Health Canada Santé Canada

Memorandum: Human Health Soil Screening Values (SSVs) for Perfluorooctanoic acid (PFOA)

Date: April 2016

Currently there are no Canadian Guidelines for PFOA in soil. In the absence of a soil quality guideline, Health Canada has developed soil screening values (SSVs) for PFOA, which can be used to determine whether the concentrations detected are likely to be of concern to human health. Screening values are developed at the request of a federal department in the event of spill, leak or other contamination event, and are based on the available scientific studies. They are not subject to a review as thorough as the CCME Soil Quality Guidelines, which undergo internal peer review and public consultation before being approved by the CCME. Soil screening values are provided as guidance, and apply to soil which humans may be exposed. Health Canada continues to monitor new research in this area.

Although the approach used for developing soil screening values is generally consistent with the CCME protocol for development of soil quality guidelines for direct contact with soil (CCME 2006) these soil screening values should not be considered as draft CCME guidelines.

The advice herein, is intended for use at federal sites, and has been provided to meet the needs of federal custodians at this time. It is not intended for use in any other context. The advice herein may change as more information becomes available regarding the toxicity of PFOA and as environmental quality guidelines are developed. Any decisions taken based on the advice provided herein are the responsibility of Federal Custodians making those decisions.

Soil screening values for residential, commercial and industrial land uses are presented. The custodian should determine the most appropriate value for application at a site based on site use. Further information on the land use scenarios and default assumptions can be found in CCME (2006).

SSVs and supporting guidance may change without notice. Please check for published values and confirm these values are appropriate for use prior to use.

Table 1: Soil Screening Value for PFOA

Land Use	Residential/Parkland	Commercial	Industrial/Commercial without Toddler
Soil Screening Value (mg/kg)	0.85[a]	1.28[a]	12.1[b]

[a]: Based on direct contact with soil;
[b]: Based on off-site migration.

Notes:

- The SSV for the protection of potable groundwater could not be calculated due to insufficient data. Concerns about PFOA in groundwater used as drinking water should be addressed on a site specific basis.
- The SSV check value for consumption of produce, meat and milk could not be calculated due to insufficient data. Concerns regarding consumption of foods and PFOA should be addressed on a site specific basis.
- Since PFOA is essentially non-volatile, the inhalation of indoor air check was not calculated.

Canada

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1.0 INTRODUCTION

Perfluorooctanoic acid (PFOA) is an anthropogenic chemical that is present in the environment through a range of broad applications including but not limited to its use in manufacturing processes and consumer products. The Government of Canada concluded that PFOA, its salts, and precursors are or may be entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity based on risk assessment activities conducted under the Canadian Environmental Protection Act, 1999 (CEPA 1999),. PFOA, its salts, and precursors were added to Schedule 1 of CEPA 1999, the List of Toxic Substances.

Historically, PFOA and other perfluoroalkyl substances (PFAS) were used in aqueous film forming foams (AFFFs) which were typically used during fire-fighting training activities carried out at fire-fighting training areas (FFTAs) at some airports and military bases across the country. As a result, PFOA and other PFA concentrations may be elevated in the environment at historic FFTAs where AFFFs were used.

The purpose of this document is to provide custodians with health-based soil screening values (SSVs) to be used to screen for contaminants of potential concern (COPCs) at federal contaminated sites. Currently, there are no approved Canadian environmental quality guidelines for the protection of human health for PFOA and the availability of PFOA guidelines and standards from other jurisdictions is limited. For example, the United States Environmental Protection Agency (US EPA) Region 4 developed a human health based soil screening level for specific regional application, and the Minnesota Department of Health developed a provisional drinking water guideline to address groundwater quality issues in industrial areas of the state. The current document summarizes the derivation of proposed toxicological reference values (TRVs) based on the available toxicological data and calculates SSVs based on these TRVs.

Health Canada is in the process of developing Soil Quality Guidelines through the Canadian Council of Ministers of the Environment (CCME) and Guidelines for Canadian Drinking Water Quality. To meet immediate needs, human health-based values for drinking water (including groundwater when used as a drinking water) and for soil quality have been prepared by Health Canada to assist federal custodians in the assessment of PFOA in these media at federal contaminated sites. These values are based on a limited review of available information and have not been formally vetted or peer reviewed. The resultant uncertainty and limitations associated with the use of these values are discussed herein.

The current document summarises the following:

- background information;
- environmental fate and behaviour;
- behaviour and effects in human and mammalian species;
- derivation of TRVs; and
- derivation of human health SSVs.

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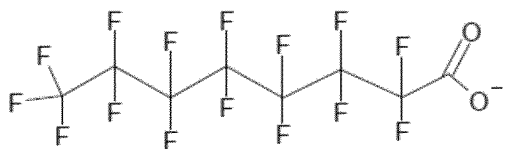
2.0 METHODOLOGY

The calculation of the SSVs and the preparation of the supporting documentation were completed following the methods described by the CCME's A Protocol for the Derivation of Environmental and Human Health Soil Quality Guidelines (CCME 2006). Health Canada provided additional background documents, including Sanexen Environmental Services Inc. (Sanexen 2015) for the derivation of the SSVs.

3.0 BACKGROUND INFORMATION

3.1 Chemical Structure and Identity

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 (PFCA), one of a broader class of chemicals known as perfluoroalkyl substances (PFAS), which belong to the even larger class of perfluorinated alkyl acids (PFAA) (Environment Canada and Health Canada, 2012). In this report, the term "PFOA" may refer to the free acid ($C_8HF_{15}O_2$; CAS number 335-67-1; 414.07 g/mol) or its conjugate base ($C_8F_{15}O_2^-$; CAS number 45285-51-6). The term APFO (ammonium perfluorooctanoate) refers to the ammonium salt ($C_8F_{15}O_2^-$ $NH4^+$; 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. The chemical structure of PFOA is illustrated below.



3.2 Physical and Chemical Properties

The information below is reproduced from Health Canada 2016.

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 (Kow) cannot be determined directly (because multiple layers are formed in octanol/water) and the parameters usually estimated from the Kow (e.g., Koc, bioconcentration factor) cannot be calculated using this method (ATSDR 2009; Environment Canada and Health Canada 2012). The values of Log Kow 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). The Henry's law constant for PFOA was estimated at 2.4×10^{-5} atm-m^3/mol (Barton et al. 2007).

The abbreviation of PFOA may refer to the free acid ($C_8HF_{15}O_2$), its conjugate base ($C_8F_{15}O_2$) or its salts. The PFOA salts used industrially are ammonium, sodium, potassium and silver salts (Opheim 2007). The three main forms of PFOA in the environment are the acid (PFOA), the dissociated perfluorooctanoate anion (PFO^-) and the ammonium salt (APFO). 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).

3.3 Geochemical Occurrence

PFOA is chemically synthesized and does not occur naturally.

3.4 Analytical Methods

The information below is reproduced from Sanexen 2015.

Most studies use a solid phase extraction (SPE) technique followed by high-performance liquid chromatography mass spectrometry (HPLC-MS/MS) or LC triple quadrupole mass spectrometry (LC-MS/MS) to detect PFAA (ATSDR 2009; Lindstrom et al. 2011).

Weremiuk et al. (2006) indicate that gas chromatography-mass spectrometry (GC MS) following derivation of the chemical and liquid chromatography coupled with electrospray ionization (ESI) tandem mass spectrometry (LC-ESI-MS/MS) is sufficient for the environmental monitoring of PFOA. Some authors have reported refined methods for detecting PFOA in environmental media. For example, Wilson et al. (2007) found that a system based on on-line solid phase extraction (SPE) and nano-LC combined with nanospray MS is sensitive enough to monitor PFOA at low parts per trillion (ppt) ranges (LOD of 500 pg/L). Zhao et al. (2007) found that combining mixed hemimicelles cetyltrimethylammonium bromide (CTAB)-coated silica SPE and LC-ESI-MS/MS was a valuable tool for analyzing trace levels of PFAS including PFOA in environmental water samples.

Sampling for PFAS should follow recent guidance to ensure that samples are representative.

The information below is reproduced from Health Canada 2016.

In spite of the significant improvements in the analytical methods for the determination of PFAS in environmental water samples, challenges, uncertainties and drawbacks still remain. Major challenges associated with the trace quantitation of (PFAS) include matrix effects and a background contamination in the analytical blanks. In order to generate accurate data, quality control (QC) procedures (matrix spikes, duplicates, spike-recovery experiments, surrogate recovery checks) are critical. In addition, the use of isotope-labelled internal standards is a standard practice and must be used in the analysis of PFAS.

3.5 Production, Use and Discharge to the Environment

The information below is reproduced from Health Canada 2016.

The main producers of PFOA are located principally in the United States, Europe and Asia. Industrial information obtained in 2004 indicates no known manufacturers of perfluoroalkyl and fluoroalkyl substances in Canada; however, APFO was imported into Canada in quantities ranging between 100 and 100,000 kg (Environment Canada and Health Canada 2012). APFO is mainly used as a commercial polymerization aid for fluoropolymer manufacturing. Fluoropolymers are used in the manufacture of stain/water-resistant coatings for textiles and

carpets, hoses, cable and gaskets, non-stick coatings on cookware and personal care products. APFO is also used in aqueous fluoropolymer dispersions that are used in paints and in photographic film additives as well as within the aerospace industry (e.g., it may be a component of aqueous film-forming foams [AFFFs] for firefighting; Environment Canada and Health Canada 2012;). Fluorochemicals (potential PFOA precursors) are also used in the treatment of food packaging materials (Environment Canada and Health Canada 2012) such as microwaveable popcorn bags (Dolman and Pelzing 2011). The term PFOA is not interchangeable with commercial mixtures containing PFOA, as these mixtures are often not well characterized and could include any product that contains even a small amount of PFOA (Environment Canada and Health Canada 2012).

3.6 Sources and Concentrations in Environmental Media

The information below is reproduced from Health Canada 2016.

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).

The estimated total daily intake of PFAA (estimates not provided for individual PFAA) in Canadians was reported to be 410 ng/day for the general population of Canada (Tittlemier et al. 2007). A summary of concentrations in different media are presented in sections below.

3.6.1 Water

The information below is reproduced from Health Canada 2016.

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) 0.51 ng/L)) in raw or finished water from samples obtained in 2012 from two water treatment plants in Calgary (Alberta Environment and Water 2013). In Quebec, raw and treated water samples were obtained monthly between April 2007 and March 2008 from seven sites (a total of 84 raw and treated water samples each). PFOA was detected in 75% of treated samples (MDL of 0.3–0.6 ng/L), with a median value of 2.5 ng/L. The detection rate and median concentrations were higher in treated water than in raw water, for which the detection rate and median were 55% and 2.0 ng/L, respectively (Ministère du Développement durable, de l'Environnement, de la Faune et des Parcs 2012). The reported PFOA concentration in 5 tap water samples from Niagara-on-the-Lake, Ontario was 2.1 ng/L (Mak et al. 2009). Lower concentrations of PFOA (0.2 ng/L) were reported in tap water from Calgary and Vancouver (Tanaka et al. 2006).

For a national survey of emerging contaminants in drinking water (including PFOA) performed by Health Canada, treated and raw water was monitored in winter and summer at 35 locations in 2009 and 30 locations in 2010. PFOA was detected (MDL of 0.023 ng/L) in 68% of raw water samples and 64% of treated water samples in summer 2009, with averages of 0.067 ng/L and 0.071 ng/L, respectively. PFOA concentrations were slightly lower in winter 2009, with an average of 0.057 ng/L in detected raw samples (59% detection) and 0.056 ng/L in detected treated samples (55% detection). Detection rates for PFOA were lower in the 2010 locations, with detection rates in the summer of 18% in raw water (average of 0.066 ng/L) and 15% in treated water (average of 0.046 ng/L), and in winter of 33% in raw water (average of 0.055 ng/L) and 27% in treated water (average of 0.05 ng/L) (Health Canada 2013a).

3.6.2 Food

The information below is reproduced from Health Canada 2016.

Food is generally considered to be the main source of PFOA exposure for the majority of the Canadian population, but exposure from food is still well below what is considered unsafe to humans. PFOA was measured in a selection of Canadian food composite samples (samples from the Canadian Total Diet Study 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 PFAA. 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. 2009).

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

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 fa 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).

3.6.3 Air

The information below is reproduced from Health Canada 2016.

The inhalation intake of PFOA for Canadians was considered negligible due to its low volatility (Tittlemier et al. 2007). The levels of PFAA in outdoor air were determined in a Canadian study conducted in 2007 in Vancouver (Shoeib et al. 2011). PFOA samples were collected using outdoor passive samplers deployed in residential yards for approximately 3 months. PFOA was detected in 4 out of 6 samples (<0.47–9.2 pg/m^3; mean: 1.4 pg/m^3) (Shoeib et al. 2011). Similar concentrations were measured in the Canadian Arctic (Resolute Bay, Cornwallis Island, Nunavut) in 2004, with a mean concentration (gas and particulate phase of atmospheric air) of 1.4 pg/m^3 (Stock et al. 2007). In indoor air, the levels of PFOA primarily depend on its concentration in air particulates and are thus related to the levels in indoor dust, as well as the number, type and age of the potential

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

3.6.4 Consumer Products

The information below is reproduced from Health Canada 2016.

Human exposure to PFOA would likely result from contact with, or the use of, certain consumer products based on use patterns (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 PFAA measured during professional ski waxing (Freberg et al. 2010).

3.6.5 Soil and Household Dusts

The information below is reproduced from Health Canada 2016.

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 PFAA in dust—older houses and those with smaller fractions of the floor covered with carpet were characterized by lower concentrations of PFAA (Kubwabo et al. 2005).

In another Canadian study conducted in the Vancouver, British Columbia, PFOA was detected in all house dust samples analyzed for this compound (n = 132). The PFOA concentrations ranged from 1.9 to 1,390 ng/g (median: 30 ng/g, mean: 97 ng/g) (Shoeib et al. 2011).

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

3.6.6 Human Biomonitoring Data

The information below is reproduced from Health Canada 2016.

Human PFOA blood levels have been shown to be influenced by gender and age. The Canadian Health Measures Survey, Cycle 1 (2007–2009) indicates that PFOA plasma levels in adult males (geometric mean [GM]: 2.94 ng/mL; 95% CI: 2.74–3.15, 95th percentile: 5.98 ng/mL, n=1376) are higher than in adult females

(GM: 2.17 ng/mL; 95% CI: 1.99–2.36, 95th percentile: 4.99 ng/ml, n=1504) (Health Canada 2010; as cited in Health Canada 2016). This effect persisted in Cycle 2 of the study (2009–2011) (Males—GM: 2.6 ng/mL, 95% CI: 2.4–2.9, 95th percentile: 6.0, n=511; Females—GM: 2.0 ng/mL, 95% CI: 1.8–2.2, 95th percentile: 4.4 ng/mL, n=506) (Health Canada 2013b).

3.7 Summary of Existing Guidelines, Guidance Values or Screening Values

Soil and water quality guidelines and criteria established for PFOA in various jurisdictions are presented in the following table.

Table 2: Existing Soil and Water Criteria and Guidelines for PFOA in Canadian and Other Jurisdictions

Jurisdiction	Criterion/Guideline	Concentration	Reference
Soil			
United States, U.S. EPA Region 4	Residential Soil Screening Level (SSL)	16 mg/kg	U.S. EPA Region 4 2009
Water			
Canada	Guideline for Canadian Drinking Water Quality - In progress	0.2 µg/L	Health Canada 2016
United States, U.S.EPA Region 4	Health Advisory (PHA) for drinking water	0.4 µg/L	U.S. EPA Region 4 2009
United States, MN	Groundwater Health Risk Limit	0.3 µg/L	MDH 2011
United States, NJ	Drinking Water Guidance Value	0.04 µg/L	State of New Jersey undated
United States, NC	Interim Maximum Allowable Concentration (IMAC) in Groundwater. North Carolina Secretary's Science Advisory Board (NCSAB) on Toxic Air Pollutant recommended reducing the IMAC to 1 µg/L based on toxicological review. Recommendation pending (NCSAB 2010).	2 µg/L	NCDENR 2006
United States, ME	Maximum Exposure Guideline (MEG) in Drinking Water	0.1 µg/L	Maine Center for Disease Control and Prevention 2014
Germany	Health-based Precautionary Value (HPV_1) – Composite PFOA/PFOS concentration	0.1 µg/L	Drinking Water Commission 2006

Source: Sanexen 2015

4.0 ENVIRONMENTAL FATE AND BEHAVIOUR

The information below is reproduced from Health Canada 2016.

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 as cited in Health Canada 2016). The first pathway involves the atmospheric transport of volatile precursors (e.g., fluorotelomer alcohol) and their oxidation to PFOA (and other PFAA) 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 Log Koc 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 Log Koc 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 ≥ 182 days in soil and water, ≥ 365 days in sediment and ≥ 2 days in air) (Environment Canada and Health Canada 2012).

The occurrence of PFOA in soils not impacted with a local source results from wet and dry atmospheric depositions. These atmospheric processes are heterogeneous (local inputs, precipitation patterns, and seasonal factors) and can potentially lead to regional variability. Large-scale regional differences were reported in a US study where measureable PFOA concentrations were found in most of the soils sampled while PFOA concentrations were lower or not measurable in soils sampled in other countries (e.g., Mexico, Norway) (Strynar et al. 2012). Considering the amount of PFOA produced and the estimated amount of PFOA present in soil, the authors estimated that soil is likely an important global sink for PFOA (Strynar et al. 2012).

Although measures are in place in North America to reduce the emissions and production of PFAS such as PFOA, the use of PFAS still causes their transfer to biosolids (i.e., municipal waste water sludge). Using biosolids as fertilizers may thus represent a source of soil and water contamination (Clarke and Smith 2011).

5.0 HEALTH EFFECTS

The information in this section, including subsections 5.1 to 5.5, is reproduced from Health Canada 2016.

The summary of literature on health effects for PFOA is based on a comprehensive review conducted by a consultant (Sanexen Environmental Services Inc. 2013), and includes only the studies of direct relevance to the derivation of the SSV.

5.1 Effects in Humans

5.1.1 Acute Toxicity

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

5.1.2 Subchronic and Chronic Toxicity

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

Most environmental studies among PFAA-exposed populations were conducted in the Mid-Ohio Valley within the C8 Science Project. The C8 Science Panel was convened as a result of a class action settlement against DuPont, and is composed of independent epidemiologists jointly selected by lawyers for the community and DuPont. The C8 Health Project is the largest study of a population exposed to PFAA 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).

5.1.2.1 Liver Effects

Some level of association between PFOA exposure and alteration in liver enzymes has been observed, but no clear trend has been defined. A negative association for bilirubin and a positive association for aspartate transaminase (AST) and gamma glutamyl transpeptidase (GGT) have been reported in workers (Sakr et al. 2007a; Sakr et al. 2007b). Abnormal increases of liver enzymes (ALT and GGT) were reported in a cross-sectional study of adults aged 18 years or older in the general U.S. population, particularly in obese or in subjects with insulin resistance and/or metabolic syndromes (Lin et al. 2010). The clinical significance of results in the occupationally-exposed population is unclear, because the magnitudes of the changes were small and inconsistent (Steenland et al. 2010a). Moreover, the high number of endpoints analyzed also increases the likelihood of chance findings. Causal interpretation of general population results is limited by the study design, and multiple covariates were not included in the analysis.

5.1.2.2 Immune Suppression

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

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

There is some level of consistency across studies since they generally observed an association between environmental PFAA 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, PFAA, 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.

5.1.2.3 Lipidemia

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

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

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

5.1.2.4 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).

5.1.2.5 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.

5.1.2.6 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).

5.1.2.7 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.

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5.1.2.8 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.

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

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

the trends reported for testicular cancers were based on 6 cases only in the high exposure group (C8 Science Panel 2012b; Barry et al. 2013).

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

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

The C8 Science Panel (2012b) provides an assessment of the probable link between PFOA exposure and cancer. The “probable link” defined by the Science Panel means that “given the available scientific evidence, it is more likely than not that among class members a connection exists between PFOA exposure and a particular human disease.” Testicular and kidney cancers were the particular types of cancer on which the association was based. However, a causal relationship cannot be determined because there were inconsistencies in the dataset, and the cancer risks were found to be equivocal across studies (lack of coherence). Moreover, the interpretation of the observed increased risk in testicular and kidney cancers is limited by the risk of residual confounding (because not all covariates and exposures to other contaminants were included in the model), the small case numbers, the uncertainties in exposure characterization (roughly estimated based on residency within a certain area), and the high number of outcomes included in the models, increasing the likelihood of chance findings. Based on these considerations, it would be premature to base a guideline on a cancer risk in epidemiology studies, without a stronger understanding of the potential causality between PFOA and the observed cancers. It is suggested to continue monitoring the epidemiological evidence to understand better the relationship between PFOA and cancer risk.

5.1.4 Developmental and Reproductive Toxicity

5.1.4.1 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 PFAA were investigated in a prospective cohort study with long-term follow-up (20 years) among pregnant women recruited within the Danish National Birth Cohort (1988–1989) and their offspring (Halldorsson et al. 2012). At 20 years of age, the female offspring from mothers with elevated serum concentration of PFOA were more likely to be overweight and to have a high waist circumference, after adjusting for mother's education, BMI, smoking, age, and infant birth weight. This large longitudinal study also showed alteration in serum biomarkers with an increase in maternal PFOA (increase in serum insulin and leptin and decrease in serum adiponectin in female offspring), suggesting biological plausibility. However, important confounders, such as physical activity and diet, were not included in the analysis, which is likely to result in spurious associations. The authors also indicated that loss to follow-up was the main limitation of the study. More studies with better adjustments and follow-up in different populations would be needed to confirm the observed associations.

The data currently available regarding an association between PFOA and reduced birth weight are not consistent. Positive associations were reported among the general population in some studies, whereas no association was reported in other studies in the general population and in communities highly exposed to PFOA through drinking water. Longitudinal studies conducted in Danish and British general populations have found inverse associations between plasma PFOA levels and birth weight (Fei et al. 2007; Andersen et al. 2010; Maisonet et al. 2012). A small unpublished study based on birth certificates for C8 Health Project Community Cohort follow-up participants found some level of association between serum PFOA and term low birth weight; however, results were inconsistent and significance was not provided for all results. These studies represent concerning findings; however, the validity of the results still need to be confirmed, because these studies presented risk of selection bias, recall bias, chance findings, uncontrolled covariates, and absence of dose–response pattern. Moreover, no significant association between serum PFOA levels or PFOA water concentrations and low birth weight was found in cross-sectional studies or highly exposed communities (Nolan et al. 2009; Stein et al. 2009; Savitz et al. 2012a; 2012b). The C8 Science panel concluded that there is no probable link between PFOA and low birth weight (C8 Science Panel 2011). However, considering that PFOA was found to be obesogen in mice (Hines et al. 2009) and humans (Halldorsson et al. 2012), and that *in utero* exposure to low doses of obesogens are known to reduce weight at birth (and induce obesity later in life; Holtcamp 2012), a link between PFOA and low birth weight cannot be ruled out and close monitoring of new studies is recommended.

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

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

5.1.4.2 Puberty and Sex Hormone Disruption

Serum PFOA levels were associated with delayed puberty in girls (reduced odds for the 2nd, 3rd, and 4th quartiles vs. the lowest quartile: delay of 142, 163 and 130 days for menarche and delay of 155, 158 or 183 days for combined high estradiol or menarche) in a cross-sectional study within the C8 Health Project (Lopez-Espinosa et al. 2011). Further investigations are needed to establish the nature of the relationship, and identify the mechanisms behind these associations. No association was found between PFOA and serum estradiol levels in perimenopausal or menopausal age groups of women (n = 25,957) from the C8 Health Project (Knox et al. 2011a).

5.1.4.3 Reproductive Toxicity

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

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

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

A prospective cohort study recruited 1,400 pregnant women (randomly out of 43,045) within the Danish National Birth Cohort (DNBC, 1988–1989) and measured PFOA concentration in their plasma (Fei et al. 2010b). Duration of breastfeeding was reported 6 and 18 months after birth by phone interviews. The risk of breastfeeding for a

shorter period was higher with increasing plasma PFOA. For example, the risk (adjusted hazard ratio) of shorter breastfeeding duration (weeks) for women with plasma PFOA > 7.0 ng/mL was 1.4 (95% CI 1.2–1.7) times higher than for those with plasma PFOA < 3.9 ng/mL, after adjusting for maternal age at delivery, pre-pregnancy BMI, maternal socioeconomic status, alcohol consumption and smoking (the trend for an increase in risk with increasing four-quartile comparison was also significant). Also, the odds (adjusted odds ratio) of weaning before 6 months of age was 1.23 (95% CI: 1.1–1.3) times higher for each 1 ng/mL increase in plasma PFOA when restricting the model to multiparous women (not significant in primiparous women), after statistical adjustments. A similar association was observed with weaning before 3 months of age. However, more studies would be needed to support these results, since PFOA plasma concentration was measured only one time, only 18% of eligible women participated in the DNBC study, there is a risk of outcome recall bias (mothers might not report accurately the date of weaning), and the authors did not rule out the possibility that reverse causation could explain the association (especially since not observed in primiparous women, and considering that women that have breastfed longer can be more likely to breastfed longer their next infants, and that PFOA is excreted in breast-milk, lowering the plasma concentration).

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

5.2 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.

5.2.1 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; as cited in Health Canada 2016), 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 LD_{50} 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 5.2.5.5.

5.2.2 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 5.2.5), hepatic effects, and serum lipid effects. Delayed mammary gland development appears to be the most sensitive target, with a LOAEL of 0.001 mg/kg bw per day (serum PFOA: 74.8 ng/mL; no NOAEL) in mice (see Section 5.2.5.1). 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.

5.2.2.1 Hepatic Effects

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

The lowest LOAEL for liver weight was in pups exposed *in utero* to 0.1 mg/kg bw per day on GD 1–17; further details on this study are provided in Section 5.2.5.4. 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; as cited in Health Canada 2016). The latter study contained a high-dose (i.e., 30 mg/kg bw per day) recovery group (with exposure cessation at test days 23 in rats and 24 in mice), with liver weight increases still present at termination of the study in both species.

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

A wide variety of short-term studies observed increases in liver weight in adult animals at higher doses. These effects were observed in rats (Metrick and Marias 1977; Goldenthal et al. 1978a; Staples et al. 1984; Kennedy et al. 1986; Biegel et al. 2001; Perkins et al. 2004; Cui et al. 2009) and in mice (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). 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 5.2.5.4.

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

The most robust study with an observed NOAEL for increased liver weight and hepatocellular hypertrophy exposed male Crl:CD rats (n=55 per dose) to 0, 0.06, 0.64, 1.94, and 6.5 mg/kg bw per day in food (Perkins et al. 2004). Two control groups were included in the study—one set of controls pair-fed with the high dose group, and one *ad libitum* feeding group. The rats were divided into sacrifice groups exposed for a duration of 4, 7, or 13 weeks (n=15 per dose per duration), and each dose (and the *ad libitum* controls) had a recovery group that was observed for 8 additional weeks after cessation of exposure at week 13 (n=10 per dose). Dose-related increases in incidence and severity of hypertrophy were observed (Table 2). Most rats exposed to ≥0.64 mg/kg bw per day had minimal-to-slight hypertrophy, which was most severe in the high-dose group exposed for 13 weeks; effects did not persist in recovery groups. Hypertrophy was not accompanied by degenerative lesions in the liver. Relative liver weight was increased at ≥0.64 mg/kg bw per day in the 4-week group and at ≥1.94 mg/kg bw per day at the longer durations; the effect did not persist in the recovery groups.

Table 3: Incidence and Severity of Hepatocellular Hypotrophy 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 5.2.3.

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).

5.2.2.2 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 5.2.2.1. The lowest LOAELs were in rats, with values of 0.3 mg/kg bw per day for decreases in cholesterol and triglycerides (Loveless et al. 2006; 2008) and 0.3 mg/kg bw per day for decreases in HDL (Loveless et al. 2008; in 2006 the LOAEL was only 3 mg/kg bw per day). Most of the effects were only observed at higher levels in mice—in Loveless et al. (2008), the LOAELs were 1 mg/kg bw per day for decreased HDL and 10 mg/kg bw per day for decreased total cholesterol and triglycerides, and most of the LOAELs in Loveless et al. (2006) were 3 mg/kg bw per day. An exception was for triglyceride increases specifically in the linear/branched APFO-exposed mice, as effects were observed at ≥0.3 mg/kg bw per day.

The effects on cholesterol and HDL did not appear to be persistent upon cessation of exposure, because total cholesterol and HDL levels returned similar to control levels when exposure was ceased at days 23 (rat) or 24 (mouse) in the 29-day study (Loveless et al. 2008). Triglyceride levels in both species continued to be lower than controls after the recovery period, but in mice the levels had increased enough to be significantly higher than the 29-day high dose group.

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

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

5.2.2.3 Other Effects

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

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

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

Indications of immunosuppression occurred at ≥3.75 mg/kg bw per day in mice. These included decreased immunoglobulin levels, changes in cellularity and subtypes of immune cells, and changes in cytokine expression (Yang et al. 2001, 2002; DeWitt et al. 2008; Loveless et al. 2008; Son et al. 2008; Qazi et al. 2009, 2010). Splenic and thymic atrophy were also observed in mice (Yang et al. 2001; 2002; Loveless et al. 2008; Qazi et al. 2009), and histological changes were observed in these organs in rats (Cui et al. 2009; Qazi et al. 2009). Studies in mice also indicated a possibility for hypersensitivity due to exposures to PFOA, with a dose-related increase of serum histamine levels at ≥1 mg/kg bw per day (Singh et al. 2012) and increased IgE after challenge with OVA in mice exposed dermally to ≥18.75 mg/kg bw per day (Fairley et al. 2007).

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

The only study indicating changes in thyroid hormone levels reported decreased free and total T3 and T4 in monkeys exposed for 6 months (Butenhoff et al. 2002;). Decreases in total and free T4 were observed at most timepoints, including termination, for monkeys exposed to 10 or 20–30 mg/kg bw per day; at termination (and not earlier timepoints), a significant decrease was also observed for total (but not free) T4 at the 3 mg/kg bw per day dose. Decreased total and free T3 was observed at most timepoints (including termination) in monkeys exposed to 20–30 mg/kg bw per day; decrease in total (not free) T3 was also observed at two mid-study timepoints, but not at termination, in low-dose monkeys. The effects were accompanied by significant increases in TSH at study termination in monkeys exposed to 3 or 10 mg/kg bw per day (no effect at high dose). The 4-week range-finding study for the Butenhoff monkey study (Thomford, 2001b) did not note any effects on TSH, or in total or free T3 or T4.

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

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

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

5.2.3 Long-Term Exposure and Carcinogenicity

Two chronic toxicity studies in laboratory animals were identified for the oral route. No inhalation or dermal study was located. As was observed in long-term carcinogenicity studies, the liver was the most sensitive target organ in the chronic studies (LOAEL = 1.3 mg/kg bw per day in male rats for increased serum liver parameters) (3M, 1983; Sibinski, 1987; Butenhoff et al. 2012b). Other effects observed in rats after chronic exposure to PFOA include an increased incidence of hyperplasia and tumors in various tissues (mammary gland in females, Leydig cells, pancreas and liver in males) and alteration of serum hormone levels (3M, 1983; Sibinski, 1987; Biegel et al. 2001).

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

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

Although the LOAEL for liver endpoints was higher in chronic studies than in shorter-term studies, the comparisons are difficult to make, as the lowest dose used in the chronic study (1.3 mg/kg bw per day) is higher than the lowest LOAELs for liver effects in the shorter-term studies (i.e., 0.1–0.3 mg/kg bw per day). However,

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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).

5.2.4 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).

5.2.4.1 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 (AL) cells and mitochondria-dependent ROS was shown to play an important role in this process (Zhao et al. 2011b).

5.2.4.2 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).

5.2.5 Reproductive and Developmental

The reproductive and developmental database for PFOA is robust. Two 2-generational studies have been developed in rats (Butenhoff et al. 2004b/York et al. 2010; White et al. 2011), and reproductive and developmental parameters have been investigated in many one-generation studies in rats, mice, and monkeys. Furthermore, early life or peripubertal exposures were performed in mice (Johansson et al. 2008, 2009; Yang et al. 2009b; Zhao et al. 2010; Dixon et al. 2012).

The most sensitive effects identified are delayed mammary gland development in the offspring of mice (Macon et al. 2011; White et al. 2011), obesity in the female offspring of mice at adulthood (Hines et al. 2009; as cited in Health Canada 2016), 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.

5.2.5.1 *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. 2009b; 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; as cited in Health Canada 2016) 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

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).

gland in the treated P0 was similar to the structure normally observed at the lactation peak at PND 10). The authors only provided information on the amount of daily ingestion of PFOA in P0 dams consuming 5 µg/L drinking water (approximately 0.05 µg per day during gestation and 0.1 µg per day during lactation [PND 1–22]). Average daily doses are estimated to be approximately 0.001 mg/kg bw per day during gestation and 0.004 mg/kg bw per day during lactation (based on mean approximate weights of 62 g during gestation and 25 g during lactation; the average maternal weight gain during gestation was 25 g, and the initial body weight of dams was not reported by the authors but is assumed to be approximately 25 g for this strain of mice). The maternal LOAEL was therefore considered to be 0.001 mg/kg bw per day.

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

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

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

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

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

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

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

Tucker et al. (2015) also investigated other sexual maturity effects. No treatment-related effects on estradiol or progesterone levels, nor on timing of vaginal opening or first estrus, were observed in either strain.

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

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

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

Other effects related to sexual maturity were accelerated puberty (≥1 mg/ kg bw per day in male mice & 20 mg/kg bw per day in female 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).

5.2.5.2 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.

5.2.5.3 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 5.2.2.1), suggesting the timing of dosing was critical for latent effects (Hines et al. 2009).

5.2.5.4 Developmental Hepatic Effects

As described in Section 5.2.2.1, 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/SvlmJ mice (n=5–22 dams/dose) were exposed by gavage to 0, 0.1, 0.3, 0.6, 1, 3, 5, 10, and 20 mg/kg bw per day on GD 1–17. Increased relative liver weight in pups was observed in all doses, and was worsened at higher doses.

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

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

A LOAEL of 0.58 mg/kg for neurodevelopmental effects was identified in NMRI male mice administered a single gavage dose of PFOA (0.58 or 8.70 mg/kg) at the age of 10 days (Johansson et al. 2008). Mice were tested for spontaneous behavior and habituation at the age of 2 and 4 months, and the susceptibility of their cholinergic system was explored in a nicotine-induced spontaneous behaviour test at the age of 4 month (Johansson et al. 2008). Data indicate time-dependent and dose-related effects on the behaviour (deranged spontaneous behaviour, lack of habituation and increased susceptibility of the cholinergic system) reflecting the advance of a brain dysfunction process induced at the time of brain growth spurt in the neonatal mouse. At both doses, the exposed mice exhibited an altered spontaneous behaviour and a hypoactive response to nicotine. Any of the three variables of the behavioural test (locomotion, rearing and total activity) were altered, indicating hypoactivity during the first 20 minutes and hyperactivity in the last 20 min period (40–60 min after start of the test), and the effects worsened with age. These effects were supported by significantly increased levels of proteins that are important for normal brain development (CaMKII, GAP-43, and synaptophysin in the hippocampus, synaptophysin and tau in the cerebral cortex, and tau in the hippocampus) in mice under the same neonatal exposure conditions (Johansson et al. 2009).

5.2.5.6 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 males and 30 mg/kg bw per day in females) and increased post-weaning mortality (in females only, at 30 mg/kg bw per day), with no effects on the F2 generation (Butenhoff et al. 2004b; York, 2002).

5.3 Toxicokinetics

5.3.1 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 . Limited inhalation or dermal studies have reported PFOA kinetics.

5.3.2 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).

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

Few data have been gathered on the human tissues to which PFOA is typically distributed. PFOA was detected in approximately one half of the analyzed liver samples (in 6 males and 6 females from Catalonia, Spain; aged 27–79 years), and was significantly higher in males than in females (Kärrman et al. 2010), but was below the

limits of quantification in livers in cadavers with environmental exposure (Olsen et al. 2003a). Neither cerebrospinal fluid (Harada et al. 2007) nor thyroid (Pirali et al. 2009) have been observed to be relevant partitioning sites for PFOA.

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

PFOA exposure can occur transplacentally and lactationally. Fetal transfer via the placenta has been demonstrated in rats (Hinderliter et al. 2005) and mice (Fenton et al. 2009). In humans, concentrations of PFOA in cord blood of newborns are similar to maternal blood concentrations (Tittlemier et al. 2004; Midasch et al. 2007; Monroy et al. 2008; Beesoon et al. 2011; Needham et al. 2011; Gützkow et al. 2012). Moreover, serum concentrations in young children have been noted to be higher than serum concentrations in their mothers in a reference (i.e., not PFOA-contaminated) area (Hölzer et al. 2008) and in an area with elevated environmental PFOA levels (Mondal et al. 2012); however, serum concentrations were similar between children and mothers in an area with elevated PFOA levels in drinking water (Hölzer et al. 2008). Lactational transfer of PFOA has been measured in various mammal species, including humans, rats, mice, and sheep (Hinderliter et al. 2005; Fenton et al. 2009; Kim et al. 2011; Needham et al. 2011). Concentrations of PFOA in milk are consistently lower than in maternal plasma (Hinderliter et al. 2005; Fenton et al. 2009); in humans, a review of milk and maternal serum concentrations found the maternal milk:serum ratios across several studies to be approximately 0.11–0.12 (Liu et al. 2011;). PFOA levels in human milk decrease significantly throughout the lactation period (Thomsen et al. 2010), and with increasing number of infants breastfed (Tao et al. 2008; Kadar et al. 2011).

5.3.3 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).

5.3.4 Excretion

Remarkable species-dependent differences in elimination half-life have been observed, with PFOA remaining in human bodies for a much longer duration than other species, including non-human primates, rats and mice (Post et al. 2012). Elimination half-lives from serum in humans is significantly longer than in non-human primates and

rats. Species- and sex-related differences are primarily attributed to elimination kinetics where, at higher doses, the kinetics of PFOA in rodents and primates do not follow one-compartment or simple first-order models (Andersen et al. 2006). Half-life values for serum elimination of PFOA in humans were derived from data obtained in retired workers (arithmetic mean = 3.8 years; range = 1.5–9.1 years; 95% CI = 3.1–4.4 years; Olsen et al. 2007). In populations exposed environmentally through the consumption of PFOA-contaminated drinking water, half-life values could be estimated using measured declines in serum or plasma PFOA levels after exposures ceased due to filtration of drinking water. The geometric average half-life in Germany was reported as 3.26 years (range = 1.03–14.67; no 95% CI reported; Brede et al. 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 half-life of PFOA in animals varies depending on experimental protocols, but is on the order of days to weeks in rodents and monkeys.

Urinary excretion is the major route of elimination in rats (particularly females, which have much greater urinary elimination rates than males) (Vanden Heuvel et al. 1991; Kudo et al. 2001) and monkeys (Butenhoff et al. 2002; 2004a). The urinary excretion process involves glomerular filtration, secretion into the tubular fluid, and reabsorption from tubular fluid. Glomerular filtration of PFOA is limited by extensive binding of PFOA to plasma proteins. Renal reabsorption of PFOA is thought to be driven by OAT proteins residing on membranes of proximal tubular cells (Yang et al. 2010; Han et al. 2012), and contribute to rat sex-related differences in renal clearance (Yang et al. 2009a). Unlike the rat, no gender differences in PFOA urinary elimination are apparent in the mouse (ATSDR 2009) or monkey (Butenhoff et al. 2004a). A dose-dependent (non-linear) upward trend for urinary excretion of PFOA was observed in male rats (Butenhoff et al. 2004b). Consistent with observations in animals given low doses, the relationship between external dose and internal dose (serum level) is linear in humans with environmental exposures to PFOA (Clewell 2009); however, non-linear kinetics—as seen in animals at higher doses—might occur at higher human exposures. The relevance of urinary clearance in humans has been questioned, as renal clearance of PFOA was substantially lower than in animals (Harada et al. 2005).

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

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

5.3.5 Toxicokinetic Models

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

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

The 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.

5.4 Mode of Action

Mode of action (MOA) 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.

5.4.1 Direct-acting Mutagenicity

Direct-acting mutagenicity and DNA reactivity was considered as a potential MOA for the development of Leydig cell tumours in rats. 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 (AL) 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. 2001), 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.

5.4.2 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 peroxisome proliferator-activated receptors (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).

5.4.2.1 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. 2001], 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. 2001); however, the same study did not measure an increase in the effect in a model peroxisome proliferator (Wyeth-14,643 [WY]).

5.4.2.2 Key Event 2 – Altered Cell Growth

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

5.4.2.3 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. 2001).

5.4.2.4 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. 2001), 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. 2001). However, inconsistencies in this observation arise as the tumour triad

was not observed at a similar dose in another two-year study in rats (Butenhoff et al. 2012b). Studies of peroxisome proliferation and tumour development in these cells in mice (which are more sensitive to peroxisome proliferation than rats) would potentially provide more useful information for the MOA analysis.

Essentiality of key event — Studies of PPAR-null mice (Yang et al. 2002; Abbott et al. 2007; Wolf et al. 2008; Nakagawa et al. 2012) provided information to evaluate the essentiality of the key events for hepatic effects; no studies of PPAR-null rats exposed to PFOA could be found. In the Abbott et al. (2007) study, PPAR-null mice had decreased sensitivity to liver weight effects, which lends some support to the MOA for this adverse outcome; however, liver weight effects still occur (albeit at higher doses) in PPAR-null mice, and hepatomegaly is induced to the same extent in wild-type and PPAR-null mice in other studies (Yang et al. 2002; Wolf et al. 2008; Nakagawa et al. 2012). The increase hepatocyte proliferation (as measured by increase in labelling index) was also similar between wild-type and PPAR-null mice (Wolf et al. 2008). Moreover, despite an absence of increased expression of PPAR-related genes in PPAR-null and humanized PPAR mice, increases in liver weight were similar among these strains and wild-type mice (i.e., mice with increased PPAR expression) (Nakagawa et al. 2012). Despite these quantitative similarities between strains for non-cancer liver effects, qualitative differences were observed—including differences in microscopic appearance and ultrastructure of hepatic cells (Wolf et al. 2008; Minata et al. 2010) Further studies that expose PPAR-null mice at lower doses and investigate other adverse outcomes, as well as studies of PPAR-null rats, would help to better evaluate the MOA.

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

The first key event (PPAR activation) does not appear to precede the adverse hepatic outcomes in rats. Both increased liver weight and hepatocellular hypertrophy were observed either at or below doses where an absence of PPAR activation was observed. Consistency (across species, strains, organs, and test systems) — PPAR activation begins at lower doses in mice than rats and monkeys, as is expected, based on knowledge of PPAR biology (Corton et al. 2014). However, in monkeys, PPAR activation is not consistent, is not accompanied by cell proliferation, and occurs only at higher doses than adverse liver effects.

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

Some evidence in rats and mice supports the occurrence of peroxisome proliferation as a mode of action for hepatocellular hypertrophy. The characteristic tumour triad of peroxisome proliferators (cancers of the testes, pancreas, and liver) was observed in rats, and the doses at which hepatocellular tumours are observed are higher than earlier key events in the peroxisome proliferation MOA. However, increases in liver weight and hepatocellular hypertrophy appear to occur at lower doses than PPAR activation in rats; therefore, although PPAR activation does occur in rats, it does not appear to be the sole driver for these two effects. . Studies of

PPAR-null mice indicate that peroxisome proliferation might play a role in observed hepatocellular hypertrophy and liver weight increases, but despite qualitative (i.e., appearance) differences between the strains, the quantitative similarities in the changes in PPAR-null vs. wild type mice indicate that other MOAs play a large role in the development of the effects. Because the peroxisome proliferation MOA does not seem to be the sole MOA involved, human relevance of PFOA-induced non-carcinogenic hepatic effects cannot be ruled out. Conversely, a detailed MOA analysis has concluded that the weight of evidence for the peroxisome proliferation MOA for PFOA-induced liver tumours was strong. The relevance of these tumours to humans is limited, as PPARα activation by PFOA is weaker in humans than in rats. Moreover, PPARα activation by various compounds in does not appear to result in hepatocellular proliferation and tumours (Corton et al. 2012; Klaunig et al. 2012).

5.4.3 Sex Hormone Disruption

Sex hormone disruption is a potential MOA that should be considered for mammary gland development delays in mice, obesity in prenatally exposed mice, and Leydig cell tumours in rats. Insufficient data exist to be able to perform a quantitative analysis of sex hormone disruption; however, a few different observations that could be relevant to the sex hormone MOA have been reported, including the muting of uterine effects when PFOA was co-administered with estradiol (Dixon et al. 2012), an enhancement of the effects of 17β-estradiol in a variety of in vitro assays, but with an absence of direct estrogenic activity (Sonthithai et al. 2015), the reversal of mammary gland development delays with the supplementation of physiological levels of estradiol or progesterone (Zhao et al. 2012), an increase in serum estradiol concentrations in male rats exposed for 1–12 months (Biegel et al. 2001), changes in estradiol genesis (decrease at lower doses and increase at higher doses) in an in vitro steroidogenesis assay (Rosenmai et al. 2013), an absence of PFOA binding to or activating human estradiol receptors in vitro (Ishibashi et al. 2007), and decreases in cholesterol levels, which might disrupt testosterone synthesis (Li et al. 2011). If more in-depth studies on the effect of PFOA on sex hormone disruption are performed, this potential MOA could be further investigated.

5.4.4 Other Modes of Action

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).

5.5 Summary and Toxicity Reference Value Recommendations

Health Canada (2016) has calculated a tolerable daily intake for PFOA based on the toxicological data summarized in Section 5.0. The following sections summarize how the proposed chronic TRV for PFOA was derived.

5.5.1 Acute Oral Toxicity Reference Value for PFOA

An acute oral TRV could not be derived for PFOA due to lack of appropriate acute toxicity data.

5.5.2 Derivation of Proposed Subchronic Oral Toxicity Reference Value for PFOA

Health Canada has not derived a subchronic oral TRV for PFOA.

5.5.3 Derivation of Proposed Chronic Oral Toxicity Reference Value for PFOA

For the purpose of calculating human health SSV for PFOA, the tolerable daily intake (TDI = 2.5×10^{-5} mg/kg bw/day, equivalent to 25 ng/kg bw/day) derived by the Drinking Water Group (DWG) of Health Canada (2016)

was adopted. A dose-response analysis was conducted by Health Canada's drinking water guideline to derive the TDI based on a toxicological review completed in 2013 (Sanexen 2013).

5.5.3.1 Cancer Assessment

Epidemiological evidence has shown an association between exposure to PFOA and increased risk of incidence of testicular and kidney cancers. 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. 2012a). The Leydig cell adenomas were accompanied by hyperplasia of Leydig cells and proliferation and adenomas of pancreatic acinar cells in the Biegel et al. (2001) study. A dose-dependent increase in mammary fibroadenomas was observed in female rats in the Butenhoff et al. (2012a) 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.

The selected key study for the cancer risk assessment is Butenhoff et al. (2012a), 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 BMDL10 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, Health Canada (2016) calculated the human-equivalent point-of-departure (PODHEQ) by dividing the BMDL10 by the AKUF, as follows:

$$\text{PODHEQ} = \frac{1.3\ \text{mg/kg bw per day} \times \text{AKUF}}{17} = 0.076\ \text{mg/kg bw per day} \times \text{AKUF}$$

where:

- 1.3 mg/kg bw per day is the $BMDL_{10}$ for Leydig cell tumours in male rats (Butenhoff et al. 2012b); and

- 17 is the dose-specific AK_{UF} for rats in the 1 mg/kg bw per day range

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

$$= \frac{0.076 \text{ [illegible]}}{25}$$

$$= 0.003 \text{ [illegible]}$$

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. 2012a); and
- 25 is the composite uncertainty factor, as described below

Health Canada (2016) identified a composite uncertainty factor of 25 which 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 PODHEQ. 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.

5.5.3.2 Non-Cancer 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 , Health Canada found that 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 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). 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. 2004a) and 10 mg/kg bw per day (Butenhoff et al. 2004a), respectively, and no effects on lactation index were observed up to 30 mg/kg bw per day (Butenhoff et al. 2004b). Further support for the potential for species sensitivity is provided in studies using PPARα-knockout mice, which were less sensitive to body weight changes and eye opening (Abbott et al. 2007) and MGD delays (Zhao et al. 2012); PPAR activation is more sensitive in mice than in other species, including rats and humans (Corton et al. 2014). Although the data from the studies described above provide indication of some reproductive and developmental effects at low doses, the data are not currently considered to be an appropriate basis for quantitative risk assessment; however, if further studies demonstrate consistency of these effects in other species or their relevance to humans, the endpoint could become a more appropriate basis for the PFOA evaluation.

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

Hepatic effects were observed at slightly higher levels than reproductive effects, but observations of changes were still made at PFOA doses of ≤0.3 mg/kg bw per day. Increased relative liver weight was observed at ≥0.1 mg/kg bw per day in prenatally-exposed mouse pups (Abbott et al. 2007; Macon et al. 2011) and at ≥0.15 mg/kg bw per day in adult mice (Kennedy, 1987; Loveless et al. 2006, 2008). Dose-related increases in incidence and severity of hepatocellular hypertrophy were observed at ≥0.3 mg/kg bw per day in rats (Perkins et al. 2004;

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

Although increased liver weight and hepatocellular hypertrophy can sometimes be considered effects that are adaptive rather than adverse in their own right, evidence of other histological effects in the liver at higher concentrations provide an indication of their progression upon continued exposure (ECETOC 2002; Hall et al. 2012). An adverse histological effect (portal mononuclear cell infiltrate) was observed in livers of male rats at the same dose where significant increases in hepatocellular hypertrophy were observed (14.2 mg/kg bw per day of PFOA for 2 years; Butenhoff et al. 2012b). Although this dose is much higher than the lowest points of departure for increased liver weight and hepatocellular hypertrophy observed in subchronic studies, the latter effects are proposed as critical effects for this assessment, as they might be sensitive indicators of the potential for the progression of adverse histological effects. Additional histological effects observed in rats in studies of shorter duration included necrosis at ≥per day 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 and epidemiology databases. Clear dose–response relationships also tended to be absent in the animal studies. Due to these weaknesses, quantitative assessments were not performed for serum lipid effects; however, based on the present database, a TDI based on liver effects is assumed to be sufficiently protective of lipid changes.

To reflect the large interspecies differences in pharmacokinetics, Health Canada (2016) calculated a human-equivalent point-of-departure (POD_{HEQ}) for hepatocellular hypertrophy as follows:

$$\text{[illegible]} = \frac{0.06 \text{ [illegible]}}{96}$$

$$= 0.000625 \text{ [illegible]}$$

where:

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

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

$$\text{[illegible]} = \frac{0.000625 \text{ [illegible]}}{25}$$

$$= 0.000625 \text{ [illegible]}$$

where:

- 0.000625 mg/kg bw per day is the POD_{HEQ} calculated for hepatocellular hypertrophy in rats, as described above; and
- 25 is the composite uncertainty factor, as described below

The composite uncertainty factor of 25 is the product of 2 components: the interspecies uncertainty factor (2.5) and intraspecies uncertainty factor (10). An interspecies uncertainty factor of 2.5 was used to reflect only the toxicodynamic component of the default interspecies uncertainty factor, because the toxicokinetic differences between rats and humans were already incorporated when calculating the PODHEQ. 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. Health Canada (2016) indicates that although large differences in pharmacokinetics are

known to occur between species, insufficient data on the mechanism of PFOA excretion precludes investigations of whether the pharmacokinetic variability would also be wide within the human population. Average half-life values calculated from longitudinal data for different populations previously exposed to PFOA were similar (averages for each population ranged from 2.3–3.8 years; Olsen et al. 2007; Bartell et al. 2010; Brede et al. 2011); however, studies providing ranges indicated that there was approximately a 10-fold difference between the lowest and highest estimates of half-life. If further studies of PFOA consistently indicate a 10-fold difference in pharmacokinetics within the population, a higher intraspecies UF might be warranted to ensure that pharmacodynamic differences between humans are also quantitatively addressed. No UF for subchronic-to-chronic extrapolation was used, as liver effects were investigated in a chronic study (Butenhoff et al. 2012a), and increasing duration of exposure did not appear to worsen the effects in the key study (Perkins et al. 2004).

5.5.3.3 Comparison of Cancer and Non-Cancer Assessment

Health Canada (2016) derived a TDI of 0.000025 mg/kg bw/day for the non-cancer assessment using data of hepatocellular hypertrophy in rats, which is more conservative than the TDI for leydig cell tumours in rats of 0.003 mg/kg bw per day. The proposed TDI of 0.000025 mg/kg bw/day that was derived for non-cancer effects is therefore considered to be sufficiently protective of the carcinogenic effects of PFOA.

6.0 CALCULATIONS FOR HUMAN HEALTH SOIL SCREENING VALUES FOR PFOA

The information below is reproduced from Sanexen 2015.

The tolerable daily intake (TDI) of 0.000025 mg/kg bw/day derived for chronic oral exposure derived by Health Canada (2016) was used for the derivation of the SSV. Details of the study on which this TDI was based are summarized in section 5.4.3.2.

The input parameters used to derive the SSVs are presented in Table 2.

Table 4: Soil Screening Value Input Parameters

Acronym	Description	Land Use[a]		
		Agr. and Res./Park.	Commercial	Industrial/ Commercial without Toddler
TDI	Tolerable Daily Intake (mg/kg bw/day) per oral route of exposure (Health Canada 2016)	2.5×10^{-5}	2.5×10^{-5}	2.5×10^{-5}
EDI	Estimated Daily Intake (mg/kg bw/day) (Sanexen 2015)	2.7×10^{-6}	2.7×10^{-6}	1.8×10^{-6}
SAF	Soil Allocation Factor (default, unitless) (CCME 2006)	0.2	0.2	0.2
BW	Body Weight (kg) (CCME 2006)	16.5	16.5	70.7
AF_G	Relative Absorption Factor for PFOA across the gut (unitless)	1	1	1
SIR	Soil Ingestion Rate (kg/day) (CCME 2006)	8×10^{-5}	8×10^{-5}	2×10^{-5}
AF_S	Relative Absorption factor for PFOA across the skin (unitless)	0.1	0.1	0.1
SR	Soil Dermal Contact Rate (kg/day) (CCME 2006)[b]	6.9×10^{-5}	6.9×10^{-5}	1.14×10^{-4}
AF_L	Relative Absorption factor for PFOA across the lung (unitless)	1	1	1
SIR_S	Soil Inhalation Rate (kg/day)[c]	6.3×10^{-9}	6.3×10^{-9}	1.3×10^{-8}
ET_1	Exposure Term 1 (default, unitless) (CCME 2006)	1	0.66	0.66
ET_2	Exposure Term 2 (default, unitless) (CCME 2006)	1	0.42	0.42
BSC	Background Soil Concentration (mg/kg) (assumed)	0	0	0
SSV_A	Soil Screening Value for agricultural land use (calculated, mg/kg)	0.85	0.85	0.85

[a]: Agr.: Agricultural, Res./Park.: Residential/Parkland.

[b]: Soil Dermal Contact Rate = (hands surface area × soil loading to exposed skin of the hands) + (arms surface area × soil loading to exposed skin of the arms) + ([toddler only] legs surface area × soil loading to exposed skin of legs)

[c]: Value derived from the daily inhalation rate provided by Health Canada (2010 as cited in Sanexen 2015) for the critical receptor, assuming the airborne concentration of suspended soil particulates above a contaminated site is 7.6×10^{-10} kg/m^3.

The human health SSV for direct exposure was derived using the following formula (CCME 2006):

$$\text{[illegible]} = \frac{\text{[illegible]}}{\text{[illegible]}}$$

6.1 Agricultural and Residential/Parkland Land Use

All human age groups are considered for these scenarios. The receptors are assumed to be present at the property 24 hours per day, 365 days per year. The most sensitive receptor for agricultural land use is a toddler (age 7 months – 4 years) for threshold (non-carcinogenic) contaminants. The SSV for the agricultural land use scenario was derived based on a toddler.

$$\text{[illegible]} = \frac{(2.5 \times 10^{-5} - 2.7 \times 10^{-6}) \times 0.2 \times 16.5}{[(1 \times 8 \times 10^{-5}) + (1 \times 6.3 \times 10^{-9} \times 1) + (0.1 \times 6.9 \times 10^{-5})] \times 1} + 0$$

$$\text{SSV} = 0.85 \text{ mg/kg}$$

6.2 Commercial Land Use

All human age groups are considered for a commercial land use scenario. The receptors are assumed to be present at the property 10 hours per day, 5 days per week, 48 weeks per year. The most sensitive receptor for commercial land use is a toddler (age 7 months – 4 years) for threshold (non-carcinogenic) contaminants. The soil screening value for the commercial land use scenario was derived based on a toddler

$$\text{[illegible]} = \frac{(2.5 \times 10^{-5} - 2.7 \times 10^{-6}) \times 0.2 \times 16.5}{[(1 \times 8 \times 10^{-5}) + (1 \times 6.3 \times 10^{-9} \times 0.42) + (0.1 \times 6.9 \times 10^{-5})] \times 0.66} + 0$$

$$\text{SSV} = 1.28 \text{ mg/kg}$$

6.3 Industrial/Commercial without Toddler Land Use

Industrial/commercial without toddler land use is generally associated with restricted access to adults. The receptors are assumed to be present at the property 10 hours per day, 5 days per week, 48 weeks per year. The most sensitive receptor for industrial/commercial without toddler land use is an adult (age ≥ 20 years) for threshold (non-carcinogenic) contaminants. The soil screening value for the industrial/commercial without toddler land use scenario was derived based on an adult.

$$\text{[illegible]} = \frac{(2.5 \times 10^{-5} - 1.8 \times 10^{-6}) \times 0.2 \times 70.7}{[(1 \times 2 \times 10^{-5}) + (1 \times 1.3 \times 10^{-8} \times 0.42) + (0.1 \times 1.14 \times 10^{-4})] \times 0.66} + 0$$

$$\text{SSV} = 15.8 \text{ mg/kg}$$

6.4 Indirect Exposure Pathways and Check Mechanisms

In addition to the direct soil contact pathways (*via* ingestion, inhalation and dermal contact with surface soil), indirect exposure pathways and CCME check mechanisms were also considered (CCME, 2006). The primary indirect exposure pathways are the migration of soil contaminants into groundwater used as drinking water and the volatilization of soil contaminants into indoor air. The check mechanisms are for offsite migration of contaminants from commercial and industrial sites to more sensitive neighbouring properties and for exposure from ingestion of food grown on contaminated soils.

6.4.1 Protection of Groundwater

The CCME protocol provides equations to develop soil quality guidelines for the protection of potable groundwater (SGQ_{PW}). For PFOA, sorption is the only chemical-specific attenuation mechanism in soil and groundwater since PFOA does not biodegrade or volatilize[2] (reviewed in OECD 2002, Barton et al. 2007 and HC 2012). Other attenuation mechanisms are purely based on hydrogeological and hydrological conditions. On this basis, K_{oc} is a key parameter to derive an SQG_{PW} for PFOA. However, the level of protection afforded by an SQG_{PW} may not be adequate because the sorption of PFOA related substances might be highly variable, with reported Log K_{oc} values ranging from 1.2 to 4.5 (corresponding to K_{oc} values ranging from 17 to 31 623 L/kg).

Consequently, no SQG_{PW} or SSV_{pw} were derived. Nevertheless, if groundwater is used for human consumption at a PFOA contaminated site, this pathway should be assessed on a site-specific basis (groundwater samples should be analyzed and compared to available drinking water guidelines to ensure the protection of human health from potable water).

6.4.2 Volatilization of Soil Contaminants into Indoor Air

Volatile organic compounds can migrate from soil into the basements of buildings. Vapours may be released from soil to the outside air at the ground surface, in addition to entering buildings. However, since buildings are enclosed spaces and are often under-pressured due to heating, the migration of vapours into buildings poses a much greater health risk than migration of vapours to the outdoors. The inhalation intake of PFOA for Canadians was considered negligible due to its low volatility (Tittlemier et al. 2007); therefore, the indoor vapour inhalation pathway is not considered to be significant in the derivation of soil screening values.

6.4.3 Off-Site Migration Check

Although soil quality guidelines for commercial and industrial sites consider on-site exposure only, wind and water erosion of soil and subsequent deposition can transfer contaminated soil from one property to another. Soil screening values for the offsite migration check were derived using the following formula (CCME 2006):

$$SSV_{OM} = (14.3 \times SSV_A) - (13.3 \times BSC) \quad ***$$

$$SSV_{OM} = 12.1 \quad *$$

where,

SSV_{OM} = soil screening value for offsite migration in mg/kg
SSV_A = soil screening value for agricultural land use = 0.85 mg/kg
BSC = background concentration of contaminant in the receiving soil = 0 mg/kg

6.4.4 Human Food Consumption Check

The check mechanism for consumption of produce, meat and milk is described in CCME, 2006 and is a required pathway for biomagnifying substances. Data on uptake of PFOA by plants from soil is limited, as is information on biotransfer of PFOA from soil to meat and dairy. Therefore the check mechanism could not be calculated.

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[2] Volatilization may occur at low pH (<5)

7.0 DATA GAPS, UNCERTAINTIES AND LIMITATIONS

The SSVs calculated for PFOA are based on direct contact pathways with soil. As the sorption of PFOA related substances is expected to be highly variable based on the range of reported Log K_{oc} values, a SSV protective of groundwater as a source of drinking water could not be derived. However, if groundwater is used for human consumption at a PFOA-contaminated site, this pathway should be assessed on a site-specific basis (groundwater samples should be analyzed and compared to available drinking water guidelines to ensure the protection of human health from potable water).

The SSVs are also not protective of consumption of produce, meat and milk as data on uptake of PFOA by plants from soil is limited, as is information on biotransfer of PFOA from soil to meat and dairy products (Sanexen 2015).

Although there were limited chronic toxicological studies available for PFOA, Health Canada considered the studies to be sufficient to calculate a TRV.

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