specific data. Despite this strength, the approach relies on single values representative of pharmacokinetics in each species, and does not necessarily account for non-linear pharmacokinetics.

IPCS guidelines on calculating CSAFs (IPCS, 2005) were applied to derive the toxicokinetic portion of the interspecies uncertainty factor (AK_{UF}). IPCS recommends that the default interspecies uncertainty factor of 10 be divided into values of 4.0 ($10^{0.6}$) for the toxicokinetic portion (AK_{UF}) and 2.5 ($10^{0.4}$) for the toxicodynamic component (AD_{UF}). The default AK_{UF} of 4.0 becomes replaced with any AK_{UF} values calculated based on chemical-specific data (IPCS, 2005). As data were not available to quantitatively evaluate toxicodynamic differences between species, no AD_{UF} was calculated.

To calculate the AK_{UF} (i.e., reflecting interspecies toxicokinetic differences), the following equation was used:

$$AK_{UF} = \frac{CL_{animal}}{CL_{human}}$$

where:

- AK_{UF} is the toxicokinetic component of the interspecies uncertainty factor; and
- CL is clearance in animals and humans (e.g., mL/kg bw per day).

In rats, a single oral dose of 0.1 mg/kg bw per day was provided to Sprague-Dawley rats (4/sex), who were followed for 22 days (males) or 5 days (females) (Kemper et al., 2003). Increased clearance and decreased half-life in female vs. male rats has been repeatedly

demonstrated (see Section 5); females appear to have increased urinary excretion of PFOA over males, but the reason for this phenomenon is not clear. For this reason, AK_{UF} values are presented separately for each sex. Clearance rates for male and female rats were 23.1, and 777, respectively.

Clearance was not reported directly for monkeys, mice, or humans, and must be calculated based on species-specific half-life values using the following equation:

$$CL = \frac{Ln\ 2 \times V_d}{T_{½}}$$

where:

- CL is clearance in animals and humans (L/kg bw per day);
- ln 2 is the natural log of 2;
- V_d is the volume of distribution, which is the theoretical volume of blood in which the amount of a chemical would need to be uniformly distributed to produce the observed blood concentration; and
- $T_{½}$ is the half-life of a compound.

A half-life of 20.15 days was obtained from cynomolgus monkeys, which was averaged from monkeys provided a daily oral dose of 10 and 20 mg/kg bw for 6 months and followed for up to 147 days post-dosing (Butenhoff et al., 2004a). No volume of distribution was presented for monkeys in the chronic exposure study, but an average value of 190 mL/kg bw was obtained from the single dose study that was presented in the same publication (Butenhoff et al., 2004a). Half-life values in mice were obtained from a study that provided a single oral dose of 1 or 10 mg/kg bw per day to CD-1 mice (3/sex/dose) that were followed for up to 80 days (Lou et al., 2009); the average value was 18.7 days. In humans, a half-life of 1387 days (3.8 years) was calculated from decreases in serum concentrations of 26 workers previously occupationally exposed to PFOA, with an average of 31 years of work and 2.6 years retired (Olsen et al., 2007). Despite the availability of half-life values for general populations, the occupationally-derived half-life was selected to be conservative, as it is the longest of half-life values estimated from longitudinal data (see Section 8.4). Volume of distribution values for PFOA are typically relatively consistent among species (Thompson et al., 2010); as no volumes of distribution were provided in the human and mouse studies, a value of 200 mL/kg bw was used to represent a chemical that is mostly distributed extracellularly. Using the above equation, the resulting clearance values were 6.5 mL/kg bw per day in monkeys, 7.4 mL/kg bw per day in mice, and 0.1 mL/kg bw per day in humans. Using the human:animal ratios of clearance values described above, the calculated AK_{UF} values for PFOA for monkeys, mice, and average, male, and female rats were 65, 74, 231 and 7774, respectively.

Clearance was selected as the dose metric for the derivation of AK_{UF} values because data for this metric were readily available in most species, and could be calculated from half-life data in humans. Moreover, the use of clearance as a dose metric is a reasonable assumption for chemicals with long half-lives (i.e., in the order of days to years). Preliminary analyses have suggested that peak concentrations might be more predictive of PFOA toxicity for certain adverse endpoints (Haber et al., 2013); PFOA was not investigated in these analyses. Although this hypothesis was not further explored for the present analysis, using clearance is considered to be a more conservative alternative to using peak concentrations as the dose metric for AK_{UF} derivation. Finally, ratios of clearance levels are considered an appropriate basis for AK_{UF}

derivation typically only if first-order kinetics are assumed to apply; however, as urinary clearance of PFOA is complex, this assumption might not be appropriate.

8.6.2 PBPK modelling

A typical approach for PBPK modelling is to use the model to calculate human-relevant PODs, which are derived by applying a human PBPK model to internal dose metrics (e.g., concentrations of PFOA in plasma) that were either calculated or measured in animals. With sufficiently validated models, this approach is considered to be the most robust approach for performing animal-to-human extrapolations. However, there is only medium confidence in human, monkey, and rat models, because different model codes were used for different species, and model fits to some datasets were not optimal. Moreover, the limited understanding of reasons for the observed sex differences in clearance in rats means there are weaknesses in how this could be addressed in the model. Finally, a major drawback in using the standard PBPK modelling approach is that human models have not been fully verified. Human data available for verification are limited to biomonitoring studies that allow for only rough estimates of exposure scenarios, and for which serum concentration measurements were typically only performed once (with a few populations with measurements at two timepoints) (see Section 5.6). Loccisano and colleagues did not develop PBPK models for mice, but Health Canada modelling approaches using mouse studies scaled the rat models using mouse data. As insufficient toxicokinetic data exist to verify whether the mouse model is appropriate, confidence in the mouse model is low. Therefore, there is insufficient confidence to use precise PBPK model results as points-of-departure for the risk assessments.

As an alternative approach to using the PBPK model for POD calculations, ratios of PBPK model-predicted dose metrics were used to calculate AK_{UF} values for relevant doses. This approach is thought to provide more robust estimates of the AK_{UF} than the traditional calculations described in Section 8.6.1, as it can address the non-linear kinetics of PFOA, identifying different values at steady state for different oral dose levels. In contrast, the AK_{UF} values calculated above are dependent on the specific doses and dose regimes used in the pharmacokinetic studies; uncertainties arise in the values obtained from these studies as the AK_{UF} values are calculated for animals administered single doses, which cannot account for non-linear kinetics, and the human data were not obtained from controlled dosing studies. Furthermore, clearance-based AK_{UF} values are ratios of low doses in humans to high doses in animals, and therefore exposures between the species are not of the same magnitude; using the PBPK model to derive the AK_{UF} allows for a more appropriate comparison of doses of the same magnitude.

The selected dose metric for the PBPK-derived AK_{UF} values was steady-state concentrations of PFOA. Steady-state concentration was selected as it is typically relevant for chemicals with long half-lives, and is a conservative assumption. Although alternative dose metrics—including peak concentrations (Haber et al., 2013)—might be more predictive of PFOA toxicity for certain adverse endpoints, additional work was not performed to further investigate the most appropriate dose metric. Plasma was selected as the relevant tissue for steady-state concentrations, as it is a metric that can act as a relevant proxy for a wide variety of organs, because blood flows to these different organs. Liver steady state concentrations were also incorporated into the assessment for comparison with plasma-based AK_{UF} values, as the liver has been identified as a primary organ for PFOA distribution in pharmacokinetic studies, and is also a potential target organ for toxicity. However, there is lower confidence in liver-based values than plasma values, as very little pharmacokinetic data exists to be able to perform verification of the PBPK model for liver concentrations. Liver concentrations could not be verified for humans,

mice, and monkeys; for rats, minimal verification could be performed, but as data were available for only one to two timepoints in each study, the comparisons are not robust. Moreover, the use of plasma concentrations as a proxy for a variety of organs simplifies the application of AK_{UF} values in the assessment, which is already complex due to the use of AK_{UF} values that are species- and dose-specific.

Using the Loccisano PBPK models described in Section 8.5, steady-state plasma and liver concentrations were obtained at various doses in each of the species. The same doses were used for each of the species. For each dose run in the PBPK model, ratios of steady-state PFOA concentrations in humans vs. other species were calculated to obtain dose- and species-specific AK_{UF} values (Summit Toxicology, 2015). Steady-state concentrations and AK_{UF} values for plasma and liver at potentially relevant doses are listed in Table 2.

To select the appropriate AK_{UF} for each POD, the POD is rounded down to the nearest value in the oral dose column (i.e., values within the same order of magnitude are used). As discussed above, low confidence is placed on the mouse PBPK model. Until a PBPK model has been developed based on mouse data, the use of rat AK_{UF} values for mice is recommended (Summit Toxicology, 2015).

Table 2: PBPK dose metrics and PBPK-derived AK_{UF} values at relevant doses

Metric	Species	Oral dose (mg/kg bw per day)			
		0.001	0.01	0.1	1
Steady-state plasma PFOA predictions (µg/mL)	Human	8.74	86.1	706	1493
	Monkey	0.17	1.61	11.5	38.9
	Mouse	0.05[a]	0.47	4.74	47.4
	Rat	0.09	0.9	8.96	89.5
Steady-state liver PFOA predictions (µg/mL)	Human	19.2	189	1555	3289
	Monkey	0.37	3.58	25.5	88.3
	Mouse	NC	NC	NC	NC
	Rat	0.32	3.16	31.6	316
AK_{UF} derived based on plasma predictions	Monkey	52	53	62	38
	Mouse[b]	184	182	149	31
	Rat	97	96	79	17
AK_{UF} derived based on liver predictions	Monkey	52	53	61	37
	Mouse[b]	NC	NC	NC	NC
	Rat	61	60	49	10

[a]NC = could not be calculated due to limitations in the PBPK model
[b]AK_{UF} values for rats will be applied due to low confidence in the PBPK model

8.6.3 Recommended interspecies extrapolation approach

The recommended approach for interspecies extrapolation is the use of a PBPK model for the calculation of the AK_{UF} component of the CSAF, using steady-state plasma concentrations as the dose metric. The use of plasma concentrations ensures the relevance of the dose metric to adverse effects that occur in a variety of organs. Organ-specific dose metrics are typically preferred over blood-based values, whenever available; however, using the plasma metrics for this assessment provides consistency in the application of the AK_{UF} over a wide variety of adverse endpoints. AK_{UF} values were calculated for liver metrics for comparison with plasma values; the behaviour of PFOA in the liver was similar to that in the plasma, and AK_{UF} estimates were on the same order in both compartments. These results indicate that plasma values are appropriate

proxies to be used for adverse hepatic effects. The liver-based values in rats were slightly lower than plasma-based values; however, greater confidence is placed in the plasma values because more data were available to verify this compartment of the PBPK model. The dose- and species-specific AK_{UF} values (for steady-state plasma concentrations) in Table 2 are applied in sections 10.1 and 10.2.

Although PBPK-derived AK_{UF} values were selected as the recommended approach for this assessment, several weaknesses have been identified. As described above, the AK_{UF} was plasma based rather than being organ specific. Steady state concentrations were also selected as the dose metric, as a conservative assumption relevant to the nature of the compound; detailed work was not performed to identify whether other dose metrics (e.g., peak concentrations) would be more appropriate for the various adverse endpoints. Steady state was also not reached in the human model at doses below 0.1 mg/kg bw per day. Furthermore, PBPK models have not been developed specifically for the mouse, and have been scaled instead from the rat, without further pharmacokinetic data for mice to be used for verification; the application of AK_{UF} values for rats is therefore recommended for use in mice in the absence of robust data in the species. AK_{UF} values for rats were derived based on male rats, which experience slower clearance of PFOA compared to female rats, in order to minimize the interspecies differences..

Despite these weaknesses, using the PBPK model to derive the AK_{UF} was thought to be equally or more robust when compared with other potential interspecies extrapolation approaches. The selected approach quantitatively incorporates pharmacokinetic differences among species; however, non-linear kinetics of PFOA are addressed, which cannot be done using the default AK_{UF}-derivation approach. Moreover, the PBPK-derived AK_{UF} values do not rely on individual pharmacokinetic studies that are often single-dose studies and not easily comparable among species. An ideal approach to address species differences would be to use blood concentrations of PFOA—either by using pharmacokinetic models to estimate the concentrations, as employed by Wambaugh et al. (2013), or using the values specifically measured in individual studies—as PODs for the assessment. However, the human PBPK models that would be used to extrapolate from this serum concentration cannot be fully verified based on existing human pharmacokinetic data, which decreases the level of comfort of using this approach to estimate precise PODs. The recommended approach was selected as a means of quantifying interspecies differences while addressing the non-linear kinetics of PFOA, without relying on precise PBPK-derived estimates of PODs.

9.0 Health effects

The summary of literature on health effects for PFOA is largely based on a comprehensive review conducted by a consultant (Sanexen Environmental Services Inc., 2013), and includes only the studies of direct relevance to the derivation of the health-based value. More specifically, this summary includes reports, reviews, and original papers published concerning PFOA in order to understand toxicity in humans exposed to PFOA via drinking water.

It should be noted, however, that PFOA can be found as part of mixtures with other PFAS. Nonetheless, the vast majority of available studies on the toxicology of PFOA are carried out using the compounds individually. Information on the toxicology of mixtures is generally a data gap. However, the value of toxicity information that could be gained from mixture studies is limited to mixtures that do not significantly change in their composition, which is not the case for environmental mixtures of PFAS.

9.1 Effects in humans

9.1.1 Acute toxicity

No information related to acute or short-term epidemiological studies could be located.

9.1.2 Subchronic and chronic toxicity

Many quality epidemiological studies have been conducted. Large cohorts of workers and environmentally-exposed populations have been followed, with observations of significant relationships between exposure to PFOA and various health endpoints, such as haematological and clinical biomarkers (cholesterol, uric acid, serum liver enzymes), cancer (testicular, kidney), preeclampsia, immunological, endocrine (thyroid), renal functions, and fecundity (semen quality, birth weight) outcomes. Although all of these studies present limitations to some extent, including in terms of study design, bias and confounders, the human weight of evidence provides a strong argument in favor of detrimental health effects of the compound. This information should support the choice of a health endpoint; however, deriving a safe human exposure dose based on studies in humans remains a challenge because of the difficulties in characterizing a dose-response pattern with current studies. Their use in the present assessment is important to verify the relevance of animal to human extrapolation, and the monitoring of future studies will help in determining the accuracy of the observed associations.

Most environmental studies among PFAS-exposed populations were conducted in the Mid-Ohio Valley within the C8 Science Project. The C8 Science Panel was convened as a result of a class action settlement against DuPont, and is composed of independent epidemiologists jointly selected by lawyers for the community and DuPont. The C8 Health Project is the largest study of a population exposed to PFAS in drinking water, containing residents of Ohio and West Virginia communities surrounding the DuPont Washington Works plant. The health survey was conducted in 2005–2006 on approximately 69,000 individuals, including children and adults. The median PFOA serum concentrations in this population were 28.2 ng/mL, compared to 4.2 ng/mL in the general American population during the same period (Frisbee et al., 2009). Some longitudinal/prospective studies were also conducted among this population after a follow-up period. Some recent data in the project have not yet been published in peer reviewed literature; summaries of these studies—as well as panel conclusions and further information on the members of the panel—are available on the C8 Science Panel website (www.c8sciencepanel.org/panel.html).

9.1.2.1 Liver effects

Some level of association between PFOA exposure and alteration in liver enzymes has been observed, but no clear trend has been defined. A negative association for bilirubin and a positive association for aspartate transaminase (AST) and gamma glutamyl transpeptidase (GGT) have been reported in workers (Sakr et al., 2007a, 2007b). The clinical significance of results in the occupationally-exposed population is unclear, because the magnitudes of the changes were small and inconsistent (Steenland et al., 2010a). Moreover, the high number of endpoints analyzed also increases the likelihood of chance findings. Abnormal increases of liver enzymes (ALT and GGT) were reported in a cross-sectional study of adults aged 18 years or older in the general U.S. population, particularly in obese or in subjects with insulin resistance and/or metabolic syndromes (Lin et al., 2010). An association between serum PFOA levels and uric acid, ALT, GGT, and total bilirubin was reported in a cross-sectional survey in the general U.S. population recruited as part of NHANES (Gleason et al., 2015). Causal interpretation of general

population results is limited by the study design, and multiple covariates were not included in the analysis.

9.1.2.2 Lipidemia

Increased exposure to PFOA has been associated with increases in serum cholesterol levels in several studies. A recent study including large cohorts of workers and environmentally-exposed residents found an increased risk of hypercholesterolemia with higher PFOA exposure compared to lower exposure (Winquist and Steenland, 2014). A small longitudinal study conducted in workers in Italy showed a positive association between PFOA and total cholesterol (Costa et al., 2009). A cross-sectional study and a longitudinal study were conducted among DuPont production workers. In the cross-sectional study, positive associations between PFOA and total cholesterol, LDL and VDLD were observed (Sakr et al., 2007a). In the longitudinal study, a negative association with bilirubin was observed, whereas positive associations between serum PFOA and total cholesterol were found after adjustment for cofounders (Sakr et al., 2007b).

Inconsistent results were found concerning the association between PFOA and cholesterol and lipoproteins in studies of fluorochemical production workers from U.S. and European 3M plants (Olsen and Zobel, 2007). No association between serum PFOA levels and plasma lipids (measured as triglycerides, HDL, LDL, and total cholesterol) was found as measured in a subsample of Canadians as part of the CHMS (Cycle 1 2007 – 2009) (Fisher et al., 2013). An increase in HDL level, a decreased total cholesterol/HDL ratio and no changes in total cholesterol and non-HDL cholesterol were observed in an occupational study (Olsen et al., 2012). Under the C8 Health Project, associations between serum PFOA and different blood components, such as an increase in cholesterol levels, were found in children and adults (Steenland et al., 2009, Frisbee et al., 2010, Kerger et al., 2011). Associations also occurred for lipoproteins (LDL, HDL), but were inconsistent between studies. A positive association with cholesterol was also found in the general U.S. population (Nelson et al., 2010), while another cross-sectional study conducted in the Mid-Ohio valley found no association (Emmett et al., 2006b). A longitudinal study conducted in 560 adults (2005–2006 with follow-up in 2010) indicated that the level of LDL decreased with the decreased serum PFOA level. A similar (but not statistically significant) pattern was found for total cholesterol; however, there were no changes for HDL or triglycerides (Fitz-Simon et al., 2013).

Overall, cross-sectional and longitudinal study data from the studies reviewed in the preceeding paragraphs indicate some level of association between serum PFOA and total cholesterol and/or LDL observed in different populations, although results were inconsistent in terms of exposure and effects observed. The strength of association was generally higher in the general population than in workers. This discrepancy could be due to the lack of lower range serum PFOA levels in occupationally exposed populations compared to the general population that is exposed to a wider range of PFOA levels (low to high). Considering the weight of evidence, the C8 Science Panel (2012a) concluded that there is a probable link between elevated cholesterolemia and PFOA. The clinical significance is uncertain, given the results inconsistencies, the unknown mechanism of action, the limits inherent to the study design, and the low magnitude of the changes. In particular, the conclusions and associations found from the cohort studies are limited by the risk of selection and misclassification bias, and uncontrolled variables, as some associations were lost when the participants were stratified by location (Costa et al., 2009; Winquist and Steenland, 2014).

9.1.2.3 Thyroid disruption

Inconsistent effects on thyroid hormone levels were observed in PFOA-exposed populations. An occupational study conducted among 552 employees in three plants found a negative association between PFOA and free thyroxine and a positive association between PFOA and triiodothyronine, after adjusting for confounders (Olsen and Zobel, 2007). However, no adjustment for PFOS was performed, and the authors indicated there were no associations between PFOA and thyroid hormones because the results were inconsistent and within normal values. Moreover, no significant association of PFOA with T3, T4, or TSH was observed in two other occupational studies (Olsen et al., 1998, 2003b). Multiple cross-sectional studies (C8 Health Project and NHANES) have evaluated the relationship between environmental exposure to PFOA and thyroid functions. These studies have reported alterations in the levels of thyroxin, T3 uptake, serum albumin, hypothyroidism in children, thyroid disease in women (Chan et al., 2011; Knox et al., 2011b; Lopez-Espinosa et al., 2012). However, temporality cannot be established with the study design, and it is not possible to know the PFOA serum levels before the development of thyroid disease. A positive correlation between maternal serum PFOA levels and fetal TSH levels (but not T3 or T4 levels) was found after adjustment for covariates in a South Korean study (Kim et al., 2011).

9.1.2.4 Hypertension and cardiovascular outcomes

Cardiovascular outcomes were not consistently found to be associated with PFOA in cohort and cross-sectional studies (Sakr et al., 2007a; Costa et al., 2009; Steenland et al., 2010b). Elevated PFOA exposures were associated with higher cerebrovascular risk in an occupational cohort study (Lundin et al., 2009), and with cardiovascular, peripheral arterial disease, systolic blood pressure, and a marker of inflammation in cross-sectional studies of the general U.S. population (Shankar et al., 2012; Min et al., 2013). These results are equivocal and were not confirmed in other occupational cohort studies (Leonard et al., 2008; Sakr et al., 2009; Steenland and Woskie, 2012), nor in another cross-sectional study in the general population (Melzer et al., 2010). The C8 Science Panel concluded there is not a probable link between exposure to PFOA and diagnosed high blood pressure and coronary artery disease (including myocardial infarction, angina and coronary bypass surgery) (C8 Science Panel, 2012a).

9.1.2.5 Kidney effects

An association between adverse kidney effects and PFOA was observed; however, several factors limit the generalizability of the results to the general population. An increased risk of renal disease was found in a cohort mortality study conducted in 5,791 workers at a DuPont Chemical Plant (Steenland and Woskie, 2012). This level of evidence does not support a causal relationship between reduced kidney function and exposure to PFOA, particularly because altered kidney function could cause an increase in serum PFOA levels. Likewise, if PFOA induces adverse effects on the kidney, elevated PFOA levels may induce alterations of the kidney function. Moreover, only a small number of cases were observed in the occupational study (as attested by the large margin of error), and many workers were lost to follow-up, increasing the risk of selection bias, and was not supported by the results of an unpublished cohort study conducted in the same region (C8 Science Panel, 2012a).

9.1.2.6 Diabetes

The possible association between PFOA and diabetes was studied in mortality studies conducted among workers occupationally exposed to PFOA (Leonard et al., 2008, Lundin et al.,

2009, Steenland and Woskie, 2012), and in two environmental studies regarding the prevalence of diabetes conducted within the C8 Health Project (MacNeil et al., 2009, C8 Science Panel, 2012b). The results from the occupational studies of employees of a 3M Company plant in Cottage Grove, MN, and of the DuPont polyfluorimer plant were inconsistent. Considering that diabetes is usually not fatal (and is not necessarily indicated on death certificates) and that mortality may thus not be the best way to study diabetes (C8 Science Panel, 2012b), the findings based on diabetes prevalence within exposed residential populations may be more reliable. The data available from cross-sectional environmental studies conducted within the C8 Health Project (MacNeil et al., 2009; C8 Science Panel, 2012b) suggest that there is no link between PFOA and Type II diabetes. Additionally, no association between serum PFOA levels and metabolic function (calculated using fasting glucose and insulin levels) was found in a subsample of Canadians as part of Cycle 1of the CHMS (Fisher et al., 2013).

9.1.2.7 Immune suppression

Studies in environmentally-exposed populations have identified associations between PFOA levels and decreased antibodies against various illnesses, but the influence of PFOA exposure on clinical immunosuppression (i.e., incidence of illnesses) appears to be more tenuous. A study in children found an inverse relationship in immune response with PFAS exposure (Grandjean et al., 2012; Grandjean and Budtz-Jørgensen, 2013), with prenatal PFOA exposure negatively correlated with antidiphtheria antibody concentrations. A two-fold increase in the PFOA concentration in children in this population was associated with increased odds of not reaching antibody protective levels for tetanus and diphtheria after vaccination at 7 years old (Grandjean et al., 2012; Mogensen et al., 2015b) and 13 years old (Grandjean et al., 2017), although antibody levels had increased at 13 years compared to 7 years of age. The prospective nature, sample size, low risk of selection bias and defined objectives make the results relevant to the studied population; however, relevance to other populations is questionable, as increased exposure to the other potential immunosuppressants occurring in this region (Faroe Islands) was not accounted for in the study. Additionally, a portion of the 13-year old cohort had received booster vaccinations during emergency room visits, which could add variance to the study design (Grandjean et al., 2017). Increased PFOA exposure was also associated with decreased antibodies against rubella (in children from a prospective birth cohort of pregnant women from Norway, 2007–2008) (Granum et al., 2013) and influenza (for A/H3N2 only; in adults living in communities with PFOA-contaminated drinking water) (Looker et al., 2014). A higher risk of not attaining the recognized influenza A/H3N2 threshold was also observed (Looker et al., 2014). Cord blood IgE decreased with maternal PFOA in female infants in a prospective cohort study of pregnant women from 2002 to 2005 in Japan (Okada et al., 2012).

Hospitalizations for infections were not associated with prenatal exposure to PFOA in a Danish Cohort (1996–2002) (Fei et al., 2010a); however, positive associations between maternal PFOA and the incidence of colds and gastroenteritis were observed in the Norwegian birth cohort (Granum et al., 2013).

There is some level of consistency across studies since they generally observed an association between environmental PFAS exposure and immunomodulatory effects in children of different ethnicities. The diversity of the study settings and the prospective nature of the observational study designs lower the risks of spurious associations and enhance generalizability of the results. However, the dataset remains relatively small with only 5 studies, which were all observational, and the risk of residual confounding, bias and chance cannot be discounted. Although all studies investigated the effects on the immune system, the outcomes were not

specific (measured different effects), no clear dose-response was observed, and most associations were weak. Conflicting results were common in the dataset, with variations observed between genders, specific microbial immunoglobulins, PFASs, infections, mother vs. child exposure, and child years, amongst other characteristics. These flaws impede concluding on a causative mechanism, and the nature of the association remains unclear. Similarly, in a systematic and critical review of the epidemiological evidence on the association between various immune-related health outcomes and exposure to PFOA and PFOS, Chang et al. (2016) concluded that the available epidemiological evidence is insufficient to reach a conclusion about a causal relationship. The authors recommended further work to confirm these suggestive associations, including large, prospective studies with repeated exposure assessment in independent populations. On the other hand, the U.S. National Toxicology Program conducted a systematic review of the literature related to PFOA-induced immunotoxicity and concluded that PFOA is presumed to be an immune hazard to humans based on moderate level of evidence in humans and high level of evidence that PFOA suppressed the antibody response in experimental animals (see Section 9.2.2.3), and after considering biological plausibility (NTP, 2016).

9.1.2.8 Autoimmune disease

The C8 Science Panel (unpublished study) found an increased risk of inflammatory bowel disease with increased cumulative exposure to PFOA, which was driven by associations for ulcerative colitis. The C8 Science Panel concluded that there is a probable link between PFOA and ulcerative colitis (C8 Science Panel, 2012c). However, there is a risk of selection bias because the panel was able to include only a portion of the sample population—participants were only included if their medical charts could be accessed and if exposure estimates could be derived. These results are concerning and should be corroborated in future studies.

9.1.3 Carcinogenicity

Several occupational and environmental cohort studies have been developed for PFOA. The U.S. studies are considered to be the highest quality studies, because they were based on registries covering all residents in the study area, were conducted in districts with large and measured contrasts in PFOA concentrations in water, were linked to cancer registry data, had a large study population and were adjusted for major confounders.

A case-only study that investigated the relationship between cancer and exposure to PFOA through drinking water among Mid-Ohio residents living near the DuPont Teflon-manufacturing plant found that higher PFOA concentrations were associated with testicular and kidney cancers in some of the areas (Vieira et al., 2013). Amongst all cancer endpoints, the odds of testicular cancer were elevated only in one of the two areas with the highest concentration of PFOA in drinking water. There was no statistically significant increase in the odds of testicular cancer in the total exposed, in the other districts, or in any dose level categories (except for the highest dose category). Kidney cancer was increased significantly in one district and in the two highest levels of individual exposure. Associations were not significant for cancers of the breast, prostate, ovarian and non-Hodgkin lymphoma. Although this study shows some cancer associations with PFOA exposure, the meaning of the cancer results remain uncertain because no dose-response was observed, the variability of the risk estimates was high, the number of cases was low, there were multiple endpoints calculated with two modelling approaches (geographical and individual), and risk of exposure misclassification bias (the lack of residential history information to account for duration of exposure, latency, migration, and other issues regarding timing of exposure

relative to cancer). The geographical analysis (testicular cancer findings in the Mid-Ohio study) shares the bias and risk of confounding inherent to ecological studies.

Cumulative exposure to PFOA (retrospective estimates of log serum concentration) was associated with an increased risk of self-reported testicular, kidney, and thyroid cancers in a large cohort (n = 32,254) of C8 Health Project participants and DuPont Teflon-manufacturing plant workers above 20 years old (mean of 53 years old), after adjusting for smoking, alcohol consumption, sex, and education, and stratifying by age (Barry et al., 2013). Some cases were included in both the Barry et al. (2013) and in the Vieira et al. (2013) studies. The associations less likely to have occurred by chance alone (lowest p-values) were the ones between PFOA cumulative log serum concentration and testicular cancer (using the geographical and the water district individual approaches) and kidney cancer (using the residential analysis, individual approach) risks; while the associations with thyroid cancer and melanoma were considered to have occurred by chance based on poor statistical support. However, the associations were inconsistent between exposure quartiles and scenarios (e.g., residential, geographical), after follow-up (with very few, or no reported cases since 2005 regarding testicular cancer while background rates indicated that 5 cases were expected), and lost for testicular, kidney, and thyroid cancer risks, when compared with rates in the general U.S. population. Moreover, the 95% CI of the hazard ratios were large, the trends for testicular, kidney, and thyroid cancer risks were likely to have occurred by chance in at least one exposure scenario, Barry et al. (2013) mentioned the likelihood of exposure and outcome misclassifications, and the trends reported for testicular cancers were based on 6 cases only in the high exposure group (C8 Science Panel, 2012b; Barry et al., 2013).

In another occupational study conducted on workers in Minnesota, increased risk of prostate cancer mortality was observed; however, uncertainty persists because of the low number of cases, leading to poor precision in the risk estimates (Lundin et al., 2009). No statistically significant excess death from kidney, liver, pancreas, testicular, thyroid or breast cancer was found in another occupational study in West Virginia (Leonard et al., 2008) nor in the six-year follow-up of this cohort, except for excess of mortality by kidney cancer (Steenland and Woskie, 2012). Caution in the interpretation of these results is required, because the results were based on a small number of cases, and there was a considerable risk of selection bias.

No increase in the incidence of prostate, bladder, pancreas or liver cancer was found in a prospective cohort study conducted in the general population of Denmark, although the PFOA plasma concentrations [plasma concentration in men with cancer: 6.8 ng/mL (5–95% percentiles: 3.1–14.0); women with cancer: 6.0 ng/mL (5–95% percentiles: 2.6–11.0)] tended to be lower than in the U.S. cohorts [mean of 76.5 ng/mL (SD = 208) in male serum concentration and 42.3 ng/mL (SD = 118) in women, in a community exposed population reported by Frisbee et al. (2009); and, as high as a mean of 2,210 ng/mL (SD = 6.4) in the serum of PFOA manufacture employees, as reported in Olsen and Zobel (2007)] (Eriksen et al., 2009). Also, no evidence of a relationship for PFOA and breast cancer was found in a small-case control study in Greenlandic Inuit (Bonefeld-Jorgensen et al., 2011).

The C8 Science Panel (2012b) provides an assessment of the probable link between PFOA exposure and cancer. The “probable link” defined by the Science Panel means that “given the available scientific evidence, it is more likely than not that among class members a connection exists between PFOA exposure and a particular human disease.” Testicular and kidney cancers were the particular types of cancer on which the association was based. However, a causal relationship cannot be determined because there were inconsistencies in the dataset, and the cancer risks were found to be equivocal across studies (lack of coherence). Moreover, the

interpretation of the observed increased risk in testicular and kidney cancers is limited by the risk of residual confounding (because not all covariates and exposures to other contaminants were included in the model), the small case numbers, the uncertainties in exposure characterization (roughly estimated based on residency within a certain area), and the high number of outcomes included in the models, increasing the likelihood of chance findings. Similarly, a systematic and critical review of epidemiological studies on the association between cancer risk in humans and exposure to PFOA and PFOS concluded that the epidemiological evidence does not support a causal association between cancer in humans and exposure to PFOA and PFOS (Chang et al., 2014). Based on these considerations, it would be premature to base a guideline on a cancer risk in epidemiology studies, without a stronger understanding of the potential causality between PFOA and the observed cancers. It is suggested to continue monitoring the epidemiological evidence to understand better the relationship between PFOA and cancer risk.

9.1.4 Developmental and reproductive toxicity

9.1.4.1 Developmental toxicity

Based on data available for gestational age, birth weight and length, head and abdomen or chest circumference, developmental milestones, miscarriage, and birth defects, previous reviews of developmental epidemiology studies concluded that developmental effects are not expected in humans (Olsen et al., 2009). Although increases in the risk of some of these outcomes occurred in individual studies, there was a lack of consistency across studies. Newer environmental studies have shown a positive association between prenatal exposure to PFOA and obesity in female offspring at age of 20 years (Halldorsson et al., 2012), and a negative association between maternal serum PFOA and birth weight and related anthropometric parameters at birth (Apelberg et al., 2007; Fei et al., 2007; 2008b; Andersen et al., 2010; Maisonet et al., 2012; Whitworth et al., 2012a).

The obesogenic properties of PFOA and other PFAS were investigated in a prospective cohort study with long-term follow-up (20 years) among pregnant women recruited within the Danish National Birth Cohort (1988–1989) and their offspring (Halldorsson et al., 2012). At 20 years of age, the female offspring from mothers with elevated serum concentration of PFOA were more likely to be overweight and to have a high waist circumference, after adjusting for mother's education, BMI, smoking, age, and infant birth weight. This large longitudinal study also showed alteration in serum biomarkers with an increase in maternal PFOA (increase in serum insulin and leptin and decrease in serum adiponectin in female offspring), suggesting biological plausibility. However, important confounders, such as physical activity and diet, were not included in the analysis, which is likely to result in spurious associations. The authors also indicated that loss to follow-up was the main limitation of the study. In a trans-Canada cohort study, no association was found between first-trimester maternal plasma PFOA concentrations and cord blood concentrations of leptin and adiponectin using data on 1705 mother-infant pairs recruited as part of the Maternal Infant Research on Environmental Chemicals (MIREC) Study (Ashley-Martin et al., 2017). However, the study authors cautioned against generalizing these findings to other Canadian populations because on average the study participants were older, more educated, had higher incomes, and were less likely to smoke than other women giving birth in Canada. More studies with better adjustments and follow-up in different populations would be needed to confirm the observed associations.

The data currently available regarding an association between PFOA and reduced birth weight are not consistent. Positive associations were reported among the general population in some studies, whereas no association was reported in other studies in the general population and

in communities highly exposed to PFOA through drinking water. Longitudinal studies conducted in Danish and British general populations have found inverse associations between plasma PFOA levels and birth weight (Fei et al., 2007; Andersen et al., 2010; Maisonet et al., 2012). Similarly, PFOA exposure (measured as maternal PFOA plasma concentration) was inversely associated with birth weight in the MIREC Study (Ashley-Martin et al., 2017). A small unpublished study based on birth certificates for C8 Health Project Community Cohort follow-up participants found some level of association between serum PFOA and term low birth weight; however, results were inconsistent and significance was not provided for all results. These studies represent concerning findings; however, the validity of the results still need to be confirmed, because these studies presented risk of selection bias, recall bias, chance findings, uncontrolled covariates, and absence of dose–response pattern. Moreover, no significant association between serum PFOA levels or PFOA water concentrations and low birth weight was found in cross-sectional studies or highly exposed communities (Nolan et al., 2009; Stein et al., 2009; Savitz et al., 2012a; 2012b). The C8 Science panel concluded that there is no probable link between PFOA and low birth weight (C8 Science Panel, 2011). Similarly, a systematic review of the epidemiology data conducted by Bach et al. (2015) concluded that the existing data are insufficient to confirm or reject an association between PFAS exposure and fetal growth. However, application of a novel systematic review methodology (called the Navigation Guide methodology), to determine whether developmental exposure to PFOA affects fetal growth in humans, concluded that there is sufficient evidence that developmental exposure to PFOA reduces fetal growth (Johnson et al., 2014). Additionally, considering that PFOA was found to be obesogen in mice (Hines et al., 2009) and humans (Halldorsson et al., 2012), and that *in utero* exposure to low doses of obesogens are known to reduce weight at birth (and induce obesity later in life; Holtcamp, 2012), a link between PFOA and low birth weight cannot be ruled out and close monitoring of new studies is recommended.

Investigation of different fetal growth indicators in association with PFOA exposure gave equivocal results. PFOA levels in maternal blood from the Danish National Birth Cohort (1996–2002) demonstrated negative associations with abdominal circumference (with a dose–response relationship) and birth length, after adjustment for multiple relevant cofounders (Fei et al., 2008b). These associations were obtained from large databases, and errors in exposure and outcome measurements and coding is possible. There is also a risk of residual confounding, as stated by the authors. Small negative associations were observed with head circumference, ponderal index and birth weight in a cross-sectional study of the general population (n = 293 singleton births) in Maryland (Apelberg et al., 2007). These must be considered with caution due to the limits inherent to the study design. Also, no associations between maternal serum PFOA levels and birth weight were observed in other general population studies in Canada (Hamm et al., 2010) or Japan (Washino et al., 2009).

There was no conclusive evidence of attention deficit/hyperactivity disorder (ADHD), learning disorder, motor developmental milestones, or behavioral or motor coordination problems based on results of cross-sectional studies conducted within the C8 Health Project and in the general population with exposure to PFOA (Fei et al., 2008a; Hoffman et al., 2010; Fei and Olsen, 2011; Stein and Savitz, 2011).

9.1.4.2 Puberty and sex hormone disruption

Serum PFOA levels were associated with delayed puberty in girls (reduced odds for the 2nd, 3rd, and 4th quartiles vs. the lowest quartile: delay of 142, 163 and 130 days for menarche and delay of 155, 158 or 183 days for combined high estradiol or menarche) in a cross-sectional study within the C8 Health Project (Lopez-Espinosa et al., 2011). Serum PFOA levels were inversely

associated with testosterone in boys aged 6–9 years from the same cross-sectional study but were not associated with any sex hormones in girls of the same age group (Lopez-Espinosa et al., 2016). Further investigations are needed to establish the nature of the relationship, and identify the mechanisms behind these associations. No association was found between PFOA and serum estradiol levels in perimenopausal or menopausal age groups of women (n = 25,957) from the C8 Health Project (Knox et al., 2011a).

9.1.4.3 Reproductive toxicity

No clear pattern of pregnancy-induced hypertension was observed in cohort studies on residents of the Mid-Ohio Valley within the C8 Health project and a cross-sectional study based on Washington County (Savitz et al., 2012b; Nolan et al., 2010; C8 Science Panel, 2011). Conversely, an unpublished prospective study presented by the C8 Science Panel (2011) addressed pregnancies among participants enrolled in the C8 Health Project. The four highest quintiles had higher odds of pregnancy-induced hypertension; however, there was no clear dose–response pattern. Based on this dataset, it would be premature to conclude a link exists between PFOA and pregnancy-induced hypertension.

Overall, no definitive association between PFOA and preeclampsia has been established. No increased occurrence of preeclampsia was observed in a study conducted among Mid-Ohio Valley residents (pregnant in 2000–2006) exposed to PFOA-contaminated drinking water (Stein et al., 2009). In a second study, risk of preeclampsia was examined among C8 Health Project participants from 1990–2005 (Savitz et al., 2012a). Self-reported preeclampsia was weakly associated with estimated serum PFOA at the time of pregnancy, and there was no dose–response pattern. The association was strengthened when restricted to pregnancies occurring after 1999.

An association between PFOA exposure and a reduction in fecundity has been observed; however, the studies were not robust and the results are inconclusive. A reduction of fecundity (increased time to pregnancy and irregular menstrual periods) was found to be associated with the plasma PFOA levels in 1,240 parous/nulliparous women; however, the information for multiple confounders was omitted from the analysis (e.g., sperm quality, occurrences of intercourses; Fei et al., 2009). Relative increases in the odds of subfecundity (time to pregnancy greater than 12 months) were reported in a case–control study on parous women enrolled in the Norwegian Mother and Child Cohort Study (with no increased odds of subfecundity in nulliparous women) (Whitworth et al., 2012b). Time to pregnancy and fecundity were not associated with serum PFOA levels in nulliparous women in a longitudinal cohort study in Denmark (Vestergaard et al., 2012). The lack of adjustment for confounders and of consistency in the results generates doubt on the link between lower fecundity and PFOA.

Three epidemiological studies reported associations of maternal serum PFOA with decreased duration of breast-feeding. A prospective cohort study recruited 1,400 pregnant women (randomly out of 43,045) within the Danish National Birth Cohort (DNBC, 1988–1989) and measured PFOA concentration in their plasma (Fei et al., 2010b). Duration of breastfeeding was reported 6 and 18 months after birth by phone interviews. The risk of breastfeeding for a shorter period was higher with increasing plasma PFOA. For example, the risk (adjusted hazard ratio) of shorter breastfeeding duration (weeks) for women with plasma PFOA > 7.0 ng/mL was 1.4 (95% CI 1.2–1.7) times higher than for those with plasma PFOA < 3.9 ng/mL, after adjusting for maternal age at delivery, pre-pregnancy BMI, maternal socioeconomic status, alcohol consumption and smoking (the trend for an increase in risk with increasing four-quartile comparison was also significant). Also, the odds (adjusted odds ratio) of weaning before 6 months of age was 1.23 (95% CI: 1.1–1.3) times higher for each 1 ng/mL increase in plasma PFOA when

restricting the model to multiparous women (not significant in primiparous women), after statistical adjustments. A similar association was observed with weaning before 3 months of age. However, more studies would be needed to support these results, since PFOA plasma concentration was measured only one time, only 18% of eligible women participated in the DNBC study, there is a risk of outcome recall bias (mothers might not report accurately the date of weaning), and the authors did not rule out the possibility that reverse causation could explain the association (especially since not observed in primiparous women, and considering that women that have breastfed longer can be more likely to breastfed longer their next infants, and that PFOA is excreted in breast-milk, lowering the plasma concentration). In a longitudinal cohort study of 468 pregnant women, recruited as part of the prospective pregnancy and birth cohort called Health Outcomes and Measures of the Environment (HOME) Study in the Cincinnati, Ohio area, Romano et al. (2016) measured serum PFOA, PFOS, perfluorononanoic acid (PFNA) and PFHxS concentrations. The duration of breastfeeding was reported in telephone interviews every three months until breastfeeding was discontinued. An association between higher maternal PFOA serum concentration and shorter duration of any breastfeeding (defined as the duration of breastfeeding notwithstanding supplementation with formula, liquids, or solid food) was observed, even after controlling for previous breastfeeding. The women in the cohort had higher average PFOA serum concentrations compared to pregnant women in NHANES. Notably, no association was found between PFOA exposure and exclusive breastfeeding; the authors suggested that other factors are likely responsible for the low rates of exclusive breastfeeding in this cohort. In a larger study of 1130 mother-child dyads from two birth cohorts recruited in the Faroe Islands, Timmermann et al. (2016) measured maternal serum PFOA, PFOS, PFHxS, PFNA, and perfluorodecanoic acid (PFDA) concentrations. The duration of breastfeeding, defined as the sum of exclusive and mixed breastfeeding, was reported either in an interview at offspring age 5 years or 18 months. An association between higher maternal serum PFOA and duration of both total and exclusive breastfeeding was observed; however, although the authors adjusted for the influence of other environmental chemicals (i.e., p,p'-DDE and polychlorinated biphenyls) they did not collect sufficient information to control previous breastfeeding. Neither study measured PFOA in drinking water.

The studies on the associations between PFOA exposure and sperm quality or hormone levels are sparse, inconsistent, and need to be corroborated in larger studies to better inform the possibility of a relationship. In a cross-sectional study conducted in 256 men from Durham, NC, a positive correlation was found between plasmatic PFOA and serum luteinizing hormone levels. No association between PFOA and semen quality measurements was found (Raymer et al., 2012). A positive association between PFOA and semen motility was identified in a group of men from one country, but not in the two other countries studied (Greenland, Poland and Ukraine). The author indicated the positive result might be attributable to chance findings (Toft et al., 2012). A prospective study has suggested that *in utero* exposure to PFAS may affect adult human male semen quality and reproductive hormone levels; however, there are concerns about the selection of participants (Vested et al., 2013).

Considering the weight of evidence, it is not possible to rule out possible adverse effects of PFOA on development and reproduction. Large cohort studies of offspring of mothers with high serum PFOA have reported an increased risk of lower abdominal circumference, length and weight at birth, as well as being overweight and having a high waist circumference 20 years after birth. These results are supported by effects on serum biomarkers (insulin, leptin, and adiponectin). Moreover, some evidence of reproductive toxicity has been observed, although to a lower extent. Higher level of exposure to PFOA has been associated with an increased risk of

pregnancy-induced hypertension, preeclampsia, shorter duration of breastfeeding, altered sperm quality and reduced fecundity in longitudinal studies. However, the dataset for each individual outcome remains relatively small and definitive conclusions on the relationship between reproduction and developmental outcomes and exposure to PFOA are mainly limited by a lack of consistencies in the results and the possibility of confounding. These limitations do not allow determining the nature of the association for the moment.

9.2 Effects on experimental animals

The vast majority of animal studies stated that exposure to PFOA was through its ammonium salt (APFO). Studies that did not state the specific salt used in their study were assumed to have used the ammonium salt, as this was the only compound used in studies that stated the PFOA salt. No studies stated whether the administered dose referred to the APFO compound, or specifically to the PFOA ion, separate from the ammonium salt. The summaries described herein use the concentrations and doses stated by authors. This approach is also used for quantitative assessments; however, as the PFOA ion contributes to 96% of the molar weight of APFO and is released from the compound upon exposure, only minor quantitative differences would result from using APFO and PFOA doses interchangeably.

9.2.1 Acute toxicity

The acute toxicity studies for PFOA or APFO indicate oral LD_{50} values of >500 and 680 mg/kg bw for male Sprague-Dawley and CD rats, respectively (Glaza, 1997), 250–500 mg/kg bw and 430 mg/kg bw for female Sprague-Dawley and CD rats, respectively (Dean and Jessup, 1978; Glaza, 1997), and <1,000 mg/kg for Sherman-Wistar rats of both sexes (Gabriel, 1976).

No mortality was reported in Sprague-Dawley rats of both sexes following inhalation exposure to PFOA at 18,600 mg/m^3 for 1 hour (Rusch, 1979).

The dermal LD_{50} in rabbits was determined to be >2,000 mg/kg bw or 4,300 mg/kg bw (Glaza, 1995; Kennedy, 1985). Higher values were obtained in rats, with a LD50 at 7,000 mg/kg bw in males and at 7,500 mg/kg bw in females (Kennedy, 1985).

Acute developmental neurobehaviour studies are discussed in Section 9.2.5.5.

9.2.2 Short-term exposure

Studies documenting the toxicity of PFOA after short-term oral exposure identified three main targets, namely reproductive and developmental effects (summarized in Section 9.2.5), hepatic effects, and serum lipid effects. Delayed mammary gland development appears to be the most sensitive target, with a LOAEL of 0.001 mg/kg bw per day (serum PFOA: 74.8 ng/mL; no NOAEL) in mice (White et al., 2011) (see Section 9.2.5.1). The lowest LOAELs for hepatic effects were 0.15 mg/kg bw per day in adult mice (Kennedy, 1987; NOAEL of 0.05 mg/kg bw per day). Serum lipid effects were observed at ≥0.3 mg/kg bw per day in rats (Loveless et al., 2006, 2008). This section will focus primarily on these key effects observed at the lowest levels, and will only briefly discuss other types of changes observed in animals.

9.2.2.1 Hepatic effects

The hepatic effects observed at the lowest levels in short-term studies were hepatocellular hypertrophy in male rats and mice (Perkins et al., 2004; Loveless et al., 2008) and increased liver weight in rats (Kennedy, 1987) and mice (Loveless et al., 2006). These studies will be described in greater detail, and other hepatic effects observed at higher levels will be discussed only briefly.

The lowest LOAEL for liver weight was in pups exposed *in utero* to 0.1 mg/kg bw per day on gestational days (GD) 1–17; further details on this study are provided in Section 9.2.5.4. In adults, the studies that observed liver weight increases at the lowest levels were Loveless et al. (2006; LOAEL of 0.3 mg/kg bw per day) and Kennedy (1987; LOAEL of 0.15 mg/kg bw per day and NOAEL of 0.05 mg/kg bw per day). These studies are described below.

A LOAEL of 0.3 mg/kg bw per day (no NOAEL) was identified in male CD-1 mice (n=10/dose) after oral exposure to PFOA (0, 0.3, 1, 3, 10 or 30 mg/kg bw per day) for 14 days (Loveless et al, 2006). Different preparations of PFOA were used (branched, linear, or combined branched/linear APFO). The LOAEL refers to increased relative liver weight in mice treated with linear and with branched APFO (most studies expose animals to a mixture that is predominantly linear APFO). Liver weights were also increased in rats, but only at ≥1 mg/kg bw per day. Absolute liver weights were significantly increased in at least one APFO form at ≥1 mg/kg bw per day in both species. In both rats and mice, the overall liver weight responses to linear and branched forms of PFOA were similar. The same researchers performed a 29-day study with linear APFO, and found no increases in liver weight at 0.3 mg/kg bw per day—absolute liver weight was increased in both species at ≥1 mg/kg bw per day, and relative liver weight was increased at ≥1 mg/kg bw per day in mice and ≥10 mg/kg bw per day in rats (Loveless et al., 2008). The latter study contained a high-dose (i.e., 30 mg/kg bw per day) recovery group (with exposure cessation at test days 23 in rats and 24 in mice), with liver weight increases still present at termination of the study in both species.

In the study with the lowest LOAEL for the endpoint (Kennedy, 1987), male and female CD rats were exposed to APFO at 0, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, and 30 ppm in food (using Health Canada default assumptions of 1 ppm in food = 0.05 mg/kg bw per day in rats [Health Canada, 1994], the approximate doses were 0.0005, 0.0015, 0.005, 0.015, 0.05, 0.15, 0.5, and 1.5 mg/kg bw per day) for 21 days. Increased absolute and relative liver weight was observed at ≥0.15 mg/kg bw per day in both males and females, with a NOAEL of 0.05 mg/kg bw per day. The same study also exposed rats for 14 weeks, and observed increases at the highest dose in the study (30 ppm in food, equivalent to 1.5 mg/kg bw per day).

A wide variety of short-term studies observed increases in liver weight in adult animals at higher doses. These effects were observed in rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Staples et al., 1984; Kennedy et al., 1986; Biegel et al, 2001; Perkins et al., 2004; Cui et al., 2009), in mice (Metrick and Marias, 1977; Liu et al., 1996; Yang et al., 2001, 2002; Lau et al., 2006; Abbott et al., 2007; Wolf et al., 2007; DeWitt et al., 2008; Son et al., 2008; Qazi et al., 2010; Yahia et al., 2010) and in monkeys (Thomford, 2001a; Butenhoff et al., 2002). Increases in liver weight appear to be generally reversible, as they were no longer observed after the exposure period in most studies with a recovery period (Palazzolo, 1993; Thomford, 2001a; Butenhoff et al., 2002; Perkins et al., 2004). In contrast, in a study of mice exposed for 10 days, the effect was still observed 10 days after ceasing exposure (Yang et al., 2001). Increases in liver weight were also observed in mice exposed *in utero* or peripubertally to PFOA; descriptions of these results can be found in Section 9.2.5.4.

The study that observed hepatocellular hypertrophy at the lowest levels exposed male Sprague-Dawley rats (n=10 per group) and male CD-1 mice (n=19–20 per group) to 0, 0.3, 1, 10, or 30 mg/kg bw per day of PFOA by for 29 days (Loveless et al., 2008). Incidence and severity of hypertrophy increased with dose, with effects of greater severity in mice. In the high-dose recovery group, hypertrophy persisted at the end of the study, despite cessation of exposure on study days 23 (rat) or 24 (mouse).

The most robust study with an observed NOAEL for increased liver weight and hepatocellular hypertrophy exposed male Crl:CD rats (n=55 per dose) to 0, 0.06, 0.64, 1.94, and 6.5 mg/kg bw per day in food (Perkins et al., 2004). Two control groups were included in the study—one set of controls pair-fed with the high dose group, and one *ad libitum* feeding group. The rats were divided into sacrifice groups exposed for a duration of 4, 7, or 13 weeks (n=15 per dose per duration), and each dose (and the *ad libitum* controls) had a recovery group that was observed for 8 additional weeks after cessation of exposure at week 13 (n=10 per dose). Significant dose-related increases in incidence and severity of hypertrophy were observed (Table 3). Most rats exposed to ≥0.64 mg/kg bw per day had minimal-to-slight hypertrophy, which was most severe in the high-dose group exposed for 13 weeks; effects did not persist in recovery groups. Hypertrophy was not accompanied by degenerative lesions in the liver. Relative liver weight was increased at ≥0.64 mg/kg bw per day in the 4-week group and at ≥1.94 mg/kg bw per day at the longer durations; the effect did not persist in the recovery groups. Thus, a NOAEL of 0.06 mg/kg bw per day for lack of hepatocellular hypertrophy is derived.

Table 3: Incidence and severity of hepatocellular hypertrophy in Perkins et al. (2004)

Dose (mg/kg bw per day)	Duration of exposure (wk)	Grade of hypertrophy			
		None	Minimal	Slight	Moderate
Ad libitum control	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	10	0	0	0
Pair-fed control	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	N/A	N/A	N/A	N/A
0.06	4	15	0	0	0
	7	15	0	0	0
	13	15	0	0	0
	13 (recovery)	10	0	0	0
0.64	4	3	12	0	0
	7	3	12	0	0
	13	2	13	0	0
	13 (recovery)	10	0	0	0
1.94	4	0	7	8	0
	7	0	14	1	0
	13	1	12	2	0
	13 (recovery)	10	0	0	0
6.5	4	0	5	9	0
	7	0	6	9	0
	13	0	3	12	0
	13 (recovery)	10	0	0	0

Higher dose studies also identified hepatocellular hypertrophy in mice (Yahia et al., 2010) and rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Cui et al., 2009).

Other histological effects observed in the liver at higher doses in short-term studies include single cell and focal necrosis in mice (Loveless et al., 2008; Yahia et al., 2010) and rats (Metrick and Marias, 1977; Goldenthal et al., 1978a; Loveless et al., 2008; Cui et al., 2009); increased mitosis in mice (Yahia et al., 2010); mild calcification in mice (Yahia et al., 2010); cytoplasmic enlargement of hepatocytes in rats (Metrick and Marias, 1977); and cytoplasmic vacuolation in rats (Cui et al., 2009). Histological effects were also observed in livers of rats exposed to PFOA for 2 years; these effects are described in Section 9.2.3.

Changes in serum levels of markers of liver damage were observed in mice at higher levels than the LOAELs for increased liver weight and hepatocellular hypertrophy. These effects included increased ALT (Son et al., 2008; Yahia et al., 2010), increased AST (Son et al., 2008; Yahia et al., 2010), increased GGT (Yahia et al., 2010), and increased ALP (Yahia et al., 2010; Qazi et al., 2010). Increased ALP was also observed in rats (Kennedy et al., 1986).

Dietary fat content has been proposed to contribute to the increased risk for PFOA-induced hepatotoxicity (Tan et al., 2013). Male Balb/c mice on a regular diet or a high fat diet were dosed with 0, 5, 10 or 20 mg/kg bw per day PFOA for 40 days. High fat diet alone did not cause any liver damage; however, high fat diet exaggerated PFOA-induced hepatotoxicity, including increased plasma AST and ALT levels, more severe hepatocellular hypertrophy, lipid droplet accumulation and necrosis and inflammatory cell inflammation. These results were supported by gene expression and metabolomics analysis that showed that a combination of high fat diet and PFOA significantly perturbed hepatic metabolism with activation of PPARα and hepatic inflammation.

9.2.2.2 Serum lipid effects

Alterations in serum lipid parameters were some of the effects observed at the lowest PFOA exposure levels in adult animals in short-term studies. The effects include changes in HDL, total cholesterol and triglycerides. Total cholesterol and HDL were decreased in most studies of mice (Loveless et al., 2006, 2008; Qazi et al., 2010) and rats (Loveless et al., 2006, 2008), but total cholesterol (along with phospholipid and free fatty acid) was increased in one high-dose study in mice (Yahia et al., 2010). Triglycerides were observed in mice to be increased in certain studies (Loveless et al., 2006; Yahia et al., 2010) and decreased in another (Loveless et al., 2008). They were decreased in both rat studies (Loveless et al., 2006, 2008).

The studies in which serum lipid changes were observed at the lowest levels were both performed by Loveless et al. (2006, 2008), which are described in greater detail in Section 9.2.2.1. The lowest LOAELs were in rats, with values of 0.3 mg/kg bw per day for decreases in cholesterol and triglycerides (Loveless et al., 2006, 2008) and 0.3 mg/kg bw per day for decreases in HDL (Loveless et al., 2008; in the 2006 study by Loveless et al. the LOAEL was 3 mg/kg bw per day). Most of the effects were only observed at higher levels in mice—in Loveless et al. (2008), the LOAELs were 1 mg/kg bw per day for decreased HDL and 10 mg/kg bw per day for decreased total cholesterol and triglycerides, and most of the LOAELs in Loveless et al. (2006) were 3 mg/kg bw per day. An exception was for triglyceride increases specifically in the linear/branched APFO-exposed mice, as effects were observed at ≥0.3 mg/kg bw per day.

The effects on cholesterol and HDL did not appear to be persistent upon cessation of exposure; total cholesterol and HDL levels returned close to control levels when exposure to 30 mg/kg bw per day dose was ceased at days 23 (rat) or 24 (mouse) in the 29-day study (Loveless et al., 2008). Triglyceride levels in mice continued to rise following cessation of exposure but triglyceride levels in rats did not change following cessation of exposure relative to the rats with

continuous exposure; in both species triglyceride levels following cessation of exposure were significantly lower than controls.

Loveless et al. (2006) investigated different forms of PFOA (branched, linear, or combined branched/linear). The linear form (the form most commonly appearing in PFOA mixtures used in studies) appeared to have the lowest LOAELs in rats for all lipid endpoints. In mice, the PFOA form did not appear to have any effect on HDL or cholesterol, but the linear/branched mixture appeared to be the only form that had any effect on triglycerides.

Additional studies saw increases in triglyceride, total cholesterol, and free fatty acid at 10 mg/kg bw per day in ICR mouse dams (Yahia et al., 2010) and reduction in total serum cholesterol in male C57BL/6 mice (Qazi et al., 2010).

Dietary fat content has been proposed to contribute to the observed differences in effects of PFOA on serum lipids in rodents versus humans (Tan et al., 2013; Rebholz et al., 2016). Consistent with the studies above, Tan et al. (2013) reported decreases in both serum cholesterol and triglycerides in a dose-related fashion in mice on the regular fat content diet, whereas serum cholesterol and triglycerides were unaffected by PFOA in mice on a high fat diet. Also, male and female C57BL/6 and male BALB/c mice fed a high fat diet containing 3.5 ppm PFOA (equivalent to 0.56 mg/kg bw per day) had significant increased plasma cholesterol (Rebholz et al., 2016). The response in C57BL/6 mice was more exaggerated compared to BALB/c mice, which the authors explained as strain-specific effects.

9.2.2.3 Other effects

Other effects besides hepatic and serum lipid effects in short-term studies of adult animals occurred at PFOA exposure levels of ≥1 mg/kg bw per day. The studies are described briefly below.

At ≥1 mg/kg bw per day, increased kidney weight was observed in several studies of mice (Yahia et al., 2010) and rats (Goldenthal et al., 1978; Butenhoff et al., 2004b; Cui et al., 2009). In many of the studies, the increases were only in relative, but not absolute, kidney weight. The effects were also often accompanied by histological effects (Butenhoff et al., 2004b; Cui et al., 2009; Yahia et al., 2010).

Changes in weight of neurologically-relevant organs occurred at ≥3 mg/kg bw per day in monkeys. These observations were an increased group mean weight of the pituitary gland and decreased absolute brain weight (Goldenthal et al., 1978). The only other neurological effect noted in adult animals exposed for a short-term duration was reduced activity and lethargy in rats (Cui et al 2009).

Indications of immunosuppression occurred at ≥0.49 mg/kg bw per day in mice. More specifically, Son et al. (2009) reported decreased numbers of splenic lymphocyte populations ($CD4^-$ $CD8^+$, $CD4^+$ $CD8^+$) in ICR mice dosed with ≥0.49 mg/kg bw per day PFOA in drinking water for 21 days. No NOAEL was identified. Additionally, PFOA exposure has been shown to induce decreased immunoglobulin levels, changes in cellularity and subtypes of immune cells, and changes in cytokine expression (Yang et al., 2001, 2002; DeWitt et al., 2008; Loveless et al., 2008; Son et al., 2008, 2009; Qazi et al., 2009, 2010). Splenic and thymic atrophy were also observed in mice (Yang et al., 2001, 2002; Loveless et al., 2008; Son et al., 2009; Qazi et al., 2009), and histological changes were observed in these organs in rats (Cui et al., 2009; Qazi et al., 2009; Son et al., 2009). Studies in mice also indicated a possibility for hypersensitivity due to exposures to PFOA, with a dose-related increase of serum histamine levels at ≥1 mg/kg bw per day (Singh et al., 2012) and increased IgE after challenge with OVA in mice exposed dermally to ≥18.75 mg/kg bw per day (Fairley et al., 2007). The U.S. NTP (2016) concluded that there is high

confidence that exposure to PFOA is associated with antibody response suppression in animals based on consistent suppression of the primary antibody response in mice.

Effects on other organs were observed at ≥10 mg/kg bw per day. These effects included hypertrophy and vacuolation of the zona glomerusa of the adrenal gland in rats (Butenhoff et al., 2004b); pulmonary congestion, thickening of epithelial walls, cell infiltration and vasodilation in rats (Cui et al., 2009); pulmonary edema in rats (Kennedy et al., 1986); and decreased heart weight in monkeys (Goldenthal et al., 1978).

Two studies reported changes in thyroid hormone levels. Butenhoff et al. (2002) reported decreased free and total T3 and T4 in monkeys exposed for 6 months. Decreases in total and free T4 were observed at most timepoints, including termination, for monkeys exposed to 10 or 20–30 mg/kg bw per day; at termination (and not earlier timepoints), a significant decrease was also observed for total (but not free) T4 at the 3 mg/kg bw per day dose. Decreased total and free T3 was observed at most timepoints (including termination) in monkeys exposed to 20–30 mg/kg bw per day; decrease in total (not free) T3 was also observed at two mid-study timepoints, but not at termination, in low-dose monkeys. The effects were accompanied by significant increases in TSH at study termination in monkeys exposed to 3 or 10 mg/kg bw per day (no effect at high dose). The 4-week range-finding study for the Butenhoff monkey study (Thomford, 2001b) did not note any effects on TSH, or in total or free T3 or T4. Martin et al. (2007) measured thyroid hormone (total and free T4, and total T3) levels in male Sprague-Dawley rats one day following daily administration of 20 mg/kg bw per day PFOA or vehicle control by oral gavage for one, three, or five days. Levels of free and total T4 and total T3 were significantly reduced at all three time points, although the magnitude of decreases was smaller for T3 compared to T4.

Decreased bodyweight or bodyweight gain was observed in many different studies. The effects were observed at LOAELs of 3 mg/kg bw per day in rats (Metrick and Marias, 1977; Goldenthal et al., 1978; Staples et al 1984; Kennedy et al., 1986; Butenhoff et al., 2004b; Cui et al., 2010), 3 mg/kg bw per day in mice (Christopher and Marias, 1977; Lau et al., 2006; Wolf et al., 2007; Asakawa et al., 2008; Son et al., 2008; White et al., 2009; Yahia et al., 2010; Suh et al., 2011), and 30 mg/kg bw per day in monkeys (Goldenthal et al., 1978). This effect was accompanied by a decrease in food consumption at ≥5 mg/kg bw per day in rats (Metrick and Marias, 1977; Butenhoff et al., 2004b; Cui et al., 2009) and at 20.7 mg/kg bw per day in mice (Asakawa et al., 2008).

Clinical signs observed in studies included soft stools, diarrhea, and frothy emesis in monkeys (Goldenthal et al., 1978) and roughed fur, muscle weakness, and cyanosis in mice (Christopher and Marias, 1977).

Few studies reported increased mortality in animals. The endpoint was observed at high levels in studies of rats (Metrick and Marias, 1977; Staples et al., 1984; Butenhoff et al., 2004b), mice (Christopher and Marias, 1977), and monkeys (Goldenthal et al., 1978b; Thomford, 2001a; Butenhoff et al., 2002).

9.2.3 Long-term exposure and carcinogenicity

Two chronic toxicity studies in laboratory animals were identified for the oral route. No inhalation or dermal study was located. As was observed in long-term carcinogenicity studies, the liver was the most sensitive target organ in the chronic studies (LOAEL = 1.3 mg/kg bw per day in male rats for increased serum liver parameters) (3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b). Other effects observed in rats after chronic exposure to PFOA include an increased incidence of hyperplasia and tumors in various tissues (mammary gland in females, Leydig cells,

pancreas and liver in males) and alteration of serum hormone levels (3M, 1983; Sibinski, 1987; Biegel et al., 2001).

Only one study included more than one dose – this study was conducted by 3M Company and the results were presented as part of laboratory reports (3M, 1983; Sibinski, 1987) and a peer-reviewed publication (Butenhoff et al., 2012b). A LOAEL of 1.3 mg/kg bw per day (no NOAEL) in male rats was identified for liver toxicity. Sprague-Dawley rats (50/sex/group) were given APFO at 0, 30 or 300 ppm in the diet for 2 years (0, 1.3 or 14.2 mg/kg bw per day for males; 0, 1.6 or 16.1 mg/kg bw per day for females). The LOAEL of 30 ppm was based on significant increases in serum liver parameters in males (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and albumin at many timepoints, which were still elevated—although not significantly at the low dose—at termination) and a dose-related increase of chronic sialadentitis in the salivary gland of males. Hepatocellular hypertrophy was also elevated in both male treatment groups, with significance only being reached at the high dose (incidence was 0% in controls, 12% at the low dose, and 80% at the high dose). Other effects in males include a dose-dependent increased incidence of Leydig cell adenomas, statistically significant at 300 ppm (14.2 mg/kg bw per day). In female rats, the first data analysis indicated a dose-dependent increase in mammary fibroadenomas, statistically significant at ≥30 ppm; however, a more recent analysis was conducted by a pathology working group using current diagnostic criteria, which concluded that PFOA treatment did not result in proliferative lesions in the mammary tissues (Hardisty et al., 2010; Butenhoff et al., 2012b). Non-neoplastic changes in the liver (hepatocellular hypertrophy, portal mononuclear cell infiltrate or cystoid degeneration at the high dose) and the lungs (alveolar macrophages and hemorrhage at the high dose) were observed, and proliferative acinar cell lesions were observed in the pancreas of rats at the high dose. PFOA did not increase the incidence of neoplastic or non-neoplastic lesions in the other organs (thyroid, pituitary, adrenal gland, kidney, uterus).

A follow-up study was performed in male CD rats given APFO in the diet (0 or 300 ppm) for 2 years (average daily dose of 13.6 mg/kg bw per day) (Biegel et al., 2001). Two controls groups were used; the first was an *ad libitum* fed (AL) group, and the second was a pair-fed (PF) group in which the food intake was controlled to match the food intake of the PFOA exposed group. Rats were evaluated at 1 and 3 months and at every 3 months for hormone status, cell proliferation in liver, testis and pancreas and hepatic peroxisome proliferation. Treatment with PFOA increased the relative liver weight at all time points (except at 24 months) compared to both controls. Hepatic β-oxidation activity was significantly elevated at all times, but cell proliferation was not increased in the liver. Pancreatic acinar cell proliferation was increased at 15, 18, and 21 months. Serum estradiol was increased during the first year of the study, serum LH at 6 and 18 months, and serum FSH at 6 months; changes in serum testosterone did not show any consistent pattern. There was a significant increase in tumours in treated animals when compared with one or both of the control groups for Leydig cell adenomas, hepatic adenomas, acinar cell adenomas and combined pancreatic adenomas and carcinomas. An increased incidence of hyperplasia was also observed in Leydig cells and acinar cells (Biegel et al., 2001).

Although the LOAEL for liver endpoints was higher in chronic studies than in shorter-term studies, the comparisons are difficult to make, as the lowest dose used in the chronic study (1.3 mg/kg bw per day) is higher than the lowest LOAELs for liver effects in the shorter-term studies (i.e., 0.1–0.3 mg/kg bw per day). However, some endpoints observed at these low doses in shorter duration studies, most notably hepatocellular hypertrophy in male rats (Loveless et al., 2008) were not observed at the lowest doses used in the chronic studies (i.e., the chronic NOAEL for this endpoint is 1.3 mg/kg bw per day).

9.2.4 Genotoxicity

The genotoxicity database indicates that PFOA compounds are not mutagenic, and generally not genotoxic (U.S. EPA, 2005; UK HPA, 2009; Environment Canada and Health Canada, 2012).

9.2.4.1 In vitro *findings*

Testing of PFOA (or its ammonium or sodium salts) produced no evidence of genotoxic activity in several Ames bacterial mutation assays and in three *in vitro* chromosomal aberration tests (two in hamster cells and one in human cells) (Environment Canada and Health Canada, 2012). More recently, PFOA (tested up to 1,000 µM) had no mutagenic activity in the *umu* test (Oda et al., 2007) and in the Ames test, with or without S9 metabolic activation (Fernandez Freire et al., 2008). PFOA did not increase oxidative DNA damage (as measured in a comet assay) in rat testicular cells exposed to 100 and 300 µM for 24 hours (Lindeman et al., 2012). In human hepatoma HepG2 cells, PFOA (up to 400 µM for 24 h) did not induce ROS generation, DNA single strand breaks or micronucleus (Florentin et al., 2011). In another study using human HepG2 cells, PFOA induced slight ROS generation (0.4-2,000 µM) without generating detectable DNA damage (200 µM) (Eriksen et al., 2010).

In contrast, positive results were obtained in one chromosome damage test in hamster cells and one micronucleus assay in human cells *in vitro*, and PFOA caused oxidative DNA damage in human hepatoma cells in culture (Environment Canada and Health Canada, 2012). PFOA (200 µM) led to mutagenicity induction in human-hamster hybrid (A_L) cells and mitochondria-dependent ROS was shown to play an important role in this process (Zhao et al., 2011b).

9.2.4.2 In vivo *findings*

Testing of PFOA (or its ammonium or sodium salts) for genotoxic potential produced no evidence of activity in three *in vivo* bone marrow micronucleus tests in mice (up to 5,000 mg/kg bw per day). PFOA caused oxidative DNA damage in the liver of rats treated through the oral route (200 ppm in diet for 2 weeks) or the intraperitoneal route (100 mg/kg bw, once) (Environment Canada and Health Canada, 2012).

9.2.5 Reproductive and developmental toxicity

The reproductive and developmental database for PFOA is robust. Two multi-generational studies have been conducted in rats (Butenhoff et al., 2004b/York et al., 2010; White et al., 2011), and reproductive and developmental parameters have been investigated in many one-generation studies in rats, mice, and monkeys. Furthermore, early life or peripubertal exposures were performed in mice (Johansson et al., 2008, 2009; Yang et al., 2009b; Zhao et al., 2010; Dixon et al., 2012).

The most sensitive effects identified are delayed mammary gland development in the offspring of mice (Macon et al., 2011; White et al., 2011), obesity in the female offspring of mice at adulthood (Hines et al., 2009), uterine effects in immature female mice (Dixon et al., 2012), liver weight changes in pups (Abbott et al., 2007; Macon et al., 2011; Onishchenko et al., 2011) and altered neurobehaviour (Johansson et al., 2008, 2009; Onishchenko et al., 2011). These effects were all observed at exposure levels of ≤0.3 mg/kg bw per day, and will be discussed in greater detail. Other reproductive and development effects occurred at higher doses, and will only be described briefly in this section.

9.2.5.1 Mammary gland effects

Changes in mammary gland development (MGD) have only been studied in mice. Delayed MGD was consistent in 1-generation (White et al., 2007, 2009; Wolf et al., 2007; Macon et al., 2011), 2-generation (White et al., 2011), and peripubertal (Yang et al., 2009; Zhao et al., 2010) studies, and has been observed to be significantly different than controls at every dose level studied (≥0.001 mg/kg bw per day) in maternal and F1 generations (both as offspring and dams). The studies primarily identified delayed MGD development (noted to be as long as 10 days in a study that exposed mice to 5 mg/kg bw per day [White et al., 2007]) and lower MGD scores[1] at many different time points. The specific mammary gland structures that were affected included ducts (reduced and delayed ductal elongation and branching), terminal ducts (decrease in number of stimulated TDs), terminal end buds (delayed time of appearance, excess of and decrease in number of TEBs), and longitudinal epithelium (reduced and delayed growth). One study also noted higher densities of darkly staining foci, along with other histological changes, at 18 months (White et al., 2009).

Three studies investigated MGD at ≤1 mg/kg bw per day (Macon et al., 2011; White et al., 2011; Tucker et al., 2015) and will be more thoroughly described below because the LOAELs from these studies are the lowest of any endpoint, including those observed in subchronic and chronic studies. The other studies observing these effects will be summarized more concisely.

A two-generation study (White et al., 2011) found that exposure of mice to low levels of PFOA in drinking water (5 µg/L) delayed mammary gland development in both P0 and F1 dams and F1 and F2 offspring, which persisted until adulthood (at least PND 63). Parental (P0) female CD-1 mice (n = 7–12 per group) were placed into different treatment groups, receiving:

- daily doses of PFOA by gavage (0, 1 or 5 mg/kg bw per day: control, G1 and G5 groups, respectively) on GD 1–17,
- PFOA in drinking water only (5 µg/L, DW group) on GD7–17, or
- PFOA by both gavage (1 mg/kg bw per day on GD1–17) and drinking water (5 µg/L on GD7–17) (G1+DW group).

On PND 1, F1 litters were pooled randomly and redistributed to dams of their respective groups (n=12–13 neonates per litter). F1 female offspring from G1 and G5 groups were not exposed after birth while F1 female offspring from DW and G1+DW groups were exposed via drinking water throughout the rest of the study (n=2–10 F1 dams per group). F1 female offspring were mated with unexposed males to produce the F2 generation. F2 female offspring from DW and G1+DW groups were exposed through drinking water up to the end of the study. Necropsies were performed on F1 and F2 females at PND 42 and PND 63, and on F1 dams and F2 female offspring at PND 10 and PND 22 (White et al., 2011).

In the P0 (i.e., directly-exposed dams), a significant increase of MGD score was observed in all the treated groups on PND 22, even at the lowest dose (5 µg/L in drinking water on GD 7–17). These elevated scores reflect a delay in the normal weaning-induced mammary involution (on PND 22, the structure of the mammary gland in the treated P0 was similar to the structure normally observed at the lactation peak at PND 10). The authors only provided information on the amount of daily ingestion of PFOA in P0 dams consuming 5 µg/L drinking water (approximately

[1] MGD is scored on a 1–4 subjective, age-appropriate developmental scale based on the number of primary ducts and large secondary ducts, lateral side branching, appearance of budding from the ductal tree, and longitudinal outgrowth of the epithelia. For female offspring, a score of 4 refers to excellent development/structure and a score of 1 to poor development/structure. For dams, a value of 4 represents well-differentiated, functionally lactating tissue characterized by extensive epithelium, reduced adiposity, and presence of secretory alveoli, consistent with the peak of lactation (PND10). A value of 1 represents little or diminishing presence of lobuloalveoli and extensive involution and regression of the tissue, with the presence of apoptotic bodies, increasing adiposity, and regressing alveoli, as anticipated at weaning (PND22).

0.05 µg per day during gestation and 0.1 µg per day during lactation [PND 1–22]). Average daily doses are estimated to be approximately 0.001 mg/kg bw per day during gestation and 0.004 mg/kg bw per day during lactation (based on mean approximate weights of 62 g during gestation and 25 g during lactation; the average maternal weight gain during gestation was 25 g, and the initial body weight of dams was not reported by the authors but is assumed to be approximately 25 g for this strain of mice). The maternal LOAEL was therefore considered to be 0.001 mg/kg bw per day.

F1 pups from all treatment groups exhibited reduced MGD scores (reduced ductal elongation and branching, delays in timing of TEB appearance) until at least 9 weeks of age (PND 63, i.e., the last time point). In F1 dams (i.e., adult F1 pups), all of the PFOA-treated groups exhibited reduced MGD scores on PND 10; low score value persisted on PND 22 in the G1+DW, whereas in the G5 group, the score became higher than the control on PND 22 (i.e., normal involution was delayed). In the F2 females, MGD scores at PND 10 and PND 22 did not differ significantly from control; however, this result may be biased due to unusually low scores in the control group. At later times, significantly reduced scores were obtained in all treated groups (PND 42 for DW, G1+DW and G5, PND 63 for G1) and were characterized by an excess of terminal end buds (TEBs) (White et al., 2011).

In summary, White et al. (2011) demonstrated that ingested PFOA alters the development of mammary glands in both dams and offspring of CD-1 mice after exposure to low, human-relevant doses of PFOA (as low as 5 µg/L in drinking water) leading to human-relevant PFOA serum concentrations in pups and dams (range of approximately 20–90 ng/mL). The corresponding dose (LOAEL) was estimated at a maternal exposure of approximately 0.001 and 0.004 mg/kg bw per day during gestation and lactation, respectively. Effects in this study occurred independently of body weight changes, and the only adverse maternal effects observed at these levels were the mammary gland changes.

Macon et al. (2011) performed two separate studies of MGD in CD-1 mice—a late-gestation study and whole-gestation study. In the late-gestation study, dams (n=13 per group) were exposed to PFOA (0, 0.01, 0.1, and 1.0 mg/kg bw per day) by oral gavage on GD 10–17. The whole-gestation study exposed dams (n=13 per group) by gavage to PFOA at 0, 0.3, 1.0 or 3.0 mg/kg bw per day on GD 1–17.

Results of the late gestation study indicate significantly reduced MGD scores (in all treated groups, with a dose-dependent relationship) at PND 21. Other effects observed in the mammary gland at PND 14 (at 0.1 and 1.0 mg/kg bw per day, respectively) included reduced longitudinal epithelial growth by 14.4% and 37.3% compared to control (reduction by 27.4% and 56.5% compared to PND 1) and a statistically significant reduction of TEBs. In the whole-gestation study, the effects observed at all doses were dose-dependent and included reduced MGD scores in female offspring, which persisted until adulthood (PND 84). The LOAELs for the late and whole gestation studies were 0.01 and 0.3 mg/kg bw per day, respectively. No decreases in pup body weight were observed in these studies; therefore, MGD delays did not arise from decreased body weight.

Tucker et al. (2015) studied MGD in both CD-1 and C57Bl/6 female mouse pups that were exposed *in utero* to PFOA. Dams were exposed to PFOA via gavage at concentrations of 0, 0.01, 0.1, 0.3, and 1 mg/kg bw per day on GD 1–17. Significant dose-related trends in decreases in MGD scores were observed in pups of both strains. In CD-1 mice, the decreases were significant at ≥0.1 mg/kg bw per day when measured at PND21, which then decreased to ≥0.01 mg/kg bw per day at PND35 and PND56. The LOAEL for C57Bl/6 was slightly higher,

with significant decreases at ≥0.3 mg/kg bw per day at PND21 and PND61. The authors also noted that average serum PFOA levels were lower in C57Bl/6 mice than in CD-1 mice.

Although the LOAEL for MGD scores was lower in CD-1 than C57Bl/6 mice, the results from this study are not sufficient to conclude that strain sensitivity occurs for the endpoint. Fewer pups were born in all C57Bl/6 groups, which resulted in a smaller sample size for the strain. This was particularly notable in the 0.01 and 0.1 mg/kg bw per day groups, which contained 8–22 CD-1 mice, but only 2–5 C57Bl/6 mice. As average MGD scores were similar between the strains at all doses, the lower sample size might have prevented statistical significance from being reached at these lower doses for C57Bl/6 mice. Moreover, the timing of MGD scoring was different for the strains at later timepoints (CD-1 mice were studied at PND 21, 35, and 56, whereas C57Bl/6 mice were only studied at PND 21 and 61), which might also affect results; MGD scores in control C57Bl/6 mice at PND 61 were lower than in control CD-1 mice at PND 35 and 56.

Tucker et al. (2015) also investigated other sexual maturity effects. No treatment-related effects on estradiol or progesterone levels, or on timing of vaginal opening or first estrus, were observed in either strain.

Several other higher-dose studies have noted delays in MGD at many different time points in female CD-1 mice (dams and offspring) exposed to gavage doses of ≥3 mg/kg bw per day (White et al., 2007, 2009; Wolf et al., 2007). These delays in MGD development are supported by data indicating reduced placental mRNA expression for genes in prolactin family (at ≥2 mg/kg bw per day; Suh et al., 2011), and a delay in lactotransferrin expression at 5 mg/kg bw per day (White et al., 2007).

A peripubertal study in mice (dosing beginning at 21 days of age) noted strain differences, with significant MGD delays at ≥5 mg/kg bw per day in Balb/c, but only at 10 mg/kg bw per day in C57Bl/6 (no inhibition occurred in either strain at 1 mg/kg bw per day; rather, stimulation was observed at this dose in C57Bl/6 mice) (Yang et al., 2009b). An additional peripubertal study (Zhao et al., 2010) noted effects at the only dose in the study, 5 mg/kg bw per day.

Although mammary gland delays can sometimes be associated with decreased body weight, two studies specifically stated that the effects were observed in absence of bodyweight disparities (White et al., 2007, 2009). One study also noted that the effect was not entirely due to underdeveloped offspring and insufficient stimulation by suckling, as the alteration of the functional mammary gland differentiation occurred prior to parturition and lactation (i.e., prior to stimulation of the gland by offspring) (White et al., 2007; 5 mg/kg bw per day).

Other effects related to sexual maturity were accelerated puberty (≥1 mg/ kg bw per day in M mice & 20 mg/kg bw per day in F mice; Lau et al., 2006), delayed sexual maturation (preputial separation & vaginal patency in rats; only at 30 mg/kg bw per day; Butenhoff et al., 2004b), and increased age of vaginal opening (at ≥5 mg/kg bw per day in C57BL/6 mice, but not Balb/c mice; Yang et al., 2009b).

9.2.5.2 Uterine effects

Histological changes in the uterus have been observed in CD-1 mice exposed to low doses of PFOA (Dixon et al., 2012). In immature mice exposed PND 18–20 to 0.01 mg/kg bw per day of PFOA by gavage, endometrial edema, hyperplasia of endometrial mucosa and glands, edema, and hypertrophy and hyperplasia of myometrium were induced. No histological effects were observed at the two higher doses in the study (0.1 and 1 mg/kg bw per day). The study also saw a dose-related increase of mucification (significant at the high dose only) in the cervix and vagina.

Differential effects were observed in uterine weight in mice. Increases in uterine weight in the Dixon et al. (2012) study were only observed in the lowest (0.01 mg/kg bw per day) group. The only other study reporting changes in uterine weight was a 4-week gavage study that exposed peripubertal Balb/c and C57BL/6 mice to 0, 1, 5, or 10 mg/kg bw per day (Yang et al., 2009b). In Balb/c mice, uterine weight was decreased at all doses (≥1 mg/kg bw per day), whereas in C57BL/6 mice, uterine weight was increased at 1 mg/kg bw per day, with a dose-dependent decrease at higher doses, which became significant only at 10 mg/kg bw per day.

9.2.5.3 Obesity in adulthood

Obesity in adulthood was noted to occur in a non-monotonic dose-response fashion in mice, in the only study that investigated this effect (Hines et al., 2009). Dose-dependent effects on body weight, appetite control (increased leptin and insulin blood concentration) and fat distribution were observed at adulthood in female CD-1 mice exposed *in utero* to PFOA. Pregnant mice (n=7–22 per dose group) were exposed daily by gavage on GD 1–17 (PFOA doses of 0, 0.01, 0.1, 0.3, 1, 3 and/or 5 mg/kg bw per day); offspring were weaned at 3 weeks and then female offspring were selected and received a standard diet for the rest of study.

At low doses (0.01, 0.1 and 0.3 mg/kg bw per day), data indicate an excessive weight gain in mice aged 20–29 weeks that coincided with increased blood levels of leptin and insulin (by approximately 2.5-fold) at 21–33 weeks of age (Hines et al. 2009). At higher doses, tissue weights at 18 months of age revealed a decreased relative weight of abdominal white fat at 1 and 5 mg/kg bw per day (no data at 3 mg/kg bw per day), and an increased relative weight of interscapular brown fat at 1 and 3 mg/kg bw per day (no effect at 5 mg/kg bw per day); overall bodyweight was decreased at the higher tested dose (5 mg/kg bw per day). No effects on bodyweight were observed at 1 or 3 mg/kg bw per day.

Similar experiments conducted in ovariectomized siblings of the exposed offspring (ovariectomy performed at PND 21/22) indicated no effect on body weight and abdominal fat weight, but an increased relative weight of interscapular brown fat at 1 mg/kg bw per day (no effect at 5 mg/kg bw per day). Although the latter data were difficult to interpret, the authors concluded that the ovaries appeared to play an important role in the overweight effect in mid-life and proposed that potential dysregulation of PPAR and its signaling through ovarian hormones may be responsible for the low-dose effects observed (Hines et al., 2009). It should be noted that exposure of 8 week-old mice to the same doses for the same period (17 days) did not lead to any effect on the same endpoints (see Section 9.2.2.1), suggesting the timing of dosing was critical for latent effects (Hines et al., 2009).

9.2.5.4 Developmental hepatic effects

As described in Section 9.2.2.1, hepatic effects are the most sensitive non-developmental effect resulting from short-term exposure to PFOA. Likewise, increases in liver weight were also observed after *in utero* or peripubertal exposure to PFOA.

The lowest maternal exposure dose at which increases in liver weight were observed in pups exposed prenatally to PFOA was 0.1 mg/kg bw per day (Abbott et al., 2007). In this study, 129S1/SvImJ mice (n=5–22 dams/dose) were exposed by gavage to 0, 0.1, 0.3, 0.6, 1, 3, 5, 10, and 20 mg/kg bw per day on GD 1–17. Increased relative liver weight in pups was observed in all doses, and was worsened at higher doses. In another study, Quist et al. (2015) reported significant increases in liver:body weight ratios at 0.3 and 1.0 mg/kg bw per day on postnatal day 21 in female offspring from pregnant CD-1 mice administered PFOA (0, 0.01, 0.1, 0.3, and 1 mg/kg bw per day) by oral gavage on GD 1-17; however, this was a transient effect as it was no longer

observed at postnatal day 91. One other study observed slight but significant effects at <1 mg/kg bw per day; the study had only 1 dose group, 0.3 mg/kg bw per day (Onishchenko et al., 2011). The effect was observed at ≥1 mg/kg bw per day in other studies in mice exposed *in utero* (Wolf et al., 2007; White et al., 2009, 2011;Macon et al., 2011) or peripubertally (Yang et al., 2009b).

Filgo et al. (2015) exposed pregnant CD-1 mice, 129/SV mice, and PPARα-null mice (on 129/SV background) to PFOA by oral gavage throughout gestation. Doses administered differed depending on the mouse strain but ranged from 0.01 to 5.0 mg/kg bw per day. Livers from female offspring (exposed in utero and during lactation) were examined histologically at 18 months of age. In CD-1 pups, there was a significant increase in centrilobular hepatocyte hypertrophy and Ito cell hypertrophy at 5 mg/kg bw per day, as well as hepatocellular adenomas at 0.3 mg/kg bw per day only. Quist et al. (2015) similarly reported hepatocellular hypertrophy in pups exposed by the same regime at postnatal day 91 with an increase in severity compared to controls at ≥0.01 mg/kg bw per day. Transmission electron microscopy of the liver slides showed cell damage and changes to mitochondrial morphology and numbers, which are not generally associated with PPARα-mediated effects. Filgo et al. (2015) reported a significant reduction in diffuse fatty change in 129/SV pups at 1 mg/kg bw per day, as well as a significant increase in bile duct hyperplasia at 3 mg/kg bw per day and significant decrease in Ito cell hypertrophy at ≥1 mg/kg bw per day in PPARα-null pup. Quist et al. (2015) reported no change in serum liver enzymes at postnatal days 21 and 91 in pups from dams fed control fat diets or high fat diets throughout lactation but did report a significant decrease in total cholesterol at ≥0.3 mg/kg bw per day in pups from dams fed high fat diet during lactation.

9.2.5.5 Neurodevelopmental effects

Neurobehavioural effects were observed in mice exposed *in utero* or shortly after birth, at the lowest doses applied in two studies—0.3 mg/kg bw per day (Onishchenko et al., 2011) and 0.58 mg/kg bw per day (Johansson et al., 2008). The effects manifested as changes in activity levels in mice.

Dietary exposure of C57BL/6/Bkl mice (n=6 dams/group) to 0 or 0.3 mg/kg (the only treatment group) of PFOA from GD 1 throughout pregnancy was found to induce gender-specific changes in offspring exploratory behaviour (first hour spent in a new environment), with an increased exploring activity in males and a decreased activity in females (Onishchenko et al., 2011). Prenatal exposure to PFOA also decreased the total number of inactive periods during the light phase in both males and females as well as in the dark phase of the circadian cycle in males. Motor coordination was slightly altered in females only. No effects were noted on locomotor activity, anxiety behaviour (elevated plus maze test), and immobility in the forced swimming test or muscle strength.

A LOAEL of 0.58 mg/kg for neurodevelopmental effects was identified in NMRI male mice administered a single gavage dose of PFOA (0.58 or 8.70 mg/kg) at the age of 10 days (Johansson et al., 2008). Mice were tested for spontaneous behavior and habituation at the age of 2 and 4 months, and the susceptibility of their cholinergic system was explored in a nicotine-induced spontaneous behaviour test at the age of 4 month (Johansson et al., 2008). Data indicate time-dependent and dose-related effects on the behaviour (deranged spontaneous behaviour, lack of habituation and increased susceptibility of the cholinergic system) reflecting the advance of a brain dysfunction process induced at the time of brain growth spurt in the neonatal mouse. At both doses, the exposed mice exhibited an altered spontaneous behaviour and a hypoactive response to nicotine. Any of the three variables of the behavioural test (locomotion, rearing and total activity) were altered, indicating hypoactivity during the first 20 minutes and hyperactivity

in the last 20 min period (40–60 min after start of the test), and the effects worsened with age. These effects were supported by significantly increased levels of proteins that are important for normal brain development (CaMKII, GAP-43, and synaptophysin in the hippocampus, synaptophysin and tau in the cerebral cortex, and tau in the hippocampus) in mice under the same neonatal exposure conditions (Johansson et al., 2009).

9.2.5.5 Other effects

Reproductive and developmental effects other than those described earlier in this section were observed at higher doses; 0.6 mg/kg bw per day was the lowest LOAEL for delayed eye opening (Abbott et al., 2007), and all other effects were observed at ≥1 mg/kg bw per day.

The additional reproductive effects in mouse included a reduced number of implants (White et al., 2011), increased resorption, dead fetuses, post-implantation loss, or prenatal loss (White et al., 2007; Suh et al., 2011; White et al., 2011;) including increases in full-litter resorption or loss (Lau et al., 2006; Wolf et al., 2007; White et al., 2009), decreased placental weight (Suh et al., 2011), increased time to parturition (Lau et al., 2006), reduced number of live fetuses (White et al., 2011), increase in number of stillborn pups (Yahia et al., 2010), decreased survival of pups (Lau et al., 2006; Wolf et al., 2007; White et al., 2009; 2011; Yahia et al., 2010) and histopathological changes in mouse placenta (Suh et al., 2011).

The additional developmental effects in mouse offspring included delayed eye opening at in 1-generation studies (Lau et al., 2006; Abbott et al., 2007; Wolf et al., 2007; White et al., 2009), skeletal effects in one-generational studies [one study observed altered ossification (enlarged fontanel, reduced ossification of sternebrae and calvaria; Lau et al., 2006), another found delayed ossification of phalanges, increased cleft sternum, and delayed eruption of incisor occurred; Yahia et al., 2010], decreased relative spleen weight, without a clear dose–response relationship (Hines et al., 2009), reduced fetal or pup weight (Staples et al., 1984; Lau et al., 2006; Abbott et al., 2007; White et al., 2007; 2009; Wolf et al., 2007; Yahia et al., 2010; Suh et al., 2011), and increased fetal weight (Yahia et al., 2010).

The only effects noted in a 2-generation study of rats included delayed growth (at ≥10 mg/kg bw per day in M and 30 mg/kg bw per day in F) and increased post-weaning mortality (in F only, at 30 mg/kg bw per day), with no effects on the F2 generation (Butenhoff et al., 2004b; York, 2002).

9.3 Mode of action

Mode of action analysis was considered for effects occurring at the lowest PFOA levels (i.e., Leydig cell tumours, hepatocellular hypertrophy, and changes in serum lipids in rats, and liver weight increases, hepatocellular hypertrophy, obesity, developmental delays, and delayed mammary gland development in mice). Only a preliminary evaluation of data could be performed for most of the MOAs; a MOA analysis using recent guidance (Meek et al., 2014) could only be performed for peroxisome proliferation effects on liver endpoints. Based on the MOA analysis, no endpoints were considered to be irrelevant to humans, and the results suggest that the TDI approach is the most appropriate method for cancer risk assessment. Results of the MOA evaluations are summarized in this section.

9.3.1 Direct-acting mutagenicity

Direct-acting mutagenicity and DNA reactivity was considered as a potential MOA for the development of Leydig cell tumours in rats. As discussed in Section 9.2.4, evidence predominantly indicates that PFOA is not mutagenic, with or without metabolic activation. PFOA

was negative for genotoxicity in a wide variety of *in vitro* and *in vivo* assays. Positive results were obtained only in one chromosome damage test in hamster cells, one micronucleus assay in human cells, and mutagenicity was observed in human-hamster hybrid (A_L) cells, but mitochondria-dependent ROS was shown to play an important role in this process. The pattern of PFOA-induced tumours also did not follow that of typical mutagens. For example, mutagens are typically expected to cause tumours in many different organs, but PFOA only affected testicular Leydig cells, liver, and pancreas (i.e., organs associated with the PPARα tumour triad) in one study (Biegel et al., 2011), and only Leydig cells in another study at similar doses (Butenhoff et al., 2012b). Furthermore, mutagens often produce a high incidence of tumours, which occur at early timepoints and at low doses. In PFOA-exposed animals, the tumours were only observed after lifetime duration to high doses in PFOA studies, and at low incidences (10–14%).

Further support for non-mutagenic activity of PFOA is provided by a study that suggests that PFOA acts as a tumour promoter. Liver tumours—primarily hepatocarcinomas—were observed in rats that underwent initiation protocols (i.e., were exposed to the mutagen diethylnitrosamine) and were exposed to feed containing 0.015% PFOA (equivalent to 7.5 mg/kg bw per day using the Health Canada [1994] assumption that 1 ppm in food is equivalent to 0.05 mg/kg bw per day in rats) on weeks 5–28 of the study (Abdellatif et al., 1990). Hepatic tumours were observed in 33% of animals (vs. 0% in controls that were initiated but not exposed to tumour promoters); therefore, effects were observed earlier (after 6 months of PFOA exposure and 7 months after initiation) and at a higher incidence than higher dose studies of rats exposed only to PFOA.

The weight of evidence for non-mutagenic MOAs of tumours (as discussed later in this section) is stronger than for direct-acting mutagenicity, which suggests that low-dose linear extrapolation is not appropriate for PFOA-induced tumours. No further MOA analysis is required for direct-acting mutagenicity, unless contradictory data are published.

9.3.2 Peroxisome proliferation

Peroxisome proliferation was considered as a potential MOA for hepatocellular hypertrophy in rats and mice, serum lipid changes and hepatocellular tumours in rats, and liver weight increase and obesity in mice. Some data exist for hepatic PPAR activity in rats and mice; therefore, this is the primary focus of the analysis. Because few studies directly measured PPAR impact on other outcomes, these could not be fully assessed; however, studies in PPAR-null mice indicate a decreased sensitivity to reproductive and developmental endpoints (including litter loss, delayed eye opening, and decreased body weight in pups [Abbott et al., 2007]) but not mammary gland development delays (Zhao et al., 2010). The evolved Bradford-Hill criteria were applied to evaluate the weight of evidence for the MOA of peroxisome proliferation for liver endpoints, which is summarized below.

Three main key events in the peroxisome proliferation MOA are considered to lead to liver histological effects and hepatocellular tumours. These key events are 1) the activation of hepatic PPARα receptors, which leads to 2) altered cell growth pathways that inhibit apoptosis and/or promote cell replication, eventually leading to 3) hepatocyte proliferation (Corton et al., 2014).

9.3.2.1 Key event 1 – PPARα activation

An absence of hepatic palmitoyl CoA oxidation was observed in rats exposed to 0.3 mg/kg bw per day of PFOA for 14 days (Loveless et al., 2006). The lowest dose at which the hepatic oxidation was observed in rats was 0.64 mg/kg bw per day after 4 weeks of exposure (Perkins et

al., 2004), with the effect regularly occurring at higher doses (at ≥1 mg/kg bw per day for 14 days [Loveless et al., 2006], ≥1.94 mg/kg bw per day for ≥4 weeks [Perkins et al., 2004], ≥2 mg/kg bw per day for 14 days [Liu et al., 1996], 7.5 mg/kg bw per day for 23 weeks [Abdellatif et al., 1990], 13.6 mg/kg bw per day for ≥1 month [Biegel et al., 2011], and approximately 20 mg/kg bw per day for ≤28 days [Elcombe et al., 2010]). In mice, hepatic palmitoyl CoA oxidation was observed at lower PFOA doses than rats, with the effect measured at ≥0.3 mg/kg bw per day after 14 days of exposure (Loveless et al., 2006) and higher doses in other studies (Yang et al., 2002; Minata et al., 2010; Nakagawa et al., 2012); moreover, increased expression of PPAR-related genes was observed in wild-type mice, but not humanized PPAR or PPAR-null mice, exposed for 2 weeks to ≥0.1 mg/kg bw per day (Nakamura et al., 2009). In rats exposed to 13.6 mg/kg bw per day of PFOA for 2 years, no increase in palmitoyl CoA oxidation was observed in Leydig cells (Biegel et al., 2011); however, the same study did not measure an increase in the effect in a model peroxisome proliferator (Wyeth-14,643 [WY]).

9.3.2.2 Key event 2 – altered cell growth

No studies of markers of altered cell growth pathways could be found.

9.3.2.3 Key event 3 – cell proliferation

An absence of hepatocyte proliferation was noted in rats exposed to 13.6 mg/kg bw per day for 1–24 months, when it was observed in positive controls (i.e., WY-exposed mice) at the same time periods (Biegel et al., 2001), but the effect was observed in rats exposed to approximately 20 mg/kg bw per day for 2–29 days (Elcombe et al., 2010). A dose-related increase in labelling index was observed in both wild-type and PPAR-null mice exposed for 7 days, with significance reached at 10 mg/kg bw per day (but not 1 or 3 mg/kg bw per day) in both strains (Wolf et al., 2008).

Cell proliferation was measured in pancreatic acinar cells, but not Leydig cells, in rats exposed to 13.6 mg/kg bw per day for 2 years (Biegel et al., 2011).

9.3.2.4 Assessment of Bradford-Hill considerations

Biological concordance — PPAR activation, leading to increased replication in hepatocytes and increased hepatic tumours, is a well-recognized MOA. Increases were observed in testicular (Leydig cell), pancreatic, and hepatocellular tumours in rats (Biegel et al., 2011), which is a recognized tumour triad for the peroxisome proliferation MOA (Corton et al., 2014); pancreatic acinar cell proliferation and hyperplasia were also observed to be increased in rats (Biegel et al., 2011). However, inconsistencies in this observation arise as the tumour triad was not observed at a similar dose in another two-year study in rats (Butenhoff et al., 2012b). Studies of peroxisome proliferation and tumour development in these cells in mice (which are more sensitive to peroxisome proliferation than rats) would potentially provide more useful information for the MOA analysis.

Essentiality of key event — Studies of PPAR-null mice (Yang et al., 2002; Abbott et al., 2007; Wolf et al., 2008; Nakagawa et al., 2012) provided information to evaluate the essentiality of the key events for hepatic effects; no studies of PPAR-null rats exposed to PFOA could be found. In the Abbott et al. (2007) study, PPAR-null mice had decreased sensitivity to liver weight effects, which lends some support to the MOA for this adverse outcome; however, liver weight effects still occur (albeit at higher doses) in PPAR-null mice, and hepatomegaly is induced to the same extent in wild-type and PPAR-null mice in other studies (Yang et al., 2002; Wolf et al., 2008; Nakagawa et al., 2012). Similarly, Filgo et al. (2015) observed significant increases and

significant trends in the development of neoplastic and non-neoplastic hepatic lesions in the female offspring from PPARα-null mice. The increase hepatocyte proliferation (as measured by increase in labelling index) was also similar between wild-type and PPAR-null mice (Wolf et al., 2008). Moreover, despite an absence of increased expression of PPAR-related genes in PPAR-null and humanized PPAR mice, increases in liver weight were similar among these strains and wild-type mice (i.e., mice with increased PPAR expression) (Nakagawa et al., 2012). Despite these quantitative similarities between strains for non-cancer liver effects, qualitative differences were observed—including differences in microscopic appearance and ultrastructure of hepatic cells (Wolf et al., 2008; Minata et al., 2010). Further studies that expose PPAR-null mice at lower doses and investigate other adverse outcomes, as well as studies of PPAR-null rats, would help to better evaluate the MOA.

Temporal and dose–response concordance — Some dose–response concordance was observed for the MOA, as PPAR activation precedes hepatocyte proliferation in rats; however, hepatocyte proliferation was absent at tumour-relevant doses in rats (Biegel et al., 2001), and occurred only at higher levels than those resulting in hepatocellular hypertrophy and increased liver weight (Elcombe et al., 2010). The sole study of hepatocyte proliferation in mice indicates its occurrence only at doses above those at which increases in hypertrophy and liver weight were observed (Wolf et al., 2008). Moreover, the absence of data on altered cell growth pathways precludes the evaluation of whether this key event is triggered by PPAR activation and is a precursor for hepatocyte proliferation.

The first key event (PPAR activation) does not appear to precede the adverse hepatic outcomes in rats. Both increased liver weight and hepatocellular hypertrophy were observed either at or below doses where an absence of PPAR activation was observed.

Consistency (across species, strains, organs, and test systems) — PPAR activation begins at lower doses in mice than rats and monkeys, as is expected, based on knowledge of PPAR biology (Corton et al., 2014). However, in monkeys, PPAR activation is not consistent, is not accompanied by cell proliferation, and occurs only at higher doses than adverse liver effects.

Analogous compounds — The tumour triad observed in male rats, along with an increase in serum estradiol, was observed similarly in both PFOA and a model peroxisome proliferator, WY. However, hepatic effect in PFOS-exposed rats appears to occur in absence of peroxisome proliferation, and the tumour triad was not observed in PFOS-exposed rats.

Some evidence in rats and mice supports the occurrence of peroxisome proliferation as a mode of action for hepatocellular hypertrophy. The characteristic tumour triad of peroxisome proliferators (cancers of the testes, pancreas, and liver) was observed in rats, and the doses at which hepatocellular tumours are observed are higher than earlier key events in the peroxisome proliferation MOA. However, increases in liver weight and hepatocellular hypertrophy appear to occur at lower doses than PPAR activation in rats; therefore, although PPAR activation does occur in rats, it does not appear to be the sole driver for these two effects. Studies of PPAR-null mice indicate that peroxisome proliferation might play a role in observed hepatocellular hypertrophy and liver weight increases, but despite qualitative (i.e., appearance) differences between the strains, the quantitative similarities in the changes in PPAR-null vs. wild type mice indicate that other MOAs play a large role in the development of the effects. Because the peroxisome proliferation MOA does not seem to be the sole MOA involved, human relevance of PFOA-induced non-carcinogenic hepatic effects cannot be ruled out. Conversely, a detailed MOA analysis has concluded that the weight of evidence for the peroxisome proliferation MOA for PFOA-induced liver tumours was strong. The relevance of these tumours to humans is limited, as PPARα activation by PFOA is weaker in humans than in rats. Moreover, PPARα activation by

various compounds in does not appear to result in hepatocellular proliferation and tumours (Corton et al., 2012; Klaunig et al., 2012).

9.3.3 Sex hormone disruption

Sex hormone disruption is a potential MOA that should be considered for mammary gland development delays in mice, obesity in prenatally exposed mice, and Leydig cell tumours in rats. Insufficient data exist to be able to perform a quantitative analysis of sex hormone disruption; however, a few different observations that could be relevant to the sex hormone MOA have been reported, including the muting of uterine effects when PFOA was co-administered with estradiol (Dixon et al., 2012), an enhancement of the effects of 17β-estradiol in a variety of *in vitro* assays, but with an absence of direct estrogenic activity (Sonthithai et al., 2016), the reversal of mammary gland development delays with the supplementation of physiological levels of estradiol or progesterone (Zhao et al., 2012), an increase in serum estradiol concentrations in male rats exposed for 1–12 months (Biegel et al., 2001), changes in estradiol genesis (decrease at lower doses and increase at higher doses) in an *in vitro* steroidogenesis assay (Rosenmai et al., 2013), an absence of PFOA binding to or activating human estradiol receptors *in vitro* (Ishibashi et al., 2007), and decreases in cholesterol levels, which might disrupt testosterone synthesis (Li et al., 2011). If more in-depth studies on the effect of PFOA on sex hormone disruption are performed, this potential MOA could be further investigated.

9.3.4 Other MOAs

Insufficient data exist to allow for the assessment of other potential MOAs considered in the MOA analysis. Some data—particularly in regards to PPAR activation/peroxisome proliferation—exist for other endpoints that were not included in the MOA analysis (i.e., effects that were observed only at higher PFOA exposure levels).

9.4 Additivity

The application of an additive approach for PFAS was considered using the World Health Organization /International Programme on Chemical Safety (WHO/IPCS) framework for risk assessment of combined exposure to multiple chemicals (Meek et al., 2011) 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 PFOS document, studies in humans (including the general population and workers) have demonstrated similarities in health outcomes associated with elevated levels of serum PFOS and PFOA, including liver effects, immune suppression, lipidemia, thyroid effects, kidney effects, cancer, and some reproductive and developmental toxicities (i.e., reduced fecundity, reduced birth weight, changes in the onset of puberty). However, elevated serum PFOS is additionally associated with delays in developmental milestones, thyroid hormone levels, and immune system effects in offspring, while elevated serum PFOA is associated with decreased duration of breastfeeding.

Similarities and dissimilarities in health outcomes in experimental animals have also been demonstrated. Studies in experimental animals have demonstrated similarities in adverse effects of treatment with PFOS and PFOA on the liver (including increased liver weight, hepatocellular hypertrophy, changes in serum enzymes), immune system effects, serum lipids, thyroid effects, neurotoxicity, reduced body weight, and tumor formation (i.e., liver), and the induction of reproductive and developmental toxicities (including neurobehaviour, liver weight changes and histopathology, reduced survival/viability of pups, and increased mortality in pups). Additionally, neither PFOS nor PFOA are considered to be direct-acting genotoxic chemicals. However, discordant results are observed in some outcomes following treatment with PFOS and PFOA. For example, chronic administration of PFOA causes hepatocellular adenomas and Leydig cell adenomas in rats; yet while an increase in the incidence of hepatocellular adenomas is observed following chronic administration of PFOS, no significant dose-responsive changes in the incidence of Leydig cell tumours were found. Furthermore, the most sensitive developmental effects observed following exposures to PFOA (i.e., delayed mammary gland development in the offspring of mice, uterine effects in immature female mice, and obesity in female offspring in mice at adulthood) are not observed following exposure to PFOS. Collectively, although some toxic effects appear to be compound-specific, there is a large degree of concordance in adverse toxicological effects induced by PFOS and PFOA in experimental animals.

There is similarity in their modes of action. The modes of action for PFOS and PFOA are not fully understood and it is likely that multiple pathways are involved in their toxic effects. The largest body of evidence points to PPARα ligand-dependent activation by PFOS and PFOA as a key initiating event in the development of liver toxicities (described in section 9.3 of each document). However, although some toxicity by PFOS and PFOA is attributable to PPARα activation, PPARα-independence has also been proposed. For example, PFOS-induced hypertrophy and lipid vacuolization occurred in the absence of peroxisome proliferation or increase in palmitoyl-CoA-oxidase activity in monkeys (Seacat et al., 2002) and transmission electron microscopy of liver sections with hepatocellular hypertrophy and hepatic inflammation observed in pups exposed to PFOA *in utero* revealed cellular damage and mitochondrial abnormalities with no evidence of peroxisome proliferation (Quist et al., 2015). Additionally, PFOS and PFOA have been shown to alter fatty acid metabolism, lipid transport, cholesterol synthesis, proteasomal activation and proteolysis, cell communication, and inflammation processes in experimental animals. Thus, although the mode of action for PFOS and PFOA-induced toxicities has yet to be elucidated, the similarity in the mechanisms activated by each compound is sufficient to suggest similar modes of action are at play.

In addition to the evaluation of data for additivity using the WHO/IPCS framework (Meek et al., 2011), evidence demonstrating the toxic effects of combined exposures were evaluated to strengthen support for the use of an additive approach for PFOS and PFOA. Only one *in vivo* mammalian study was found. Tatum et al. (2010) reported in a conference proceeding that a binary mixture of PFOS and PFOA (6 mg/kg bw per day and 4 mg/kg bw per day, respectively)

behaves additively by dose addition (also known as concentration addition) on reproductive and developmental toxicity endpoints (i.e., maternal weight gain, pup body weight, maternal and neonatal liver weight) in CD-1 mice exposed to the mixture and to PFOS and PFOA individually by oral gavage on gestational days 1-17. The authors additionally reported less than additive behaviour for neonatal mortality (i.e., the mixture of PFOS and PFOA caused less neonatal mortality compared to PFOS and PFOA alone).

This finding is in general agreement with *in vitro* studies on the combined action of PFOS and PFOA (and other PFAS). In studies of binary mixtures of PFOS and PFOA, additivity has been observed at the level of apoptotic potential in mouse HEPG2 liver cells (Hu and Hu, 2009), mortality in zebrafish embyros (Ding et al., 2013), and PPARα activation in Cos-1 cells (Wolf et al., 2014). The additive effects reported by Wolf et al. (2014) and Ding et al. (2013) were observed at low exposure concentrations but deviations from additivity were observed at higher doses. Similarly, deviations from additivity showing less than additive effects (i.e., the mixture response is less than would be expected under conditions of additivity) have been observed at the level of PPARα activation in Cos-1 cells (Carr et al., 2013) and toxicity in cyanobacteria (Rodeo-Palomares et al., 2012) in studies of binary mixtures of PFOS and PFOA, as well as on cellular viability in human liver HL-7702 cells exposed to a simple mixture of 11 PFAS, including PFOS and PFOA. Greater than additive effects on cellular viability have also been reported in human liver HL-7702 cells (Hu et al., 2014) and in rare minnow hepatocytes (Wei et al., 2009) in studies of binary mixtures of PFOS and PFOA, and in human U2OS bone osteosarcoma cells exposed to a simple mixture of five PFAS, including PFOS and PFOA (Wilson et al., 2016). Wilson et al. (2016) further investigated glucocorticoid receptor transactivation but the mixture responses were too weak to report, as were the estrogen receptor and androgen receptor activities in human MVLN breast cancer cells and hamster CHO-K1 ovary cells, respectively, exposed to a mixture of seven PFAS including PFOS and PFOA (Kjeldsen and Bonefeld-Jorgensen, 2013). Gene expression changes measured following exposure to PFOS and PFOA alone or in a binary mixture demonstrated that mechanisms activated following exposure to mixtures and individual chemicals are complex and can differ depending on the treatment (Wei et al., 2009). The differences reported among studies are largely attributable to the biological model, the concentrations used, and the particular composition/complexity of the mixtures.

The absence of *in vivo* studies investigating the additivity of PFAS was identified as a major data gap. However, based on the evaluation of the exposure and toxicological data for PFOS and PFOA in consideration of the WHO / IPCS framework for the risk assessment of combined exposures (Meek et al., 2011; 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

PFOA and its salts have been classified as possibly carcinogenic to humans (Group 2B) by IARC, based on limited epidemiological evidence demonstrating associations between PFOA and testicular and renal cancers, and on limited evidence in experimental animals (Benbrahim-Tallaa et al., 2014). When evaluated under the *Canadian Environmental Protection Act*, PFOA, its salts and its precursors met the criteria for persistence and immediate or long-term harmful effect on the environment or its biological diversity, but were not deemed to be bioaccumulative, nor entering the environment under conditions that constitute or may constitute a danger in Canada to human life or health (Environment Canada and Health Canada, 2012).

The benchmark dose (BMD) approach was used wherever possible to calculate potential PODs, because it is derived on the basis of data from the entire dose-response curve for the critical effect rather than from the single dose group at the NOAEL (IPCS, 1994). A lower confidence limit of the benchmark dose (BMDL) has been suggested as an appropriate replacement of the NOAEL (Crump, 1984). More specifically, a suitable BMDL is defined as a lower 95% confidence limit estimate of dose corresponding to a 1–10% level of risk over background levels. Definition of the BMD as a lower confidence limit accounts for the statistical power and quality of the data (IPCS, 1994). Benchmark dose values representing a 10% increase in adverse effect over background rates (BMD_{10}) and their lower 95% confidence limits ($BMDL_{10}$) were calculated using the U.S. EPA Benchmark Dose Software (BMDS Version 2.6.0.86; U.S. EPA, 2015).

Large pharmacokinetic differences exist between animals and humans, with lower clearance (i.e., higher half-life values) in humans than in rats, mice, and monkeys. These differences result in higher target tissue doses in humans when exposed to the same external doses as animals. Default approaches for interspecies extrapolation (e.g., interspecies uncertainty factor of 10, allometric scaling) are therefore not considered to be sufficiently protective of humans. As described in Section 8.6, AK_{UF} values (i.e., the component of the CSAF reflecting interspecies toxicokinetic differences) were calculated with a PBPK model to address pharmacokinetic differences between animals and humans. As different AK_{UF} values were calculated for various doses, the values can also address non-linearity in pharmacokinetics. Weaknesses still exist with this approach, as outlined in detail in Section 8.6, including the use of the steady-state plasma concentration as a dose metric, rather than selecting organ-based values or exploring whether other dose metrics (e.g., peak concentrations) are more appropriate. However, despite the weaknesses, the approach was determined to be the best of the available options. This approach was selected over the use of serum concentrations as points-of-departure (PODs), because human PBPK models were determined to not be sufficiently robust for precise estimates of human exposure levels corresponding to serum-based PODs.

10.1 Cancer risk assessment

Epidemiological evidence has shown an association between exposure to PFOA and increased risk of incidence of testicular and kidney cancers (see Section 9.1.3). The associations were observed in large-scale epidemiology studies in a community with elevated PFOA concentrations in water (C8 project). However, causality and a point-of-departure cannot be determined from these studies due to the lack of consistency between studies (no association found in some prospective studies in Denmark and the U.S.). Limitations were also observed in the studies that found a positive association, including the risk of residual confounding (because not all covariates and exposures to other contaminants were included in the model), the small case numbers, the uncertainties in exposure characterization (rough estimates based on residency within a certain area), and the high number of outcomes included in the models, increasing the likelihood of chance findings.

Two chronic duration studies identified testicular Leydig cell adenomas in male Crl:CD BR (CD) rats exposed to PFOA for 2 years. The first study observed these adenomas at 13.6 mg/kg bw per day (the only dose tested in the study; Biegel et al., 2001); the other study observed a dose-related increase in incidence of adenomas, with significance achieved at the high dose (14.2 mg/kg bw per day; 3M, 1983; Sibinski, 1987; Butenhoff et al., 2012b). The Leydig cell adenomas were accompanied by hyperplasia of Leydig cells and proliferation and adenomas of pancreatic acinar cells in the Biegel et al. (2001) study. Dose-dependent increases in mammary

fibroadenomas was observed in female rats in the Butenhoff et al. (2012b) study, but were not considered proliferative lesions using current diagnostic criteria.

Although the mode of action for PFOA-induced tumours has not yet been elucidated, the weight of evidence more strongly suggests that PFOA is a non-mutagenic compound (see Sections 9.2.4 and 9.3). For this reason, the tolerable daily intake (TDI) approach is the most appropriate method for deriving a health-based value (HBV) for cancer.

The selected key study for the cancer risk assessment is Butenhoff et al. (2012b), as it is the only chronic study with more than one dose level. Incidence of Leydig cell tumours was 0, 2, and 7, in rats exposed to 0, 1.3, and 14.2 mg/kg bw per day, respectively. As significance was only observed at the high dose, the NOAEL and LOAEL for Leydig cell tumours in this study are 1.3 and 14.2 mg/kg bw per day, respectively. The use of benchmark dose modelling is not typically recommended for studies containing only two dose groups (U.S. EPA, 2012b); however, the approach was performed for comparison with the NOAEL. Three models (Log Logistic, Log Probit, and Multistage) had the best fit (all models had the lowest Akaike information criterion [AIC] among all considered models). The $BMDL_{10}$ values for these three models ranged from 1.06 to 1.26 mg/kg bw per day, and were therefore similar to the NOAEL of 1.3 mg/kg bw per day, which is used as the POD for the analysis.

To reflect the large interspecies differences in pharmacokinetics, the human-equivalent point-of-departure (POD_{HEQ}) can be calculated by dividing the NOAEL by the AK_{UF}, as follows:

$$POD_{HEQ} = \frac{1.3 \text{ mg/kg bw per day}}{17}$$

$$= 0.076 \text{ mg/kg bw per day}$$

where:

- 1.3 mg/kg bw per day is the NOAEL for Leydig cell tumours in male rats (Butenhoff et al., 2012b); and
- 17 is the dose-specific AK_{UF} for rats in the 1 mg/kg bw per day range (as described in Section 8.6.2).

Using the calculated POD_{HEQ}, the cancer TDI was calculated as follows:

$$TDI = \frac{0.076 \text{ mg/kg bw per day}}{25}$$

$$= 0.003 \text{ mg/kg bw per day}$$

where:

- 0.076 mg/kg bw per day is the POD_{HEQ} associated with the NOAEL for Leydig cell tumours in male rats (Butenhoff et al., 2012b); and
- 25 is the composite uncertainty factor, as described below.

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (×2.5) and intraspecies uncertainty factor (×10). A value of 2.5 is used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the

toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. A default value of 10 was applied for the intraspecies uncertainty factor. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOA excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. Average half-life values calculated from longitudinal data for different populations previously exposed to PFOA were similar (averages for each population ranged from 2.3–3.8 years; Olsen et al., 2007; Bartell et al., 2010; Brede et al., 2010); however, studies providing ranges indicated that there was approximately a 10-fold difference between the lowest and highest estimates of half-life. If further studies of PFOA consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed.

Using this TDI, the HBV for drinking water can be calculated as follows:

$$\text{HBV} = \frac{0.003 \text{ mg/kg bw per day} \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= 0.028 \text{ mg/L}$$

$$\approx 0.03 \text{ mg/L (30 µg/L)}$$

where:

- 0.003 mg/kg bw per day is the TDI derived above;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and
- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7).

10.2 Non-cancer risk assessment

Although epidemiological evidence has shown an association between the exposure to PFOA and multiple health outcomes, such as dysfunctions of the immunological system and alterations in birth weight and lipid levels (see Section 9.1.3), a POD cannot be derived from these studies due to limitations, including in terms of study design, bias and confounders.

The lowest LOAELs for PFOA were for reproductive and developmental effects in mice, with effects observed at levels as low as 0.001–0.01 mg/kg bw per day for delayed mammary gland development (Macon et al., 2011; White et al., 2011; Tucker et al., 2015), at 0.01 mg/kg bw per day for estrogenic effects in the uterus (Dixon et al., 2012) and weight changes in adult females exposed prenatally (Hines et al., 2009), and at 0.6 mg/kg bw per day for delayed eye opening (Abbott et al., 2007). These endpoints were not used as the basis of the risk assessment for several reasons. Estrogenic effects in the uterus (endometrial edema, hyperplasia of endometrial mucosa and glands, hypertrophy and hyperplasia of myometrium, and increase in weight in the uterotrophic assay) were excluded from the assessment because they did not occur

in a dose–related manner—significant increases were observed in mice exposed only to 0.01 mg/kg bw per day, and not at higher levels (0.1 or 1 mg/kg bw per day; Dixon et al., 2012). A non-monotonic response was also observed for body weight changes in adult female mice exposed *in utero*, with increased body weight at 0.01–0.3 mg/kg bw per day (not 1 mg/kg bw per day) and in serum leptin and insulin at 0.01 and 0.1 mg/kg bw per day (not 0.3 or 1 mg/kg bw per day; Hines et al., 2009). Moreover, slight changes (although significant) in mammary gland development and bodyweight are indicative of treatment-related changes, but not necessarily adversity—there was no evidence of insufficient milk intake or inability to thrive in pups of dams with MGD changes, and weight changes were low (measured at <10%). The observation of delayed eye opening at ≥0.6 mg/kg bw per day in mice (Abbott et al., 2007) was not corroborated in other studies, as the effect had a LOAEL of 3 mg/kg bw per day (NOAEL=1 mg/kg bw per day; Lau et al., 2006), and was not observed at 3 mg/kg bw per day in another study (Albrecht et al., 2013). Mammary gland development effects might also be affected by strain sensitivity—the majority of the low-dose effects have only been observed in CD-1 mice exposed *in utero*, and other strains were typically only studied at higher doses and in peripubertal mice. A recent *in utero* study comparing MGD in both CD-1 and C57Bl/6 mice at doses of 0.01–1 mg/kg bw per day potentially provided support for low dose effects in a second strain of mice, albeit at slightly higher doses (LOAEL = 0.01 vs. 0.3 mg/kg bw per day in CD-1 and C57Bl/6 mice, respectively); however, a small sample size at low doses for C57Bl/6 mice (as few as two pups) might have precluded the observation of significant changes at similar doses to CD-1 mice. Finally, species sensitivity might be occurring for these effects, as one- and two-generation studies in rats identified similar effects only at much higher doses, if at all; the NOAELs for body weight changes and delayed sexual maturation in pups were around 3 mg/kg bw per day (Staples et al., 1984; Butenhoff et al., 2004b) and 10 mg/kg bw per day (Butenhoff et al., 2004b), respectively, and no effects on lactation index were observed up to 30 mg/kg bw per day (Butenhoff et al., 2004b). Further support for the potential for species sensitivity is provided in studies using PPARα-knockout mice, which were less sensitive to body weight changes and eye opening (Abbott et al., 2007) and MGD delays (Zhao et al., 2012). PPAR activation is more sensitive in mice than in other species, including rats and humans (Corton et al., 2014); note that this study is specific to the mode of action of liver tumours and its conclusions are not necessarily applicable to other effects. Although the data from the studies described above provide indication of some reproductive and developmental effects at low doses, the data are not currently considered to be an appropriate basis for quantitative risk assessment; however, if further studies demonstrate consistency of these effects in other species or their relevance to humans, the endpoint could become a more appropriate basis for the PFOA evaluation.

Few epidemiological studies have investigated the developmental effects described above, which limits the ability to conclude on the relevance of these effects in humans. The human observations related to weight gain in adulthood after developmental PFOA exposures were increased odds of women being overweight and having increased biomarkers of adiposity at 20 years of age after *in utero* exposures (with maternal serum levels of 5.8 ng/mL, as compared with levels of 2.3 ng/mL) (Halldorsson et al., 2012). Estrogenic observations were limited to delayed puberty in girls, and slight associations between PFOA concentration and shorter duration of breastfeeding. As previously discussed, care should be taken before concluding on health effects based on these epidemiological studies. The nature of the observed associations between PFOA exposure and the developmental outcomes need to be investigated further because of the lack of consistency across studies, the non-specificity of the outcomes, the misunderstanding of the mechanism of action, the borderline significance and lack of strength and dose-response of many

results, and the presence of various limitations inherent to the study design, such as the possibility of residual confounding, biases due to errors in outcome measurements, and chance.

Hepatic effects were observed at slightly higher levels than reproductive effects, but observations of changes were still made at PFOA doses of ≤0.3 mg/kg bw per day. Increased relative liver weight was observed at ≥0.1 mg/kg bw per day in prenatally-exposed mouse pups (Abbott et al., 2007; Macon et al., 2011) and at ≥0.15 mg/kg bw per day in adult mice (Kennedy, 1987; Loveless et al., 2006, 2008). Dose-related increases in incidence and severity of hepatocellular hypertrophy were observed at ≥0.3 mg/kg bw per day in rats (Perkins et al., 2004; Loveless et al., 2008) and mice (Loveless et al., 2008) exposed subchronically to PFOA. Although increases in hepatocellular hypertrophy and liver weight were observed at slightly lower levels in other studies, Perkins et al. (2004) was selected as a key study that was representative of the database for the endpoint. Hepatocellular hypertrophy was observed in male rats in the Perkins study at ≥0.64 mg/kg bw per day, which is on the same order of magnitude as the studies demonstrating LOAELs of 0.1–0.3 mg/kg bw per day. A major advantage presented by the Perkins study is that a NOAEL was observed (0.06 mg/kg bw per day), whereas the LOAELs in the majority of other low dose studies were the lowest administered doses. A similar NOAEL of 0.05 mg/kg bw per day can be obtained from Kennedy et al. (1987) when Health Canada (1994) assumptions for food intake and bodyweight in rats (Health Canada, 1994) are used, but the authors did not provide actual values of measured doses. A further advantage of the Perkins study over the other low-dose studies is that the study duration was longer, with exposure durations of up to 13 weeks; moreover, in addition to *ad libitum* controls, the study provided pair-fed controls to ensure that effects did not result from food consumption quantities. Finally, PPAR-α activity was measured in the Perkins study, and was only increased at ≥1.94 mg/kg bw per day; because this suggests that hepatocellular hypertrophy was not resulting from peroxisome proliferation, human relevance of this endpoint cannot be excluded. A NOAEL of 0.06 mg/kg bw per day is also supported by the most conservative NOAEL for hepatic biochemical effects, which was estimated at 0.055 mg/kg bw per day in male rats demonstrating increased alkaline phosphatase levels in conjunction with increased liver weight (Kennedy et al., 1986), using default assumptions for bodyweight and ingestion rates (Health Canada, 1994), and linearly scaling from periodic to continuous exposure. The NOAEL is also approximately 10-fold lower than the NOAEL and 30-fold lower than the LOAEL for hepatic necrosis (0.56 and 1.72 mg/kg bw per day, respectively) observed in rats exposed for 90 days (Goldenthal et al., 1978a).

Although increased liver weight and hepatocellular hypertrophy can sometimes be considered effects that are adaptive rather than adverse in their own right, evidence of other histological effects in the liver at higher concentrations provide an indication of their progression upon continued exposure (ECETOC, 2002; Hall et al., 2012). An adverse histological effect (portal mononuclear cell infiltrate) was observed in livers of male rats at the same dose where significant increases in hepatocellular hypertrophy were observed (14.2 mg/kg bw per day of PFOA for 2 years; Butenhoff et al., 2012b). Although this dose is much higher than the lowest points of departure for increased liver weight and hepatocellular hypertrophy observed in subchronic studies, the latter effects are proposed as critical effects for this assessment, as they might be sensitive indicators of the potential for the progression of adverse histological effects. Additional histological effects observed in rats in studies of shorter duration included necrosis at ≥1.72 mg/kg bw per day (Goldenthal et al., 1978a; Loveless et al., 2008), cytoplasmic vacuolation at ≥5 mg/kg bw per day (Cui et al., 2009), and fatty change, angiectasis, congestion, and acidophil lesion at 20 mg/kg bw per day (Cui et al., 2009). Therefore, increased liver weight and hepatocellular hypertrophy are considered in the dose–response assessment—despite their

potential to be adaptive, rather than adverse, effects—as a means of preventing the more serious histological effects observed in other studies or at higher doses. The use of conservative endpoints for liver effects is also somewhat supported by epidemiology studies, in which some associations between PFOA exposure and increases in liver enzymes (including AST, ALT, and GGT) were observed; however, the associations between serum PFOA levels and liver effects cannot be used to draw definitive conclusions in humans because of limitations. These limitations include the lack of consistency and specificity of the outcomes, the weakness of the effects, and the study designs presenting many limitations (e.g., do not allow for verification of temporality). Serum levels at which these effects were observed in humans were on the order of 1,000 ng/mL in occupational studies and <10 ng/mL in environmental studies, which were lower than serum concentrations associated with the NOAEL and LOAEL for the 13-week Perkins study (7,100 and 41,000 ng/mL, respectively).

Changes in serum lipid levels were also observed around the levels at which hepatic effects occur. The lowest dose at which serum lipid changes were observed was 0.3 mg/kg bw per day in rats exposed for 14 days (decreased total cholesterol; Loveless et al., 2006) or 29 days (decreased total and HDL cholesterol; Loveless et al., 2008). Typical observed changes were decreases in total cholesterol, HDL, and triglycerides. These effects are important for consideration during the assessment of PFOA risks, as epidemiology studies generally demonstrated positive associations between PFOA and serum cholesterol levels. Inconsistencies in effect were observed not only in between the two databases, but also within both the toxicology (see Section 9.2.2.2) and epidemiology (see Section 9.1.2.2) databases. Clear dose–response relationships also tended to be absent in the animal studies. Due to these weaknesses, quantitative assessments were not performed for serum lipid effects; however, based on the present database, a TDI based on liver effects is assumed to be sufficiently protective of lipid changes.

Benchmark doses (BMD_{10}) and their 95% lower confidence limits ($BMDL_{10}$) were calculated for hepatocellular hypertrophy for male rats (Perkins et al., 2004). The analysis was performed using the U.S. EPA's BMDS (version 2.6.0.1) and BMD models were selected based on visual inspection of the curve, goodness of fit p-value ≥0.1, and BMD/BMDL ratios <10. Eight models were selected according to these criteria. The logprobit model provided the best fit (i.e., lowest Akaike information criterion). Estimated BMD values were BMD_{10} of 0.13 mg/kg bw per day and $BMDL_{10}$ of 0.05 mg/kg bw per day.

To reflect the large interspecies differences in pharmacokinetics, a human-equivalent point-of-departure (POD_{HEQ}) was calculated for hepatocellular hypertrophy as follows:

$$POD_{HEQ} = \frac{0.05 \text{ mg/kg bw per day}}{96}$$

$$= 0.000521 \text{ mg/kg bw per day}$$

where:

- 0.05 mg/kg bw per day is the $BMDL_{10}$ for hepatocellular hypertrophy in rats from Perkins et al. (2004), which was selected to represent the hepatocellular hypertrophy and liver weight increase database; and
- 96 is the dose-specific AK_{UF} for rats in the 0.01 mg/kg bw per day range (as described in Section 8.6.2).

Using the calculated POD_{HEQ}, the non-cancer TDI was calculated as follows:

$$TDI = \frac{0.000521 \text{ mg/kg bw per day}}{25}$$

$$= 0.000021 \text{ mg/kg bw per day}$$

where:

- 0.000521 mg/kg bw per day is the POD_{HEQ} calculated for hepatocellular hypertrophy in rats, as described above; and
- 25 is the composite uncertainty factor, as described below.

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (×2.5) and intraspecies uncertainty factor (×10). An interspecies uncertainty factor of 2.5 was used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the POD_{HEQ}. Likewise, a default value of 10 was applied for the intraspecies UF. The default value was assumed to be sufficient in the absence of data on intraspecies differences. Although large differences in pharmacokinetics are known to occur between species, insufficient data on the mechanism of PFOA excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. Average half-life values calculated from longitudinal data for different populations previously exposed to PFOA were similar (averages for each population ranged from 2.3–3.8 years; Olsen et al., 2007; Bartell et al., 2010; Brede et al., 2010); however, studies providing ranges indicated that there was approximately a 10-fold difference between the lowest and highest estimates of half-life. If further studies of PFOA consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed. No uncertainty factor was used for subchronic-to-chronic extrapolation, as liver effects were investigated in a chronic study (Butenhoff et al., 2012b), and increasing duration of exposure did not appear to worsen the effects in the key study (Perkins et al., 2004).

Using this TDI, the HBV for drinking water can be calculated as follows:

$$HBV = \frac{0.000021 \times 70 \text{ kg} \times 0.2}{1.5 \text{ L/day}}$$

$$= 0.00019 \text{ mg/L}$$

$$\approx 0.0002 \text{ mg/L } (0.2 \text{ µ/L})$$

where:

- 0.000019 mg/kg bw per day is the TDI derived above,;
- 70 kg is the average body weight of an adult;
- 0.2 is the default allocation factor for drinking water, used as a "floor value", since drinking water is not a major source of exposure and there is evidence of widespread

presence in at least one of the other media (air, food, soil, or consumer products) (Krishnan and Carrier, 2013); and

- 1.5 L/day is the daily volume of water consumed by an adult; dermal and inhalation exposures from bathing and showering are not considered to be significant routes of exposure (as described in Section 5.7).

10.3 Comparison of cancer and non-cancer risk assessment

The HBV for the non-cancer assessment, which was 0.0002 mg/L for hepatocellular hypertrophy in rats, is more conservative than the HBV for Leydig cell tumours of 0.03 mg/L. The HBV of 0.0002 mg/L that was derived for non-cancer effects is therefore considered to be sufficiently protective of the carcinogenic effects of PFOA.

10.4 Application of additive approach

In keeping with a precautionary approach, the currently available data support the implementation of an additive approach for PFOS and PFOA when evaluating situations where PFOS and PFOA co-occur in drinking water. Given that PFOS and PFOA are the predominant PFAS detected in Canadian water samples and the lack of toxicological data on PFAS besides PFOS and PFOA, the additive approach was not extended to other PFAS. Of the existing additivity approaches for risk assessment (i.e, hazard index, point of departure index, combined margin of exposure index, toxic unit summation, and relative potency factors/toxic equivalency factors; Meek et al., 2011; SCHER, 2012; 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:

$$\frac{\text{PFOA concentration}}{\text{MAC}_{\text{PFOA}}} + \frac{\text{PFOS concentration}}{\text{MAC}_{\text{PFOS}}} < 1$$

Or

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

10.5 International considerations

The U.S. EPA (2016) has established a lifetime health advisory (LHA) of 0.07 µg/L (0.000 07 mg/L) for PFOA. This LHA was derived from a LOAEL of 1.0 mg/kg bw per day for reduced ossification and accelerated puberty (in males) in pups following maternal exposure to PFOA on GD 1–17 by oral gavage (Lau et al., 2006). A reference dose (RfD) of 0.000 02 mg/kg bw per day (0.02 µg/kg bw per day) was derived by applying pharmacokinetic modeling to serum PFOA concentrations to calculate a human equivalent dose (HED) (equivalent to an uncertainty factor of 189 from the LOAEL to the HED to account for interspecies differences in toxicokinetics). An additional uncertainty factor of 300 (10 for intraspecies differences, 3 for interspecies toxicodynamic differences, and 10 for use of LOAEL) was applied to the HED (U.S. EPA, 2016). From the RfD, a health advisory of 0.07 µg/L was calculated assuming a drinking water exposure level of 0.054 L/kg bw per day (the 90th percentile drinking water intake for lactating women; a 3.78 L/day equivalent is calculated assuming 70 kg body weight). Additionally, when PFOA co-occurs with PFOS at the same time and location in a drinking water source, the U.S. EPA recommends comparing the sum of the concentrations of PFOS and PFOA to the LHA of 0.07 µg/L.

The Australia Department of Health (2017) has established a health-based drinking water quality value of 0.56 µg/L (0.000 56 mg/L) for PFOA based on a TDI calculated by Food Standards Australia and New Zealand (FSANZ, 2017). This drinking water quality value was derived from a NOAEL of 1 mg/kg bw per dayfor decreased body weight gain occurring at doses ≥ 3 mg/kg bw per day in mouse pups following maternal exposure to PFOA on GD 1-17 by oral gavage (Lau et al., 2006). A TDI of 0.000 16 mg/kg bw per day (1.6 µg/kg bw per day) was derived by applying pharmacokinetic modeling to serum PFOA concentrations to calculate a HED (equivalent to an uncertainty factor of 204 from the NOAEL to the HED to account for interspecies toxicokinetic differences). An additional uncertainty factor of 30 (10 for intraspecies differences and 3 for interspecies toxicodynamic differences) was applied to the HED. From the TDI, a drinking water quality value of 0.56 µg/L was calculated using a body weight of 70 kg, water consumption of 2 L/day, and an allocation factor of 0.1.

A drinking water guideline of 10 µg/L (0.01 mg/L) was derived by the UK Health Protection Agency (UK HPA, 2007, 2009) based on a TDI of 3,000 ng/kg bw per day (3 µg/kg bw per day) previously derived by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (UK COT, 2006). This TDI was based on a POD of 0.3 mg/kg bw per day, corresponding to the lowest $BMDL_{10}$ for increased liver weights in rats exposed for 13 weeks (data from Palazzolo, 1993 and Perkins et al., 2004); this value was similar to the $BMDL_{10}$ (0.31 mg/kg bw per day) for hepatic necrosis in F0 and F1 male rats (data from Butenhoff et al., 2004b). An uncertainty factor of 100 (for intra- and inter-species variation) was applied. The drinking water guideline (10 µg/L) was derived from the TDI using an allocation

factor of 50%, a body weight of 5 kg and a water ingestion rate of 0.75 L per day for bottle-fed infants (UK HPA, 2007).

In their scientific opinion document on contaminants in the food chain, the CONTAM panel under the European Food Safety Authority derived a TDI of 1,500 ng/kg bw per day (1.5 µg/kg bw per day) based on a $BMDL_{10}$ of 0.3 mg/kg bw per day in rats (EFSA, 2008). This value refers to the lowest $BMDL_{10}$ identified for effects on the liver (Palazzolo, 1993; Butenhoff et al., 2004b; Perkins et al., 2004) among those (0.3–0.7 mg/kg bw per day) derived from a number of studies in mice (Lau et al., 2006) and male rats (Sibinski, 1987; Palazzolo, 1993; Butenhoff et al., 2004b; Perkins et al., 2004). The $BMDL_{10}$ was divided by an uncertainty factor of 200 (10 for interspecies differences, 10 for intraspecies differences and 2 to compensate for uncertainties relating to the internal dose kinetics).

11.0 Rationale for guideline

PFOA is an anthropogenic compound used in the manufacture of stain/water-resistant coatings for various consumer products. Environmental concentrations, and therefore potential exposure levels, may be higher in areas near facilities using high amounts of PFOA and near locations with extinguished fires if PFOA-containing fire-fighting foams were used. Canadians can be exposed to PFOA in food, consumer products, dust, and drinking water. The major sources of PFOA are expected to be food and consumer products, however, the proportion of exposure from drinking water can increase in individuals living in areas with contaminated drinking water. Based on its physico-chemical properties, exposure to PFOA via inhalation and dermal routes during showering or bathing is expected to be negligible.

Chronic exposure to PFOA has been associated with both cancer and non-cancer effects in animals and humans. HBVs for both endpoints have been calculated, with the non-cancer effects resulting in a lower, more conservative value.

Epidemiological studies have shown associations between exposure to PFOA and multiple non-cancer health outcomes, such as dysfunctions of the immunological system and alterations in birth weight and lipid levels. However, these studies cannot be used to derive the non-cancer HBV for PFOA due to limitations in terms of design, bias, confounding, and possibility of chance findings. In animals, non-cancer effects observed at the lowest levels of exposure include reproductive and developmental effects, liver effects and changes in serum lipid levels. For various reasons described in section 10.2, the most appropriate endpoint to derive a HBV for PFOA is hepatocellular hypertrophy (liver effects) in rats, occurring at the same levels as the changes in serum lipid levels. Using a TDI approach, a HBV of 0.0002 mg/L (0.2 µg/L) has been calculated for the non-cancer effects of PFOA based on liver effects in rats. This HBV is considered to be sufficiently protective of both cancer and non-cancer effects of PFOA.

A MAC of 0.0002 mg/L (0.2 µg/L) is established for PFOA in drinking water. This MAC for PFOA can be measured by available analytical methods and is achievable by municipal and residential treatment technologies.

However, when detected in drinking water, PFOA is often found with other PFAS, including PFOS. There is currently insufficient science to develop guidelines for PFAS other than PFOS and PFOA. Given the similarity of the health effects used to establish the MACs for PFOS and PFOA, and the extensive characterization of their toxicity and toxicokinetics, as well as the limited information on the risks and uncertainties of other PFAS, current science 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.

12.0 References

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Appendix A: Reported full-scale drinking water treatment plant PFOA removal data

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

Water Source	Treatment Train[1]	Influent concentration[2] (ng/L)	Effluent concentration[2] (ng/L)	% Removal of PFOA	Reference
Groundwater	DBF, UV, Cl_2	10	9.4	6	Quinones and Snyder, 2009
Surface water	O_3, COA/FLOC, DBF, Cl_2	1.4	1.4	0	Quinones and Snyder, 2009
Surface water	PAC, CHLM, DBF	1.7	1.9	-12	Quinones and Snyder, 2009
Surface water	Cl_2, COA/FLOC, DBF, UV	22	22	0	Quinones and Snyder, 2009
Planned potable indirect reuse facility	MF/RO, UV/H_2O_2, SAT	41	ND	100	Quinones and Snyder, 2009
Planned potable indirect reuse facility	Cl_2, DL, SAT	29	57	-97	Quinones and Snyder, 2009
River water	RSF, O_3, GAC, Cl_2	1.0 (summer)	0.93 (summer)	7	Takagi et al., 2008
River water	RSF, O_3, GAC, Cl_2	0.87 (summer) 3.2 (winter)	2.8 (summer) 1.6 (winter)	-222 (summer) 50 (winter)	Takagi et al., 2008
River water	RSF, O_3, GAC, Cl_2				Takagi et al., 2008
Lake water	RSF, GAC, Cl_2	4.6 (summer) 4.5 (winter)	0.16 (summer) <0.1 (winter)	97 (summer) >98 (winter)	Takagi et al., 2008
River, lake, subsoil and groundwater (7 plants)	RSF, Cl_2	0.56 – 22 (sum) 0.54 – 4.2 (win)	0.45 – 22 (sum) 0.37 – 4.5 (win)	20 – 0 (summer) 31 to -7 (winter)	Takagi et al., 2008
River water	Membranes, Cl_2	0.37 (summer) 0.26 (winter)	0.29 (summer) 0.20 (winter)	22 (summer) 23 (winter)	Takagi et al., 2008
Lake water	SSF, Cl_2	2.7 (summer) 1.8 (winter)	2.3 (summer) 1.9 (winter)	15 (summer) -6 (winter)	Takagi et al., 2008
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.3 (summer) 3.3 (winter)	3.7 (summer) 1.3 (winter)	-185 (summer) 60 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.6 (summer) 3.3 (winter)	2.3 (summer) 1.7 (winter)	44 (summer) 48 (winter)	Takagi et al., 2011
River water	COA/FLOC/SED, SF, O_3, GAC, Cl_2	1.2 (summer) 2.8 (winter)	1.6 (summer) 1.9 (winter)	-33 (summer) 32 (winter)	Takagi et al., 2011
River water	SED, O_3, GAC, Cl2, SF	1.4 (summer) 3.3 (winter)	2.2 (summer) 2.0 (winter)	-57 (summer) 39 (winter)	Takagi et al., 2011
Lake water	COA/FLOC/SED, SF, GAC (reactivated), Cl_2	4.4 (summer) 4.1 (winter)	<0.5 (summer) <0.5 (winter)	>89 (summer) >88 (winter)	Takagi et al., 2011
Ground water	UF, Cl_2	16	16	0	Atkinson et al., 2008
Ground water	GAC (not in operation), super chlorination and dechlorination	135	130	3	Atkinson et al., 2008

Water Source	Treatment Train[1]	Influent concentration[2] (ng/L)	Effluent concentration[2] (ng/L)	% Removal of PFOA	Reference
Ground water	GAC (2 parallel GAC trains each having 6 beds; contactors are mature and act as biological contactors; not been regenerated for some years), Cl_2	42	45	-7	Atkinson et al., 2008
Ground and surface water (60:40)	SSF, O_3, GAC (6 beds-no regeneration for several years), Cl_2using $NaOCl^-$	20.6	25	-21	Atkinson et al., 2008
Ground water	Cl_2 using NaOCl				Atkinson et al., 2008
River water	COA/FLOC/SED, O3, GAC, RSF	5.3 (Aug) 5.8 (Oct)	9.4 (Aug) 6.4 (Oct)	-77 (Aug) -10 (Oct)	Shivakoti et al., 2010)
River water	COA/FLOC/SED, O3, GAC, RSF	5.8 (Aug) 8.8 (Oc)	3.9 (Aug) 4.2 (Oct)	33 (Aug) 53 (Oct)	Shivakoti et al., 2010)
Treated wastewater	De-nitrification, pre-O_3, OA/FLOC/SED, DAF, O_3, GAC (acts as biological contactor), O_3	2,2 (Oct) 3.7 (Nov) 3.6 (Nov)	<LOR (0.3) (Oct) 0.6 (Nov) 0.7 (Nov)	100 (Oct) 84 (Nov) 81 (Nov)	Thompson et al., 2011b
River water	COA/FLOC/SED, RSF, Cl_2	5.02	0.73	85	Kunacheva et al., 2010)
Treated wastewater	Clarifier/lamellar settler ($FeCl_3$&$(NH_4)_2SO_4$, NaOCl addition), UF, RO, UV+H_2O_2, stabilization/disinfection (addition of lime, CO_2, NaOCl)	38 39 23	<LOR (0.5) ND <LOR (0.2)	100 100 100	Thompson et al., 2011
River water	COA/FLOC, RSF, O_3, GAC, SSF	8.2	<0.23	<97	Eschauzer et al., 2012
River water	Cl_2, COA/FLOC, RSF, O_3, GAC	116	33	69	Flores et al., 2013
River water	Cl_2, COA/FLOC, RSF, O_3, GAC, UF, RO	86	13	86	Flores et al., 2013

[1] COA/FLOC/SED = coagulation/flocculation sedimentation; DAF = dissolved air flotation; DL=dilution; GAC = granular activated carbon; O_3 =ozonation; RSF = rapid sand filtration; SSF = slow sand filtration; SF = sand filtration; NaOCl = sodium hyochlorite; Cl_2 = chlorine; RO = reverse osmosis; UF = ultrafiltration; IX = ion exchange; UV/H_2O_2 = ultraviolet irradiation/hydrogen peroxide; SAT = soil aquifer treatment; CHLM = chloramines;
[2]LOR = limit of reporting; ND = not detected

Appendix B: List of acronyms

AFFF	aqueous film-forming foam
ALT	alanine transaminase
APFO	ammonium perfluorooctanoate
BMD	benchmark dose
BMDL	lower confidence limit on the benchmark dose
$BMDL_{10}$	lower 95% confidence limit on the benchmark dose for a 10% response
BV	bed volume
CAS	Chemical Abstracts Service
CI	confidence interval
CSAF	chemical specific adjustment factor
DI	direct injection
DL	detection limit
EBCT	empty bed contact time
EPA	Environmental Protection Agency (U.S.)
ESI	electrospray ionization
GAC	granular activated carbon
GD	gestational day
GM	geometric mean
HBV	health-based value
HED	human equivalent dose
HPLC	high performance liquid chromatography
ISO	International Standard Association
IT	ion-trap
LC	liquid chromatograph
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantitation
LLE	liquid-liquid extraction
MAC	maximum acceptable concentration
MDL	method detection limit
MGD	mammary gland development
MG/D	million gallons per day
MOA	mode of action
MRL	minimum reporting level
MS/MS	tandem mass spectrometry
NF	nanofiltration
NHANES	National Health and Nutrition Excamination Survey (U.S.)
NOAEL	no-observed-adverse-effect level
NOM	natural organic matter
PAC	powdered activated carbon
PBPK	Physiologically-based pharmacokinetic
PEFT	polytetrafluoroethylene
PFA	perfluoroalkyl

PFAA	perfluorinated alkyl acid
PFAS	perfluoroalkyl substance
PFCA	long-chain perfluorocarboxylic acids
PFDA	perfluorodecanoic acid
PFHxS	perfluorohexanesulfonate
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctane sulfonate
PND	postnatal day
POD	point of departure
POD_{HEQ}	human-equivalent points-of-departure
PTFE	polytetrafluoroethylene
RBF	river bank filtration
RO	reverse osmosis
SPE	solid phase extraction
TDI	tolerable daily intake
TDS	total diet study
UCMR3	third Unregulated Contaminant Monitoring Rule (U.S.)
WAX	weak anion exchange