

**Screening Assessment Report**  
**Perfluorooctanoic Acid, its Salts, and its Precursors**

**Environment Canada**  
**Health Canada**

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## Synopsis

Under the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of perfluorooctanoic acid (PFOA), Chemical Abstracts Service Registry Number<sup>1</sup> 335-67-1, its salts and its precursors under sections 68 and 74 of CEPA 1999. The ammonium salt of PFOA and some precursors to PFOA, present on Canada's Domestic Substances List (DSL), were categorized under section 73 of CEPA 1999. While PFOA itself is not on the DSL, PFOA can be formed in the environment through degradation from a variety of other perfluorinated chemicals. PFOA was identified for assessment based on its persistent nature, widespread occurrence in biota, presence in the Canadian Arctic due to long-range transport, and international interest in emerging science indicating a potential concern for the environment and human health from PFOA and its salts. In addition, precursors to PFOA were considered in this assessment on the basis of their contribution to the total presence of PFOA and its salts in the environment.

PFOA is an anthropogenic substance belonging to a class of chemicals known as perfluorocarboxylic acids (PFCAs). PFCAs, in turn, belong to the broader class of chemicals known as perfluoroalkyls (PFAs). In this assessment, the term "PFOA" may refer to the acid, its conjugate base or its principal salt forms. Historical uses of PFOA include applications in industrial processes and in commercial and consumer products. PFOA and its salts are used as polymerization aids in the production of fluoropolymers and fluoroelastomers. PFOA, itself, is not manufactured in Canada; however, quantities of the ammonium salt are imported.

## Environment

PFOA may be found in the environment due to releases from fluoropolymer manufacturing or processing facilities, effluent releases from wastewater treatment plants, landfill leachates and due to degradation/transformation of PFOA precursors. This assessment defines precursors as substances where the perfluorinated alkyl moiety has the formula  $C_nF_{2n+1}$  (where  $n = 7$  or  $8$ ) and is directly bonded to any chemical moiety other than a fluorine, chlorine or bromine atom. Such precursors may include parent compounds, chemical products containing PFOA (either as part of formulations or as unintended residuals) and substances transforming to intermediates that ultimately degrade to PFOA. Potential precursors also include related fluorochemicals (e.g., fluorotelomer alcohols [FTOHs], fluorotelomer iodides and fluorotelomer olefins), some of which are currently found in commercial products and detectable in the atmosphere and can degrade or transform to PFOA through biotic or abiotic pathways.

Once in the environment, PFOA is extremely persistent and not known to undergo significant further abiotic or biotic degradation under relevant environmental conditions.

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PFOA is highly soluble in water and typically present as an anion (conjugate base) in solution. It has low vapour pressure; therefore, the aquatic environment is expected to be its primary sink, with some additional partitioning to sediment. The presence of PFOA in the Canadian Arctic is likely attributable to the long-range transport of PFOA (e.g., via ocean currents) and/or of volatile precursors to PFOA (e.g., via atmospheric transport).

PFOA has been detected at trace levels in the northern hemisphere. In North America, higher levels were measured in surface waters in the vicinity of US fluoropolymer manufacturing facilities (<0.025–1900 µg/L) and in groundwater near US military bases (not detected [ND] to 6570 µg/L). PFOA was detected in effluent from Canadian wastewater treatment facilities at concentrations ranging from 0.007 to 0.055 µg/L. PFOA was also detected in the influent at US wastewater treatment facilities at concentrations ranging from 0.0074–0.089 µg/L.

Trace levels of PFOA have been measured in Canadian freshwater (ND–11.3 µg/L) and freshwater sediments (0.3–7.5 µg/kg). PFOA has also been detected in a variety of Canadian biota (ND–90 µg/kg wet weight [kg-ww] tissue) in southern Ontario and the Canadian Arctic. The highest concentration of PFOA in Canadian organisms was found in the benthic invertebrate *Diporeia hoyi* at 90 µg/kg-ww, followed by turbot liver at 26.5 µg/kg-ww, polar bear liver at 13 µg/kg-ww, caribou liver at 12.2 µg/kg-ww, ringed seal liver at 8.7 µg/kg-ww and walrus liver at 5.8 µg/kg-ww. Following an accidental release of fire-fighting foam in Etobicoke Creek (Ontario), PFOA was measured in common shiner liver at a maximum concentration of 91 µg/kg-ww. However, current PFOA concentrations in Canadian biota (tissue specific and whole body) are below the highest concentration found in US biota (up to 1934.5 µg/kg-ww in gar liver).

Temporal or spatial trends in PFOA concentrations in guillemot eggs, lake trout, thick-billed murres, northern fulmars or ringed seals could not be determined. However, temporal trends were found for PFOA concentrations in polar bears (1972–2002 and 1984–2006) and sea otters (1992–2002). PFOA doubling time in liver tissue was calculated to be  $7.3 \pm 2.8$  years for Baffin Island polar bears and  $13.9 \pm 14.2$  years for Barrow, Alaska, polar bears; central East Greenland polar bears showed an annual increase of 2.3% in PFOA concentrations. Concentrations of PFOA also increased significantly over a 10-year period for adult female sea otters.

Unlike other organic pollutants that are persistent and found in biota, PFOA is present mainly in its ionic form in environmental media. Due to the perfluorination, the perfluorinated chains are both oleophobic and hydrophobic. PFOA primarily binds to albumin proteins in the blood of biota and, as a result, is present in blood and highly perfused tissues such as liver and kidney, rather than lipid tissue. The numeric criteria for bioaccumulation, outlined in the *Persistence and Bioaccumulation Regulations* of CEPA 1999, are based on bioaccumulation data for freshwater aquatic species (fish) only and for substances that preferentially partition to lipids. As a result, the criteria may not completely reflect the bioaccumulation potential of PFOA that is preferentially partitioning in the proteins of liver, blood and kidney in terrestrial and marine mammals. There is experimental evidence indicating that PFOA is not highly bioaccumulative in

fish. Reported laboratory bioconcentration factors for fish species (primarily rainbow trout) ranged from 3.1–27. In the pelagic aquatic food web of Lake Ontario, two studies indicate that PFOA concentrations do not biomagnify with increasing trophic level. However, these results should not be extrapolated to non-aquatic species, since gills provide an additional mode of elimination for PFOA that air-breathing organisms, such as terrestrial and marine mammals, do not possess. Field studies indicating biomagnification factors greater than 1 for Arctic and other mammals (such as narwhal, beluga, polar bear, walrus, bottlenose dolphins, and harbour seals) suggest that PFOA may bioaccumulate and biomagnify in terrestrial and marine mammals. Reported field biomagnification factors for terrestrial and marine mammals ranged from 0.03–31. Polar bears, as the apex predator in the Arctic marine food web, have been shown to be the most contaminated with PFOA relative to other Arctic terrestrial organisms.

In traditional toxicity studies, PFOA exhibits moderate to low acute toxicities in pelagic organisms, including fish (70–2470 mg/L). PFOA exhibits low chronic toxicities in benthic organisms (>100 mg/L). There is one study on the toxicity of PFOA and its salts in avian wildlife. In this study, PFOA was found to have no effect on embryonic pipping success for white leghorn chickens at concentrations up to 10 µg/g of embryos. However, PFOA accumulated in the liver of these embryos to concentrations 2.9–4.5 times greater than the initial whole-egg concentration.

There are studies showing the potential for PFOA to affect endocrine function where visible effects may not be apparent until the organisms reach adulthood. In female and male rare minnows, 3–30 mg/L PFOA elicited inhibition of the thyroid hormone biosynthesis genes, induced vitellogenin expression in males, developed oocytes in the testes of male fish and caused ovary degeneration in females.

There are other studies showing hepatotoxicity, immunotoxicity, and chemosensitivity. For example, a PFOA concentration of 20 mg/L increased the chemosensitivity in marine mussels. PFOA at 25.9 mg/L activated the mammalian peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) in the livers of Baikal seals—PPAR $\alpha$  plays a critical physiological role as a lipid sensor and a regulator of lipid metabolism. Field data also reveal that there may be increases in indicators of inflammation and immunity in bottlenose dolphins related to PFOA concentrations, suggesting possible autoimmune effects. Another field study has also suggested that low levels of PFOA may alter biomarkers of health in loggerhead sea turtles. In 2-year carcinogenicity bioassays in rats, males administered a high dose of PFOA ammonium salt (APFO) in the diet had significantly higher incidences of adenomas of the liver hepatocytes, Leydig cells in the testes and pancreatic acinar cells. Liver tumours in male rats may be induced via liver toxicity resulting from PFOA-induced peroxisome proliferation, and additional pathways secondary to peroxisome proliferation may be involved in the generation of tumours at other sites. There is some evidence to suggest that PFOA may be capable of causing indirect oxidative DNA damage.

## Human Health

In humans, PFOA is well absorbed by all routes of exposure; it has not been demonstrated to be metabolized and has a relatively long half-life. Salts of PFOA are expected to dissociate in biological media to produce the perfluorooctanoate (PFO) moiety, and are therefore considered toxicologically equivalent to PFOA. Low concentrations of PFOA have been identified in blood samples from non-occupationally exposed Canadians, including newborns, indicating environmental exposure to PFOA and/or compounds that can degrade to PFOA. The available data indicate that Canadians are exposed to PFOA and its precursors in the environment, including via air, drinking water and food; and from the use of consumer products, such as new non-stick cookware and perfluorinated compound (PFC)-treated apparel and household materials such as carpets and upholstery. Canadians are also potentially exposed to PFOA *in utero* and through lactational transfer. The relative contributions of PFOA and its salts and precursors to total PFOA exposure were not characterized; rather the focus was on aggregate exposure to the moiety of toxicological concern, PFOA.

Epidemiological studies have not identified a causal relationship between PFOA exposure and adverse health effects in humans. Therefore, toxicity studies in laboratory animals were used to determine the critical effects and associated serum levels of PFOA. Following oral dosing of APFO, increased liver weight in mice and altered lipid parameters in rats were observed in short-term (14-day) toxicity studies; increased liver weight was noted in a 26-week toxicity study in monkeys; and increased liver weight in dams, alterations in fetal ossification and early puberty in male pups were found in a developmental toxicity study in mice.

In 2-year carcinogenicity bioassays in rats, males administered a high dose of APFO in the diet had significantly higher incidences of adenomas of the liver hepatocytes, Leydig cells in the testes and pancreatic acinar cells. No evidence of carcinogenic activity was seen in the female rats. Liver tumours in male rats may be induced via liver toxicity resulting from PFOA-induced peroxisome proliferation, and additional pathways secondary to peroxisome proliferation may be involved in the generation of tumours at other sites. As primates are much less susceptible than rodents to peroxisome proliferation, the PFOA-induced tumours in male rats are considered to have little or no relevance for humans. Although blood levels of PFOA were not determined in the chronic studies, the oral dose of APFO was several times higher than those in the critical short-term and subchronic studies. Although there is some evidence to suggest that PFOA may be capable of causing indirect oxidative DNA damage, the genotoxicity database indicates that PFOA is not mutagenic. Thus, as the tumours observed in male rats are not considered to have resulted from direct interaction with genetic material, a threshold approach is used to assess risk to human health.

The assessment of PFOA is based on a comparison of the margin between the levels of PFOA in the blood (serum or plasma) of humans and serum levels that are associated with the development of adverse effects in laboratory animals. This approach aggregates exposure to PFOA from all sources, including those resulting from releases from

fluoropolymer manufacturing or processing facilities, effluent releases from sewage treatment plants, landfill effluents, or degradation/transformation of PFOA precursors.

Comparison of the PFOA serum levels associated with adverse effects in laboratory animals (13–77 µg/mL) with the serum or plasma levels found in non-occupationally exposed adults, infants and children (0.00162–0.0195 µg/mL) results in margins of exposure greater than 660. These margins are considered to be adequately protective to account for uncertainties in the hazard and exposure databases.

## Conclusion

The ecological assessment is based on a weight-of-evidence approach regarding persistence, bioaccumulation, temporal trends in some species (i.e., the polar bear), long-range transport and the widespread occurrence and concentrations of PFOA in the environment and biota (including remote areas of Canada). Based on the available information, it is concluded that PFOA, its salts and its precursors are entering 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. In addition, it is concluded that PFOA and its salts meet the criteria for persistence as set out in the *Persistence and Bioaccumulation Regulations*. PFOA and its salts do not meet the criteria for bioaccumulation as set out in the *Persistence and Bioaccumulation Regulations*. Nevertheless, the weight of evidence is sufficient to conclude that PFOA and its salts accumulate and biomagnify in terrestrial and marine mammals.

Based on the available information on the potential to cause harm to human health and the resulting margins of exposure, it is concluded that PFOA and its salts are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Precursors of PFOA were not individually assessed, but were considered in terms of their contribution to total PFOA exposure because they can degrade to PFOA in the environment.

Therefore, based on available information for environmental and human health considerations, it is concluded that PFOA, its salts and its precursors meet one or more of the criteria set out in section 64 of CEPA 1999.

Where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

## Introduction

This screening assessment was conducted pursuant to sections 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999).

A screening assessment was undertaken on perfluorooctanoic acid (PFOA) (Chemical Abstracts Service Registry Number [CAS RN] 335-67-1) and its salts. In addition, precursors to PFOA were considered on the basis of their contribution to the total presence of PFOA and its salts. This assessment defines precursors as substances where the perfluorinated alkyl moiety has the formula  $C_nF_{2n+1}$  (where  $n = 7$  or  $8$ ) and is directly bonded to any chemical moiety other than a fluorine, chlorine or bromine atom.

The ammonium salt, CAS RN 3825-26-1, and the precursors, CAS RN 53515-73-4, CAS RN 678-39-7, CAS RN 65530-61-2, and CAS RN 70969-47-0 are on the Domestic Substances List (DSL) and were found to meet the ecological categorization criteria for persistence and/or bioaccumulation potential and/or inherent toxicity to non-human organisms. However, none of these substances were considered to be a high priority for assessment of potential risks to human health, based upon application of the simple exposure and hazard tools developed by Health Canada for categorization of substances on the DSL.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999. Screening assessments examine scientific information and develop conclusions by applying a weight-of-evidence approach and precaution

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure. Data relevant to the screening assessment of these substances were identified in original literature, review and assessment documents and stakeholder research reports and from recent literature searches, up to February 2011 for ecological sections of the document and up to April 2011 for the human health sections of the document. In addition, an industry survey on perfluoroalkyls/fluoroalkyls was conducted for the years 2000 and 2004 through *Canada Gazette* Notices issued pursuant to section 71 of CEPA 1999 (Canada 1999; Canada 2000b, 2004). These surveys collected data on the Canadian manufacture, import, uses and releases of perfluoroalkyls/fluoroalkyls. Toxicological studies were also submitted by industry under section 70 of CEPA 1999.

The approach taken in the ecological screening assessment is to examine relevant scientific and technical information and develop conclusions based on multiple lines of evidence, including persistence, exposure, trends, toxicity, bioaccumulation and widespread occurrence in the environment. Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population as well as information on health hazards. Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The

screening assessment does not present an exhaustive or critical review of all available data. Instead, it presents the critical studies and lines of evidence supporting the conclusions<sup>2</sup>.

This draft screening assessment was prepared by staff in the Existing Substances programs at Health Canada and Environment Canada. The draft ecological assessment has undergone external written peer review/consultation. The draft human health screening assessment was externally reviewed by staff of Toxicology Advice & Consulting Limited; Dr. Sean Hayes (Summit Toxicology); Dr. Greg Kedderis (private consultant); Dr. Kannan Krishan (University of Montreal); and Dr. Donna Vorhees (Science Collaborative) for adequacy of data coverage and defensibility of the conclusions. Statements in this document do not necessarily reflect the opinions of the reviewers. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment Canada.

The critical information and considerations upon which the draft assessment is based are summarized below.

### **Substance Identity**

Information on the identity of PFOA is presented in Table 1. PFOA is an anthropogenic compound with a chain length of eight carbons, seven of which are perfluorinated. It belongs to the broad class of chemicals known as perfluorocarboxylic acids (PFCAs), which, in turn, belong to the broader class of chemicals known as perfluoroalkyls (PFAs). In this assessment, the term “PFOA” may refer to the acid, its conjugate base or its principal salt forms (Table 2). 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. PFOA may also be referred to as C8, as well as by other synonyms or trade names. A more detailed discussion of the identity, nomenclature and trade names of PFOA is provided in Ellis et al. (2004b). The most common commercially used salt form of PFOA is the ammonium salt, referred to as APFO (see chemical structure in Table 1).

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<sup>2</sup> A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA 1999 does not preclude actions being taken under other sections of CEPA or other Acts.

Table 1. Substance identity

<b>Chemical Abstracts Service Registry Number (CAS RN)</b>	335-67-1				
<b>Chemical name</b>	Perfluorooctanoic acid				
<b>National Chemical Inventories (NCI) names<sup>1</sup></b>	Octanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluoro- (TSCA) Octanoic acid, pentadecafluoro- (AICS, ASIA-PAC, NDSL, NZIoC, PICCS, SWISS) Pentadecafluorooctanoic acid (ECL, EINECS, PICCS, REACH) Perfluorooctanoic acid (ENCS)				
<b>Other names</b>	EF 201; Eftop EF-201; NSC 95114; Pentadecafluoro-1-octanoic acid; Pentadecafluoro- <i>n</i> -octanoic acid; Perfluorocaprylic acid; Perfluoro-1-heptanecarboxylic acid; Perfluoroheptanecarboxylic acid; <i>n</i> -Perfluorooctanoic acid				
<b>Chemical group</b>	Discrete organics				
<b>Major chemical class or use</b>	Perfluoroalkyls				
<b>Major chemical subclass</b>	Perfluorocarboxylic acids				
<b>Chemical formula</b>	C <sub>8</sub> HF <sub>15</sub> O <sub>2</sub>				
<b>Chemical structure (salt and acid form)</b>	<table style="width: 100%; border: none;"> <tr> <td style="text-align: center; width: 50%;"><b>Ammonium Salt</b></td> <td style="text-align: center; width: 50%;"><b>Acid</b></td> </tr> <tr> <td style="text-align: center;"> </td> <td style="text-align: center;"> </td> </tr> </table>	<b>Ammonium Salt</b>	<b>Acid</b>		
<b>Ammonium Salt</b>	<b>Acid</b>				
<b>SMILES<sup>2</sup></b>	FC(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(=O)O				

<sup>1</sup>NCI 2009 : AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Commercial Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); NDSL (Non-Domestic Substances List (Canada)); NZIoC (New Zealand Inventory of Chemicals); PICCS (Philippine Inventory of Chemicals and Chemical Substances); REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals (European Commission)); SWISS (Swiss Giftliste 1 and Inventory of Notified New Substances); TSCA (*Toxic Substances Control Act* Chemical Substance Inventory).

<sup>2</sup>Simplified Molecular Input Line Entry Specification

Environment Canada considered perfluoroalkyl compounds on the basis of expert judgement, chemical structures and biodegradation estimation modelling using CATABOL (c2004–2008) (Mekenyan et al. 2002). Using these approaches, the structures were analyzed for their potential to degrade to PFOA. CATABOL (c2004–2008) was trained on the basis of the Japanese Ministry of International Trade and Industry (MITI) biodegradation test results (OECD TG 301C) and predicts biodegradation over a period of 28 days. It is acknowledged that due to the limited perfluorinated degradation data in the training set, some degradation products generated by CATABOL (c2004–2008) may be of limited reliability. It should also be noted that the degradation process will be

longer for perfluorinated chemicals, but it is difficult to estimate how much longer, especially for high-molecular-weight substances such as oligomers and polymers.

Precursors to PFOA (Table 2) have been considered in this assessment; however, this list should not be considered exhaustive. A more complete list can be found in the *Canada Gazette* Notice with respect to certain perfluoroalkyl and fluoroalkyl substances, at <http://www.gazette.gc.ca/archives/p1/2005/2005-01-15/html/notice-avis-eng.html>. It should also be noted that some precursors to PFOA may also be considered as precursors to long-chain (C9-C20) PFCAs. This assessment defines precursors as substances where the perfluorinated alkyl moiety has the formula  $C_nF_{2n+1}$  (where  $n=7$  or  $8$ ) and is directly bonded to any chemical moiety other than a fluorine, chlorine or bromine atom.

**Table 2. List of PFOA and its principal salts and precursors<sup>1</sup>**

Name	CAS RN	Molecular formula	Listing (DSL or NDSL)
PFOA free acid (Octanoic acid, pentadecafluoro-)	335-67-1	$C_8HF_{15}O_2$	NDSL
Perfluorooctanoate (PFO, conjugate base of the free acid)	45285-51-6	$C_8F_{15}O_2^-$	Not listed
Branched perfluorooctanoic acid	90480-55-0	$C_8HF_{15}O_2$	Not listed
<b>Principal salts</b>			
PFOA ammonium salt (APFO, Octanoic acid, pentadecafluoro-, ammonium salt)	3825-26-1	$C_8F_{15}O_2^-NH_4^+$	DSL
Ammonium salt, linear/branched PFOA (Octanoic acid, pentadecafluoro-, branched, ammonium salt)	90480-56-1	$C_8F_{15}O_2^-NH_4^+$	Not listed
PFOA sodium salt	335-95-5	$C_8F_{15}O_2^-Na^+$	NDSL
PFOA potassium salt	2395-00-8	$C_8F_{15}O_2^-K^+$	Not listed
PFOA silver salt	335-93-3	$C_8F_{15}O_2^-Ag^+$	NDSL
<b>Potential precursors<sup>1</sup></b>			
2-Propenoic acid, 2-methyl-, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyl ester, polymer with 2-propenoic acid	53515-73-4	$(C_{15}H_{11}F_{15}O_4)_x$	DSL
Propanamide, 3-[( $\gamma$ - $\omega$ -perfluoro- $C_{4-10}$ -alkyl)thio] derivatives	68187-42-8	NA	DSL

Name	CAS RN	Molecular formula	Listing (DSL or NDSL)
Poly(difluoromethylene), $\alpha$ -fluoro- $\omega$ -[2-[[2-(trimethylammonio)ethyl]thio]ethyl]-, methyl sulfate	65530-57-6	NA	DSL
Poly(difluoromethylene), $\alpha, \alpha'$ -[phosphinicobis( oxy-2,1-ethanediyl)]bis[ $\omega$ -fluoro-	65530-62-3	NA	DSL
Poly(difluoromethylene), $\alpha$ -fluoro- $\omega$ -[2-(phosphonoxy)ethyl]-	65530-61-2	NA	DSL
Thiols, C <sub>8-20</sub> , $\gamma$ - $\omega$ -perfluoro, telomers with acrylamide	70969-47-0	NA	DSL
Carbamic acid, [2-(sulfothio)ethyl]-, C-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl) ester, monosodium salt	82199-07-3	NA	DSL
Carbamic acid, [2-(sulphothio)ethyl]-, C-( $\gamma$ - $\omega$ -perfluoro-C <sub>6-9</sub> -alkyl) esters, monosodium salts	95370-51-7	NA	DSL
1,3-Propanediol, 2,2-bis[[( $\gamma$ - $\omega$ -perfluoro-C <sub>4-10</sub> -alkyl)thio]methyl] derivatives, phosphates, ammonium salts	148240-85-1	NA	NDSL
1,3-Propanediol, 2,2-bis[[( $\gamma$ - $\omega$ -perfluoro-C <sub>6-12</sub> -alkyl)thio]methyl] derivatives, phosphates, ammonium salts	148240-87-3	NA	NDSL
Thiols, C <sub>4-20</sub> , $\gamma$ - $\omega$ -perfluoro, co-telomers with acrylic acid and acrylamide	NA	NA	Not listed
1-Decanol, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro (or 1,1,2,2-tetrahydroperfluoro-1-decanol or 8:2 fluorotelomer alcohol)	678-39-7	C <sub>10</sub> F <sub>17</sub> H <sub>5</sub> O	DSL
Octanoyl fluoride, pentadecafluoro-	335-66-0	C <sub>8</sub> F <sub>16</sub> O	NDSL
Octanoic acid, pentadecafluoro-, methyl ester	376-27-2	C <sub>9</sub> H <sub>3</sub> F <sub>15</sub> O <sub>2</sub>	NDSL
Octanoic acid, pentadecafluoro-, ethyl ester	3108-24-5	C <sub>10</sub> H <sub>5</sub> F <sub>15</sub> O <sub>2</sub>	NDSL
8:2 Fluorotelomer acrylate polymers <sup>2</sup>	NA	NA	NA
1,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-heptadecafluoro-10-iododecane (C8-2 iodide)	2043-53-0	NA	NA
2-propenoic acid, 2-methyl-, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl methacrylate (C8-2 methacrylate)	1996-88-9	NA	DSL
2-propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl acrylate (C8-2 acrylate)	27905-45-9	NA	DSL

Name	CAS RN	Molecular formula	Listing (DSL or NDSL)
3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptafluorodec-1-ene (C8-2 olefin)	21652-58-4	NA	NA
Phosphoric acid surfactants (e.g., 8:2 polyfluoroalkyl phosphoric acid diester or 8:2 diPAP) <sup>4</sup>	NA	$x:2$ diPAP (F(CF <sub>2</sub> ) <sub>x</sub> CH <sub>2</sub> CH <sub>2</sub> O) <sub>2</sub> P(O)OH	NA
Perfluorooctylsulfonamides <sup>3</sup>	NA	F[CF <sub>2</sub> ] <sub>8</sub> SO <sub>2</sub> NR R' where R and R' can be CH <sub>2</sub> CH <sub>2</sub> OH, CH <sub>3</sub> , CH <sub>2</sub> CH <sub>3</sub> , or H	NA
1,3-Propanediol, 2,2-bis[[ $\gamma$ - $\omega$ -perfluoro-C10-20-alkyl]thio]methyl] derivs., phosphates, ammonium salts	148240-89-5	NA	NDSL
Oxirane, methyl-, polymer with oxirane, mono[2-hydroxy-3-[( $\gamma$ - $\omega$ -perfluoro-C8-20-alkyl]thio]propyl] ethers	183146-60-3	NA	NDSL
Poly(difluoromethylene), $\alpha$ -fluoro- $\omega$ -(2-sulfoethyl)-	80010-37-3	NA	NDSL
2-Propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-heneicosafuorododecyl ester, polymer with 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptafluorodecyl 2-propenoate, alpha-(2-methyl-1-oxo-2-propenyl)-omega-[(2-methyl-1-oxo-2-propenyl)oxy]poly(oxy-1, 2-ethanediyl), 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,16-nonacosafuorohexadecyl 2-propenoate, octadecyl 2-propenoate, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,14-pentacosafuorotetradecyl 2-propenoate and 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17,18,18,18-tritriacontafuorooctadecyl 2-propenoate	116984-14-6	NA	not listed
Pentanoic acid, 4,4-bis[[ $\gamma$ - $\omega$ -perfluoro-C8-20-alkyl]thio]derivs., compds. with diethanolamine	71608-61-2	NA	NDSL

CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List; NA, not available; NDSL, Non-Domestic Substances List.

- 1 Precursors are as identified through CATABOL (c2004–2008), expert judgment, and literature and are non-exhaustive.
- 2 Van Zelm et al. (2008)
- 3 De Silva et al. (2009)
- 4 D'Eon and Mabury (2007)

## Physical and Chemical Properties

Water solubility is a key property affecting PFOA and its salts in the environment. The free acid and the ammonium salt are solid at 20°C. The free acid readily dissociates to perfluorooctanoate (PFO), the conjugate base that is commonly measured in environmental media and biological samples. The conjugate base of the PFOA acid and its salts is highly soluble in water. It has been noted that PFOA salts self-associate at the surface but disperse with agitation and form micelles at higher concentrations (US EPA 2003).

Solubility is dependent on the acid dissociation constant ( $pK_a$ ) of the acid form, and the  $pK_a$  value commonly reported and used is approximately 2.5 (Kissa 1994). However, Burns et al. (2008) determined a  $pK_a$  of  $3.8 \pm 0.1$ , suggesting that the neutral species can exist in the environment. Jasinski et al. (2009) determined a  $pK_a$  of  $3.3 \pm 0.4$ . Goss and Arp (2009), using analogues and molecular models, suggested that the  $pK_a$  ranges from 0 to 4. Goss (2008) suggested that PFOA is expected to have a low  $pK_a$ , such that > 99% of the compound will occur in its anionic form (i.e., PFO) under most environmental conditions suggesting that the environmental partitioning of PFOA will be dominated by the anionic form.

The physical and chemical properties of PFOA are summarized in Table 3.

**Table 3. Physical/chemical properties of PFOA**

Property	Value	Type	Reference
Molecular mass (g/mol)	414.0639	–	–
Melting point (°C)	52–54		Barton et al. 2007
Vapour pressure (Pa)	2.2 (at 20°C)	Calculated	Barton et al. 2007
Henry's law constant (Pa·m <sup>3</sup> /mol)	2.4	Calculated	Barton et al. 2007
log $K_{ow}$ (dimensionless)	5 ± 0.5	Modelled	Jasinski et al. 2009
	3.62–6.30	Modelled	Arp et al. 2006
log $K_{oa}$ (dimensionless)	5.73–6.80	Modelled	Arp et al. 2006
log $K_{oc}$ (dimensionless)	2.06 (sediment pH 5.7–7.6)	Experimental	Higgins and Luthy 2006
Water solubility (g/L)	3.5 (neutral to alkaline pH)		Barton et al. 2007
	0.0007 (acidic pH)		
$pK_a$ (dimensionless)	2.5	Experimental	Kissa (1994)
	3.8 +/- 0.1	Experimental	Burns et al. (2008)

Property	Value	Type	Reference
	0–4	Modelled and analogues	Goss and Arp (2009)

Abbreviations:  $K_{oa}$ , octanol–air partition coefficient;  $K_{ow}$ , octanol–water partition coefficient;  $K_{oc}$ , sediment organic carbon coefficient;  $pK_a$ , acid dissociation constant.

<sup>1</sup> Value in parentheses provided in the original reference.

## Sources

PFOA and its salts are of anthropogenic origin with no known natural sources (Kissa 1994). Surveys of industry conducted in 2000 and 2004 under the authority of section 71 of CEPA 1999 were used to collect data on the Canadian manufacture, import and export of certain perfluoroalkyl and fluoroalkyl substances, their derivatives and polymers, including PFOA (Canada 2000b, Canada 2004).

Results from the 2000 survey indicated that PFOA and its salts were not manufactured in Canada. Approximately 600 000 kg of PFAs were imported into Canada between 1997 and 2000. Imports of PFOA and its salts were reported by one company. The import of PFOA and its salts (<1000 kg) represented a very small proportion of the PFAs imported and consisted almost exclusively of the ammonium salt used in industrial applications. The volumes reported do not include quantities possibly imported in manufactured items (Environment Canada 2001). The reported uses for PFOA and its salts included use as a polymer, component of a formulation and other uses (i.e., batteries, coatings, lubricants) (Environment Canada 2001). Owing to its physicochemical properties, PFOA may be used as a replacement for perfluorooctane sulfonate (PFOS) in applications that had not previously used PFOA (US EPA 2002).

Industrial information was also obtained for the 2004 calendar year on the Canadian manufacture, import and export of perfluoroalkyl and fluoroalkyl (PFA/FA) substances, including PFCAs (Canada 2004). Information from this survey indicated no known manufacture of PFA/FA substances in Canada. The survey also indicated that the PFOA ammonium salt was imported into Canada in quantities ranging between 100 – 100 000 kg (Environment Canada 2005) under the North American Industry Classification System (NAICS) code “Chemical and Allied Product Wholesaler”.

PFOA has been synthesized by two main industrial processes: Simons electrochemical fluorination and telomerization (US EPA 2002). The first method relies on an electric current that is passed through a solution of anhydrous hydrogen fluoride containing, typically, an octanoic acid derivative. In this manner, all hydrogen atoms are replaced by fluorine, yielding 30–45% linear perfluorooctanoyl fluoride, along with a variable mixture of other isomers, homologues and by-products (US EPA 2002). The perfluorooctanoyl fluoride is then separated and hydrolyzed to yield a mix of ~ 70% linear and various branched isomers of PFOA (Riddell et al. 2009). The salts of PFOA are prepared by the base neutralization of the parent acid using the appropriate metal-containing base. The second method, telomerization, involves the reaction of a molecule known as a telogen (e.g., pentafluoroethyl iodide) with two or more molecules called taxogens (e.g., tetrafluoroethylene). This process yields telomer iodides, which can be

oxidized to produce a carboxylic acid—for instance, > 99% linear PFOA (Prevedouros et al. 2006)—and reacted with ethylene to produce a further iodide. These iodides can then be reacted to form a multitude of functional materials. The telomerization process generally results in mixtures of compounds with even ranges of carbon numbers.

## Uses

APFO is used primarily as a commercial polymerization aid in the manufacture of fluoropolymers such as polytetrafluoroethylene and polyvinylidene fluoride (US Government 2003; OECD 2006; Prevedouros et al. 2006), which are used in various sectors, including the automotive, electronics, construction and aerospace industries. Fluoropolymers are used in the manufacture of stain- and water-resistant coatings on textiles and carpet; hoses, cable and gaskets; non-stick coatings on cookware; and personal care products (US Government 2003). APFO is also used as a constituent in aqueous fluoropolymer dispersions, which are formulated into paints, photographic film additives and in the textile finishing industry (OECD 2006). Aqueous fire-fighting foams may also contain APFO as a component (OECD 2006; Prevedouros et al. 2006). Fluorochemicals that are potential PFOA precursors are used in the treatment of food packaging materials to enhance their properties as a barrier to moisture and grease (Begley et al. 2005). Thus, although APFO is typically not intended to remain in manufactured articles, trace amounts may be present as a contaminant or degradation product.

## Releases to the Environment

Releases to the environment may occur during manufacturing and processing operations and throughout the service life and subsequent disposal of articles containing PFOA. Potential point sources thus include direct releases from manufacturing or processing facilities. Indirect releases may result, for example, from the degradation or transformation of precursors in wastewater treatment plants (WWTPs) and landfills. Such precursors may include parent compounds or chemical products containing PFOA. Potential precursors include related fluorochemicals that are detectable in the atmosphere (e.g., 8:2 fluorotelomer alcohols [FTOHs], which have eight fluorinated carbons and a two-carbon ethyl alcohol group) and can degrade or transform to PFOA through biotic or abiotic pathways.

### Direct Releases

PFOA and its salts are not manufactured in Canada (Environment Canada 2001). There are no published data on direct releases to air, water or land from Canadian industrial facilities (Ellis et al. 2004b).

Muir and Scott (2003), Scott et al. (2003) and Boulanger et al. (2005) reported the presence of PFOA in sewage treatment plant (STP) effluents entering the Great Lakes.

Measured PFOA concentrations in treated effluents from STPs in Thunder Bay and Sault Ste. Marie, Ontario, ranged from 7.9 to 24 ng/L (Scott et al. 2003). PFOA was also measured in a North Toronto STP effluent at 38 ng/L (Muir and Scott 2003). Crozier et al. (2005) measured PFOA in effluent waters (concentrations ranging from 7 – 55 ng/L) and biosolids (concentrations ranging from 0.7 – 0.9 ng/g) from Ontario sewage treatment plants. Crozier et al. (2005) also noted that PFOA was detected at 7 ng/L in one STP influent and then measured at 7 ng/L in the same STP's effluent, suggesting no removal of PFOA during the sewage treatment plant processes. Precursors such as fluorotelomer saturated carboxylates (FTCAs) and FTOHs degradation products have been measured in influent and primary treatment samples, but not in secondary treatment waters (Sinclair and Kannan 2006).

Boulanger et al. (2005) conducted a lakewide mass budget analysis of eight perfluorooctane surfactants, including PFOA, for Lake Ontario. Boulanger et al. (2005) cited and used a 3M Company 1999 study which analyzed the finished effluents from six wastewater treatment plants (WWTP) for three perfluorinated compounds (PFCs), including PFOA. Four WWTPs were located in US cities with known sources of manufacture or industrial use of PFCs, and two WWTPs were located in US cities with no known sources. All WWTPs had detectable concentrations of PFOA, ranging from 41.2 to 2420 ng/L. Boulanger et al. (2005) used a PFOA concentration in WWTP effluent of  $549 \pm 840$  ng/L from this 3M Company 1999 study for the mass budget analysis. Boulanger et al. (2005) noted that there was a high degree of uncertainty associated with this concentration owing to the limited number of samples studied, and the study did not include actual WWTP effluent discharge to the Great Lakes system. The Boulanger et al. (2005) mass budget calculations showed the inflow from Lake Erie and wastewater discharges to be the major sources, whereas outflow through the St. Lawrence River was the dominant loss mechanism, indicating that there are unaccounted sources to Lake Ontario. Boulanger et al. (2005) suggested that the cleaning and care of surface-treated products by consumers and uses of perfluorooctane surfactants in industrial processes may lead to the presence of these substances in WWTP discharges. It was also suggested that discarded treated articles in landfills and the subsequent treatment of landfill leachates by municipal water treatment works may introduce significant amounts of perfluorooctane surfactants into the environment. Dinglasan-Panlilio and Mabury (2006) found that different fluorinated materials and/or products all contained free or unbound fluorinated telomer alcohols. The authors suggested that the residual fluorinated telomer alcohol contribution to the atmospheric load of fluorinated telomer alcohols is significant and may be the dominant source, given that the release of these residual fluorinated telomer alcohols may occur all along the supply chain from production through application to actual consumer use.

There are some Canadian data on releases of PFOA from landfills (i.e., garbage dumps, open-pit-burning dumps and metal waste dumps) (Ikonomou 2006). PFOA was detected in the Arctic landfill sediment at 22–1083 ng/g and in Kamloops, British Columbia landfill sediments up to 186 ng/g. PFOA was detected in landfill leachates in Waterloo, Ontario (458 ng/L), Cambridge, Ontario (1144 ng/L), Moncton, New Brunswick (88 ng/L), Halifax, Nova Scotia (2040 ng/L), Charlottetown, Prince Edward Island (642

ng/L), Toronto, Ontario (880 ng/L), Kelowna, British Columbia (146 ng/L), and Calgary, Alberta (238 ng/L). Based on the average concentration of PFOA, the annual estimated total loading in leachate is 0.1 kg (Conestoga-Rovers & Associates 2011). PFOA has been detected in landfill leachates (91.3–516 ng/L) (Kallenborn et al. 2004) in other countries that, like Canada, do not manufacture perfluorochemicals. The 6:2 FTOH, 8:2 FTOH and 10:2 FTOH (i.e., precursors to PFOA) have been measured in the air at two landfill sites in Ontario; concentrations were < 5000 pg/m<sup>3</sup> (upwind) and < 25 000 pg/m<sup>3</sup> for on-site (Ahrens et al. 2010b).

### Indirect Releases

Potential sources for the formation of PFOA, such as the degradation or transformation of precursors, could lead to indirect environmental releases and contribute to the total amount of PFOA found in the environment.

D'Eon et al. (2007) determined that PFOA can be formed from polyfluoroalkyl phosphate surfactants (PAPS) such as 8:2 PAPS via cleavage of the phosphate ester linkage, releasing free 8:2 FTOH, with subsequent biotransformation to PFOA. Lee et al. (2010) showed that microbial mediated biodegradation products (i.e., 8:2 FTOH and 10:2 FTOH) from 8:2 mono-substituted PAPS and 10:2 monosubstituted PAPS (which may be present in commercial products) may be present in WWTP influent and effluent.

Wallington et al. (2006) used a three-dimensional global atmospheric chemistry model (IMPACT) to indicate that *n*-C<sub>8</sub>F<sub>17</sub>CH<sub>2</sub>CH<sub>2</sub>OH (i.e., 8:2 FTOH) degrades in the atmosphere to give PFOA and other PFCA. Schenker et al. (2008) used a global-scale multispecies model (CliMoChem) to indicate that, until the year 2000, the contribution of atmospheric fluxes from perfluorooctanesulfonyl fluoride-based substances to the atmospheric deposition of PFOA in the Arctic was similar to the contribution from fluxes from FTOHs. Depending on the location and season, molar PFOA concentrations in the atmosphere are considered to be the correct order of magnitude to explain observed levels in Arctic biota (Wallington et al. 2006). The seasonal behaviour of PFOA is such that relatively high PFOA concentrations (>1.5 × 10<sup>3</sup> molecules/cm<sup>3</sup>) extend throughout the Arctic during the Arctic summer, whereas winter PFOA concentrations are lower by an order of magnitude (Wallington et al. 2006).

The formation of PFOA through the thermolysis of fluoropolymers has been reported by Ellis et al. (2001, 2003). The results from these studies indicate the potential for this process to produce PFOA. However, Ellis et al. (2001, 2003) stated that this process is unlikely to release significant quantities of PFOA to the environment and would not contribute to its long-range transport. The onset of thermolysis of fluoropolymers occurs at 365°C (not an environmentally relevant temperature). These temperatures could be reached in industry and in household applications and, as such, the thermolysis of fluoropolymers could be considered a source of PFOA.

FTOHs have been shown to metabolize to PFOA in rats and rainbow trout (Hagen et al. 1981; Butt et al. 2010b). A β-oxidation mechanism was proposed by Hagen et al. (1981)

to account for the formation of PFOA in rats. Butt et al. (2010a) found that exposure to 7:3 FTCA did not result from the formation and accumulation of PFOA in rainbow trout; however, PFOA was formed in the 8:2 FTCA and 8:2 fluorotelomer unsaturated carboxylate (FTUCA). The author proposed a beta-oxidation pathway proceeding from 8:2 FTUCA  $\rightarrow$  7:3  $\beta$ -keto acid  $\rightarrow$  7:2 ketone  $\rightarrow$  PFOA, or that PFOA could be formed directly through the  $\beta$ -oxidation of the 7:3 keto acid. Butt et al. (2010b) exposed rainbow trout to 8:2 fluorotelomer acrylate (FTAc) via dietary exposure and found that 8:2 FTCA, 8:2 FTUCA and 7:3 FTCA were formed; however, the overall formation and accumulation of PFOA was low. Frömel and Knepper (2010) suggested that ultimate ethoxylate shortening of fluorotelomer ethoxylates (FTEOs) may result in FTOHs and thus contribute as a potential source of PFCs such as PFOA.

Dinglasan et al. (2004) showed aerobic biodegradation of 8:2 FTOH with an initial half-life of  $\sim$ 0.2 day per milligram of initial biomass protein followed by a second half-life of 0.8 day per milligram in a mixed microbial culture obtained from sediment and groundwater taken from a contaminated site, enriched on 1,2-dichloroethane and subsequently maintained using ethanol as the sole carbon source. This mixed culture was chosen because it was acclimated to degradation of chlorinated alkanes and alcohols and, therefore, considered to be active on fluorinated alcohols. The degradation of the alcohol occurred primarily through a mechanism leading to a telomer acid, which then underwent  $\beta$ -oxidation to yield PFOA, accounting for 3% of the total mass of FTOH initially at day 81. However, because this study was limited to identification and quantification of known or predicted transformation products, potential unknown transformation products were not identified. FTOHs were capable of metabolizing to PFOA in municipal wastewater treatment sludge (Pace Analytical 2001). Liu et al. (2007b) showed the microbial transformation of 8:2 FTOH to PFOA in clay soil and two pure soil bacterial cultures (*Pseudomonas* species).

Wang et al. (2005) conducted aerobic biodegradation studies of  $^{14}\text{C}$ -labelled 8:2 FTOH in diluted activated sludge from a WWTP. Three transformation products were identified: 8:2 saturated acids, 8:2 unsaturated acids and PFOA, representing 27%, 6.0% and 2.1%, respectively, of the initial  $^{14}\text{C}$  mass after 28 days. Results suggested that perfluorinated acid metabolites such as PFOA account for only a very small portion of the transformation products observed over the time frame considered (Wang et al. 2005). Wang et al. (2005) also suggested that the biological fate of 8:2 FTOH is determined by multiple degradation pathways, with neither  $\beta$ -oxidation nor any other enzyme-catalyzed reaction as a single dominant mechanism. A study by Dinglasan et al. (2005) showed that the oxidation of the 8:2 FTOH to the telomer acid occurred via the transient telomer aldehyde. The telomer acid was then further transformed via a  $\beta$ -oxidation mechanism, leading to the unsaturated acid and PFOA. However, a complete mass balance was not achieved, and the authors attributed this to binding of metabolites to biomass and other biological macromolecules, unaccounted metabolites, uptake of intermediates (formation of covalent linkages) or alternative degradation pathways (Dinglasan et al. 2005).

FTOHs may be released from polymeric materials or chemicals that incorporate FTOHs, or residual amounts of FTOHs that failed to be covalently linked to polymers or

chemicals during production. FTOHs are used in fire-fighting foams, personal care and cleaning products, and oil, stain, grease and water repellent coatings on carpet, textiles, leather and paper (US EPA 2006a). FTOHs are also used in the manufacture of a wide range of products, such as paints, adhesives, waxes, polishes, metals, electronics and caulks. During the years 2000–2002, an estimated  $5 \times 10^6$  kg of these compounds per year were produced worldwide, 40% of which was in North America (Dinglasan et al. 2004). Fluorotelomer-based raw materials and products are manufactured by a series of steps, beginning with Telomer A. Global Telomer A production between 2000 and 2002 was between 5000 and 6000 tonnes per year (Prevedouros et al. 2006).

Yoo et al. (2010) measured FTOHs in soil from fields (near Decatur, Alabama) to which sewage sludge had been applied. Sludges generated at a WWTP in Decatur, Alabama, have been applied to agricultural fields for more than decade; this WWTP received waste streams from industries that work with fluorotelomer compounds (Washington et al. 2010). Yoo et al. (2010) found that sludge-amended fields had surface soil FTOH concentrations ranging from 5 to 73 ng/g dry weight. The highest FTOH concentration was for 10:2 FTOH, which had concentrations ranging from < 5.6 to 166 ng/g dry weight. The half-lives for FTOHs ranged from 0.85 to 1.8 years, suggesting that sludge application is a possible pathway for the degradation of FTOHs to PFOA and other PFCAs. Washington et al. (2010) also found that these sludge-amended fields have high concentrations of PFCAs, including PFOA (<320 ng/g dry weight).

Measured vapour pressures of FTOHs range from 140 to 990 Pa. The calculated dimensionless Henry's Law constants for this class of compounds (e.g., 270 at 25°C for 8:2 FTOH) using the limited data available for water solubility and vapour pressure reveal the propensity of these compounds to partition to air (Dinglasan et al. 2004). Ellis et al. (2004a) showed the potential for FTOHs to react in the atmosphere with hydroxyl radicals to yield PFOA. Smog chamber studies indicate that FTOHs can degrade in the atmosphere to yield a homologous series of PFCAs (Ellis et al. 2004a). It is believed that oxidation of FTOHs in the atmosphere is initiated by reaction with hydroxyl radicals (Dinglasan et al. 2004; Ellis et al. 2004a). It was shown that perfluorooctyl sulphonamides react with hydroxyl radicals to yield PFOA (Hatfield et al. 2002). Although these experiments were conducted at environmentally unrealistically high concentrations of hydroxyl radicals and the results were qualitative rather than quantitative, they do show the potential for related products to react atmospherically to produce PFOA.

Stock et al. (2004, 2007) showed that there is a significant concentration of FTOHs present and widely disseminated in the North American atmosphere. A recent air sampling campaign detected FTOHs at tropospheric concentrations typically ranging from 17 to 135 pg/m<sup>3</sup>, with urban locations having higher concentrations than rural areas (Martin et al. 2002; Stock et al. 2004). Loewen et al. (2008) studied atmospheric concentrations of FTOHs and lake water concentrations over an altitudinal transect in western Canada. Lake water samples were collected at Cedar Lake (a small lake near Golden, British Columbia), at Bow Lake in Banff National Park (Banff, Alberta) and at another unnamed small lake in Banff National Park (Banff, Alberta). Passive air samplers

were deployed on altitudinal transects (800–2740 above sea level) from Golden, British Columbia, to Banff National Park. Loewen et al. (2008) noted that the amount of 8:2 and 10:2 FTOHs (<2.0 ng/sampler) increased with increasing altitude. Lake water concentrations of PFOA along the elevation transect were below 1 ng/L. No clear trend was evident between altitude and PFOA concentrations. Ellis et al. (2004a) and Wallington et al. (2006) indicated that telomer alcohols may be responsible in part for the presence of PFCAs in the Arctic and other non-urban areas where concentrations of peroxy radicals far exceed those of nitrogen oxides. It was noted that since the reaction of 8:2 FTOH with nitric oxide competes with the reaction that forms PFOA, the formation of PFOA should decrease with increasing nitrogen oxide concentrations. The production of PFOA is therefore suppressed in source regions that typically have nitrogen oxide concentrations of 100 parts per trillion (ppt) or greater.

In conjunction with the atmospheric measurements of the alcohols made by Martin et al. (2002) and Stock et al. (2004) and with the profile of the linear to branched isomers observed in Canadian Arctic samples (De Silva and Mabury 2004), Ellis et al. (2004a) concluded that telomer alcohols were a plausible source for some PFOA in remote regions. This conclusion is supported by Stock et al. (2007), who measured FTOHs in air at Cornwallis Island, Nunavut, in 2004. Mean concentrations of FTOHs ranged from 2.8 to 14 pg/m<sup>3</sup>. This conclusion is also supported by observations of PFOA in US rainwater (Scott et al. 2003, 2006b). These results indicate that FTOHs are widely disseminated in the troposphere and are capable of long-range atmospheric transport. In addition, De Silva et al. (2009) detected branched PFOA isomers in Arctic and Lake Ontario sediment and surface water, Lake Ontario biota and humans; however, branched PFOA isomers were not detected in ringed seals and polar bears above the detection limits (3.6 ng/g).

Gewurtz et al. (2009) found PFOA as well as 8:2 FTUCA and 10:2 FTUCA in window film concentrations from indoor/outdoor/downtown/suburban/rural/carpet stores locations in Toronto, Ontario. Nilsson et al. (2010) found PFCs, including PFOA, in the blood of ski wax technicians (PFOA concentrations ranged from 4.8 to 535 ng/L). Nilsson et al. (2010) suggested that fluorinated organic compounds are added to glide waxes to prevent adhesion of snow, ice and dirt; fluorinated ski waxes are applied using heat of approximately 130–220°C, during which airborne particles and fumes containing a blend of gaseous organochlorine compounds are emitted. However, the authors did not analyze the glide waxes themselves to determine the presence of PFCs.

## Environmental Fate

The high water solubility of PFOA, coupled with the negligible volatility of ionized species, suggests that all PFOA species will partition primarily to the aquatic environment. Solubility is dependent on the acid dissociation constant ( $pK_a$ ) of the acid form. Goss (2008) suggested that PFOA is expected to have a low  $pK_a$ , such that > 99% of the compound will occur in its anionic form (i.e., PFO) under most environmental conditions. As such, modelling results presented in peer-reviewed literature for global fate, transport/partitioning and bioaccumulation should be viewed with caution, as they

may not have accounted for the pH of the environmental compartment in conjunction with the  $pK_a$  values of the compound. The ammonium salt of PFOA may have some ability to re-enter the gas phase from water (US EPA 2002). However, studies have shown that if this process occurs, then it occurs to a negligible extent around pH 8.5 (Oakes et al. 2004).

Once in the aqueous phase, PFOA may partition to sediments, as evident by its detection in this medium (Giesy and Newsted 2001; Stock et al. 2007). A comparison of concentrations observed in the aqueous phase and in sediments suggests that sediments are unlikely to be a major sink for PFOA (Oakes et al. 2004; Masunaga and Odaka 2005). However, the adsorption and desorption properties of APFO were investigated in one activated sludge sample and four soil samples (Dekleva 2003). Dekleva (2003) found that the average adsorption of APFO ranged from 40.8% to 81.8%. Adsorption coefficient ( $K_d$ ) values ranged from 0.41 to 36.8 L/kg. Organic carbon adsorption coefficient ( $K_{oc}$ ) values ranged from 48.8 to 229 L/kg, and organic matter adsorption coefficient ( $K_{om}$ ) values ranged from 28.4 to 133 L/kg. These values indicate that PFOA is more likely to sorb to organic carbon in soils than to other soil solids. Moody and Field (1999) suggested that since PFOA could be measured in groundwater in areas where PFOA is no longer used, a fraction of the compound must be bound to soil and slowly released to water. However, it is recognized that the presence in groundwater may simply reflect the slow migration of PFOA rather than soil binding. It is unlikely that terrestrially deposited PFOA will undergo any long-range transport (Franklin 2002).

## Persistence and Bioaccumulation Potential

### Persistence

Available data indicate that PFOA does not significantly photodegrade under relevant environmental conditions (Todd 1979; Nubbe et al. 1995; Scrano et al. 1999; Hatfield 2001; Hori et al. 2004, 2005, 2008), does not hydrolyze (Ellis et al. 2004b), does not undergo significant abiotic or biotic degradation (Reiner 1978; 3M Company 1979, 1980b, 1985b; Pace Analytical 1997; Oakes et al. 2004; Moriwaki et al. 2005; Cheng et al. 2008), and is not susceptible to reductive fluorination by anaerobic microbial communities (Liou et al. 2010).

**Table 4. Summary of persistence data**

PFOA identity	Medium	Study	Degradation half-life	References
Conjugate base	Water	Photolysis	> 349 days	Todd 1979; Hatfield 2001
Conjugate base	Water	Photolysis Hydrolysis Biodegradation Volatility	> 35 days	Oakes et al. 2004
Conjugate base	Water	Hydrolysis	~ 235 years	US EPA 2002
Conjugate base	Air	Hydroxyl reaction	~ 90.1 days	Hurley et al. 2004
Conjugate base	Sludge	Biodegradation	> 2.5 months	Pace Analytical

PFOA identity	Medium	Study	Degradation half-life	References
				2001
Conjugate base	Soil/sludge	Anaerobic microbial reductive fluorination	> 110 days	Liou et al. 2010

Half-life values for PFOA and its salts are estimated and remain highly speculative owing to the short study periods. The atmospheric lifetime of PFOA with respect to hydroxyl radicals has been predicted to be 130 days (Hurley et al. 2004). Franklin (2002) calculated an atmospheric lifetime of PFOA to be in the order of days when it was emitted from a ground source, and therefore likely not subject to long-range transport. However, if PFOA is produced from an atmospheric source (i.e., via precursors) and if the major loss mechanism is wet or dry deposition, then it may have a lifetime of 20–30 days before deposition (Ellis et al. 2004b). This would be sufficient time to allow transport over many thousands of kilometres, implying a long-range transport mechanism. The presence of PFOA in the Canadian Arctic also may provide evidence for the long-range transport of either PFOA (e.g., via ocean currents) (Caliebe et al. 2004; Yamashita et al. 2005) or volatile precursors to PFOA through the atmosphere (Stock et al. 2007). Webster and Ellis (2010) proposed sea spray as a mechanism for the generation of PFOA in the gas phase from PFO in a water body, which has the potential to contribute large amounts of PFOA to the atmosphere and thereby significantly contribute to the concentrations measured in remote areas.

There is a possibility that the presence of PFCs in the Canadian Arctic may be due, in part, to the presence of former military bases (Iqaluit, Sarcpa Lake, Resolution Island) and/or Distant Early Warning Line (DEW) stations (northern shores of Alaska to Cape Dyer on the Baffin Island coast) that may have used perfluorinated-based products (Stow et al. 2005; Poland et al. 2001). These sites are considered remediated, but PFCs such as PFOA were not measured or analyzed, with available literature (Stow et al. 2005; Poland et al. 2001) only identifying the concentrations of polychlorinated biphenyls (PCBs) and metals during the remediation process. PFOA has been detected in Arctic landfills at 22–1083 ng/g (i.e., garbage dumps, open-pit-burning dumps and metal waste dumps) (Ikonomou 2006), suggesting that there are sources from local consumer/industrial activities. Nonetheless, PFOA has been measured in biota and various environmental media in remote Arctic areas far from local or regional sources.

A suggested hypothesis for the presence of PFOA in biota in remote regions is that a precursor (e.g., FTOHs) is emitted to the atmosphere and ultimately degrades to yield PFOA through biotic and abiotic degradation. Ellis et al. (2004a) showed that the atmospheric lifetime of short-chain FTOHs, as determined by their reaction with hydroxyl radicals, was approximately 20 days. Piekarz et al. (2007) estimated that atmospheric residence times of 6:2 FTOH, 8:2 FTOH and 10:2 FTOH were 50, 80 and 70 days, respectively.

Shoeib et al. (2006) collected air samples during a crossing of the North Atlantic and the Canadian Arctic Archipelago in July 2005 to investigate concentrations of FTOHs. The

highest concentrations of FTOHs were for 8:2 FTOH (5.8–26 pg/m<sup>3</sup>), followed by 10:2 FTOH (1.9–17 pg/m<sup>3</sup>) and then 6:2 FTOH (ND–6.0 pg/m<sup>3</sup>). Ju et al. (2008) measured PFOA in the sea microlayer (air/water interface) and subsurface seawater near the Dalian coastal waters in China. PFOA concentrations in the sea microlayer ranged from 0.26 to 1.19 ng/L. In the subsurface water, PFOA concentrations ranged from 0.17 to 0.67 ng/L. The detection of PFOA in oceanic waters suggests another potential mechanism for its long-range transport to remote locations such as the Canadian Arctic.

Mass calculations for marine transfer of PFO to the Arctic resulted in a flux between 2 and 12 tonnes per year using pK<sub>a</sub> between 2–3 at pH 4 and 7 (Prevedouros et al. 2006). Armitage et al. (2006) estimated a net PFO flux of between 8 and 23 tonnes per year to the Arctic using pK<sub>a</sub> between 2.5–2.8 at pH 5–8. PFOA was measured in polar ice caps from three areas in the High Arctic (Melville ice cap, Northwest Territories; Agassiz ice cap, Nunavut; and Devon ice cap, Nunavut) (Young et al. 2007). PFOA concentrations ranged from 0.012 to 0.147 ng/L, suggesting that contamination may be a result of atmospheric input. Between 1996 and 2005, there was no significant trend of PFOA concentrations (regression analysis,  $p = 0.140$ ) (Young et al. 2007). Fluxes were calculated using the density corrected concentration, multiplied by the yearly accumulation. These fluxes are estimates and may not be representative of actual deposition in this region due to wide variations in precipitation rates. PFOA showed a flux ranging between 114–587 kg/year in 2005 (Young et al. 2007).

In summary, PFOA has the potential for long-range transport and has been shown to be persistent, with studies indicating no abiotic or biotic degradation in the environment under relevant environmental conditions. Therefore, based on the empirical and physical-chemical properties, PFOA and its salts meet the persistence criteria in water, soil, sediment and air (half-lives in soil and water  $\geq 182$  days and half-life in sediment  $\geq 365$  days; half-life in air  $\geq 2$  days or evidence of atmospheric transport to remote regions such as the Arctic) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

### **Bioaccumulation**

PFCAs, including PFOA, have the combined properties of oleophobicity, hydrophobicity, and hydrophilicity over different portions of these molecules. The carboxylate functional group attached to the perfluorinated chain, for example, imparts polarity to the molecule. Due to these properties, the assumption that the hydrophobic and lipophilic interactions between compound and substrate are the main mechanisms governing partitioning is considered not applicable for PFOA. Although the octanol-water partition coefficient ( $K_{ow}$ ) has been calculated or modelled for the neutral form of PFOA and its various salts (see Table 2), current literature suggests that the  $K_{ow}$  is a problematic parameter for ionized surfactants because of their tendency to aggregate at the interface of a liquid-liquid system. Consequently, the  $K_{ow}$  has not been considered a reliable indicator of bioaccumulation potential for perfluorinated substances. However, Webster and Ellis (2011) are stating that PFCAs, including PFOA, are not surface-active, and that the  $K_{ow}$  is a predictor of both lipid and protein partitioning in biota. Therefore, the authors are

stating that the equilibrium distribution models for the hydrophobic neutral partitioning of PFCAs, including PFOA, are applicable.

Regulatory criteria (bioconcentration factors [BCFs] and bioaccumulation factors [BAFs]) have been developed under CEPA 1999 (Canada 1999) to determine whether a substance is to be considered bioaccumulative. However, these threshold criteria are based on historical experience with neutral, non-metabolized organic substances. These criteria, based on the Federal Toxic Substances Management Policy (TSMP) persistence and bioaccumulation criteria, were developed in the mid-1990s and formally published in 1995 (Canada 1995b). The criteria identify lipophilic substances with the potential to bioaccumulate, primarily in freshwater aquatic systems (fish). Substances that meet the criteria, i.e.,  $BAF$  or  $BCF \geq 5000$  or  $\log K_{ow} \geq 5$ , have significant potential for bioaccumulation at the organism level and biomagnification through the food web. However, information on BAFs, BCFs or  $\log K_{ows}$  is only one part of the overall weight of evidence in determining the overall potential of a substance to accumulate in organisms. Furthermore, a substance may be deemed to be sufficiently bioaccumulative to cause concern, even if regulatory criteria are not met.

Given the number of available experimental studies, the emphasis in this assessment has been placed on the results of experimental bioaccumulation and biomagnification studies.

#### *Bioaccumulation/Bioconcentration/Biomagnification Studies*

PFOA is absorbed in juvenile rainbow trout (*Oncorhynchus mykiss*), with a BCF of 4.0 (Martin et al. 2003b). Dietary exposure to PFOA in the same species did not result in PFOA bioaccumulation ( $BAF = 0.038$ ) (Martin et al. 2003b). Carp (*Cyprinus carpio*) were exposed to two concentrations of PFOA (5 and 50  $\mu\text{g/L}$ ) for 28 days in a flow-through system (Kurume Laboratory 2001). The chemical was prepared for exposure by using a dispersant made up of hydrogenated castor oil and mixed in acetone. Water quality was monitored daily for the duration of the experiment. BCFs ranged from 3.1 at the low concentration to  $<5.1$ – $9.1$  at the high concentration, indicating low bioaccumulation (Kurume Laboratory 2001). Although experiments with fish and other aquatic species provide evidence that PFOA is not highly bioaccumulative, these results should not be extrapolated to other non-aquatic animals. Fish gills may provide an additional mode of elimination and uptake that air-breathing organisms such as birds, terrestrial organisms and marine mammals do not possess (Kelly et al. 2004). The high water solubility of PFOA causes its tendency to escape from the gills into water to be relatively high, whereas the tendency of PFOA to escape to air across the alveolar membrane of the lung is relatively low because of its low vapour pressure and negative charge. For example, the half-life of PFOA in fish was 3 days (Martin et al. 2003a), whereas the half-life in male rats was 11 days (Ylinen and Auriola 1990); in humans, it was 4.37 years (Kudo and Kawashima 2003) and 3.8 years (Olsen et al. 2007).

Two species of wild turtles (red-eared slider, *Trachemys scripta elegans*; and Reeves' turtle, *Chinemys reevesii*) were examined for BCFs. In Japan, these turtles occupy the highest trophic level of the food chain in the river ecological system and have small territories (Morikawa et al. 2006). PFOA concentrations in surface water ranged from

16.7 to 87 100 ng/L, and PFOA was observed in almost all serum samples (91 of 94), where concentrations ranged from <200 to 870 000 ng/L. The calculated serum BCFs ranged from 0.8 to 15.8 (Morikawa et al. 2006). The authors noted that the reported BCFs decreased as PFOA concentrations in surface water increased, suggesting that the absorption of PFOA from the gut might be a saturable process. However, it should be noted that these BCFs are actually BAFs, as the wild turtles' exposure to PFOA was probably not limited to surface water only.

Kannan et al. (2005a) measured PFOA concentrations in a benthic food chain of the Great Lakes and found that despite relatively high concentrations of PFOA in water, it was not detected in invertebrates or fish. Preliminary (unpublished) results from one Canadian Arctic study showed a biomagnification factor (BMF) of 8 from ringed seal (*Pusa hispida*) liver to polar bear (*Ursus maritimus*) liver (Butt and Smithwick 2004). In the pelagic aquatic food web of Lake Ontario, PFOA concentrations did not increase with increasing trophic level (as determined by stable isotopes of nitrogen) (Martin et al. 2004b). In fact, PFOA concentrations were lower in the top-predator lake trout (*Salvelinus namaycush*) than in the invertebrate opossum shrimp (*Mysis relicta*) (Table 5). For example, a trophic magnification factor (TMF) for PFOA was calculated as 0.37 for the slimy sculpin (*Cottus cognatus*)–burrowing amphipod (*Diporeia hoyi*) relationship; for the upper end of the food web (*Mysis relicta*–alewife [*Alosa pseudoharengus*]–rainbow smelt [*Osmerus mordax*]–lake trout), the calculated TMF was 0.58 (Martin et al. 2004b). The different ends of the aquatic food web could indicate differences in benthic and pelagic natures of the relationships. TMFs less than 1 indicate no biomagnification. In another study, the trophic level–corrected BMFs were calculated for several Arctic biota (Tomy et al. 2004). Tomy et al. (2004) determined TMFs for the entire food web based on the relationship between  $\delta^{15}\text{N}$  and contaminant concentration. Trophic level was determined relative to the clam, which was assumed to have a trophic level of 2 (i.e., primary herbivore). For each individual sample of zooplankton, fish and marine mammal, trophic level was determined using the following relationship:

$$\text{TL consumer} = 2 + (\delta^{15}\text{N consumer} - \delta^{15}\text{N clam}) / 3.8$$

where TL consumer is the trophic level of the organism and 3.8 is the isotopic enrichment factor. The second method determined biomagnification factors ( $\text{BMF}_{\text{TL}}$ ) for individual species corrected for trophic level:

$$\text{BMF}_{\text{TL}} = [\text{predator}] / [\text{prey}] / (\text{TL predator}/\text{TL prey})$$

where [predator] and [prey] are the wet weight (ww) concentrations of analyte in the predator and prey species, respectively, and TL is the trophic level based on  $\delta^{15}\text{N}$  for the predator and prey. The resulting BMFs for PFOA were often greater than 1, suggesting a potential for PFOA to biomagnify for the clam (*Mya truncata*; *Serripes groenlandica*)–walrus (*Odobenus rosmarus*), Arctic cod (*Boreogadus saida*)–narwhal (*Monodon monoceros*) and cod–beluga (*Delphinapterus leucas*) food chain (Table 5). These results may reflect food web differences and perhaps not only the bioaccumulation potential for PFOA (e.g., one food web had fish as a top predator and the other had a mammal).

Martin et al. (2004a) found that polar bears, which occupy the highest trophic level in the Canadian Arctic, have higher levels of PFOA than all other Arctic organisms examined. Butt et al. (2008) determined regionally-based ringed seal/polar bear BMF values for PFOA that ranged from 45 – 125. These regionally based BMFs were calculated by grouping ringed seal populations to corresponding similarly located polar bear populations in the Canadian Arctic. Tomy et al. (2009) determined PFOA TMFs for a marine food web in the western Canadian Arctic (Hendrickson Island and Holman Island) comprising of the Beaufort Sea beluga whale (*Delphinapterus leucas*), ringed seal (*Phoca hispida*), Arctic cod (*Boreogadus saida*), Pacific herring (*Clupea pallasii*), Arctic cisco (*Coregonus autumnalis*), a pelagic amphipod (*Themisto libellula*), and a Arctic copepod (*Calanus hyperboreus*). TMFs ranged from 0.1 (ringed seal/Arctic cod) to 2.2 (Arctic cod/*Calanus hyperboreus*).

Houde et al. (2005) reported BMFs of 1.8–13 using whole-prey homogenates and whole-body bottlenose dolphin (*Tursiops truncatus*) conjugate base concentrations in the bottlenose dolphin food web at Charleston, South Carolina. Kelly et al. (2009) found a TMF of 3.28 over the Canadian Arctic (Hudson Bay region) marine food web (macroalgae, bivalves, fish, seaduck and beluga whale). Martine van den Heuvel-Greve et al. (2009) found BMFs of 3.8 and 23, respectively, for the benthic and the pelagic food webs with harbour seals (*Phoca vitulina*) as the apex predator. BMFs for other species in the Westerschelde, Netherlands estuary ranged from 0.03 to 31.

Jeon et al. (2010a) studied the effects of salinity on the whole-body bioaccumulation of PFCs, including PFOA, in the Pacific oyster (*Crassostrea gigas*). With increasing salinity (10–34 practical salinity units [psu]), the BCFs fluctuated from 0.8 to 3.0 whereas the BAFs increased from 9.6 to 19.4. The authors suggest that the increased accumulation is mainly because of the increase in dietary uptake due to a possible altered physiology of oysters with changing salinity. The authors also suggest that there is an enhanced sorption of PFCs to particulate matter, which can increase the risks to benthic organisms and filter-feeding bivalves.

Jeon et al. (2010b) determined the serum and liver BCFs of PFCs, including PFOA, on blackrock fish (*Sebastes schlegeli*) at varying salinities (10, 17.5, 25 and 34 psu). The bioconcentration at 34 psu was greater for the PFCs (except for PFOA) than at other salinities. The serum BCFs ranged between 578 (at 10 psu) and 357 (at 34 psu). The liver BCFs ranged from 73 to 93.

Kwadijk et al. (2010) determined the BAFs between water and eel (30–45 cm fillets) (*Anguilla anguilla*) from 21 locations in the Netherlands. The water-eel BAF for PFOA was calculated to be 1.09 and the BAF for the linear isomer of PFOA was 1.12.

Table 5 provides a summary of the available bioaccumulation data.

**Table 5. Summary of bioaccumulation data**

Species <sup>1</sup> (tissue)	BAF	BCF	BMF	TMF	References
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Species <sup>1</sup> (tissue)	BAF	BCF	BMF	TMF	References
Juvenile rainbow trout (carcass)	0.038	4.0			Martin et al. 2003a, b
Juvenile rainbow trout (liver)		8.0			Martin et al. 2003b
Juvenile rainbow trout (blood)		27			Martin et al. 2003b
Carp		3.1–9.1			Kurume Laboratory 2001
Wild turtles (serum)	0.8–15.8				Morikawa et al. 2006
Fathead minnow (whole body)		1.8			3M Company 1995
Polar bear (liver) : ringed seal (liver)			8		Butt and Smithwick 2004
Polar bear (liver): ringed seal (liver)			45-125		Butt et al. 2008
Walrus (liver) : clam (whole body)			1.8		Tomy et al. 2004
Narwhal (liver) : cod (whole body)			1.6		Tomy et al. 2004
Beluga (liver) : cod (whole body)			2.7		Tomy et al. 2004
Beluga (liver) : deepwater redfish (liver)			0.8		Tomy et al. 2004
Black-legged kittiwake (liver) : cod (whole body)			0.3		Tomy et al. 2004
Glaucous gull (liver) : cod (whole body)			0.6		Tomy et al. 2004
Cod (whole body) : zooplankton (whole body)			0.04		Tomy et al. 2004
<i>Mysis relicta</i> : alewife : smelt : lake trout; whole-body homogenates				0.37-0.58	Martin et al. 2004b
Ringed seal/Arctic cod (liver)				0.1	Tomy et al. 2009
Beluga/Arctic cod (liver)				0.9	Tomy et al. 2009
Beluga/ Pacific herring (liver)				1.3	Tomy et al. 2009
Beluga/ Arctic cisco (liver)				0.7	Tomy et al. 2009
Cod (liver)/ <i>Calanus hyperboreus</i> (whole body)				2.2	Tomy et al. 2009
Cod (liver)/ <i>Themisto libellula</i> (whole body)				0.8	Tomy et al. 2009
Lake trout : alewife	0.63				Martin et al. 2004b
Lake trout : smelt	0.5				Martin et al. 2004b
Lake trout : sculpin	0.02				Martin et al. (2004b)
Bottlenose dolphin (whole body) : prey (whole body)			1.8–13		Houde et al. 2005
Sediment : macroalgae : bivalves: fish : seaduck : beluga whale				3.28	Kelly et al. 2009
Zooplankton/Herring			1.6		van den Heuvel-Greve et al. (2009)
Herring/Sea bass			0.6		van den Heuvel-

Species <sup>1</sup> (tissue)	BAF	BCF	BMF	TMF	References
					Greve et al (2009)
Herring/Harbour seal			14		van den Heuvel-Greve et al (2009)
Sea bass/Harbour seal (benthic food web for Harbour seal)			23	1.2	van den Heuvel-Greve et al (2009)
Peppery furrow shell/flounder			31		van den Heuvel-Greve et al (2009)
Lugworm/flounder			0.03		van den Heuvel-Greve et al (2009)
Flounder/Harbour seal (pelagic food web for Harbour seal)			3.8	1.2	van den Heuvel-Greve et al (2009)
<i>Chlorella ellipsoidea</i> / Pacific oyster	9.6–19.4	0.8–3.0			Jeon et al. (2010a)
Water/sediment/eel	1.09–1.12				Kwadijk et al. (2010)
Seawater/blackrock fish (serum)		357–578			Jeon et al. (2010b)
Seawater/blackrock fish (liver)		73–93			Jeon et al. (2010b)

Abbreviation: NA, not available.

<sup>1</sup> Species names not given in text: fathead minnow (*Pimephales promelas*); deepwater redfish (*Sebastes mentella*); black-legged kittiwake (*Rissa tridactyla*); glaucous gull (*Larus hyperboreus*).

The minimum concentration of a substance in an organism that will cause an adverse effect (the critical body burden) is used to determine the potential to cause direct toxicity. From a physiological perspective, it is the concentration of a substance at the site of toxic action within the organism that determines whether a response is observed, regardless of the external concentration. When the potential for toxicity in consumer organisms is being determined, it is also the concentration in the whole body of a prey item that is of interest, since the prey is often completely consumed by the predator (including individual tissues and organs, such as the liver and blood). As perfluorinated substances partition to liver and blood, the site of toxic action is often considered to be the liver. Thus, from a toxicological perspective, bioaccumulation (BCFs, BAFs and BMFs) based on concentrations in individual organs, such as the liver, may be more relevant when the potential for direct organ-specific toxicity (i.e., liver toxicity) is being predicted.

Bioaccumulation may also indicate either direct exposure in organisms that have accumulated PFOA, or indirect exposure in organisms that consume prey containing PFOA (via food chain transfer). This is especially true for organisms at the higher trophic levels (e.g., polar bear), where whole-body analysis is not feasible. While it is feasible to measure whole-body bioaccumulation in smaller species at lower trophic levels, the lower trophic status of the organism means that the estimated overall bioaccumulation for perfluorinated substances may be underestimated. BCFs and (particularly) BMFs based on concentrations in whole organisms may provide a useful measure of overall potential for transfer up the food chain. Conder et al. (2008) noted that the concentration of

perfluorinated acids on a whole body mass basis has been estimated to be 2–10 times lower than the concentrations of perfluorinated acids in blood and liver of trout.

As such, it is considered that based on whole-body data, PFOA has low to moderate potential to accumulate in aquatic species. However, based on organ-specific data, PFOA may be considered to accumulate and biomagnify in terrestrial and marine mammals. Therefore, based on the available empirical values, PFOA and its salts do not meet the bioaccumulation criterion (BAF or BCF  $\geq$  5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000a). However, there is scientific evidence that PFOA and its salts accumulate and biomagnify in terrestrial and marine mammals.

## Potential to Cause Ecological Harm

### Ecological Exposure Assessment

#### *Air*

Loewen et al. (2008) studied atmospheric concentrations and lake water concentrations of FTOHs over an altitudinal transect in western Canada. Lake water samples were collected at Cedar Lake (a small lake near Golden, British Columbia), at Bow Lake in Banff National Park (Banff, Alberta) and at another unnamed small lake in Banff National Park (Banff, Alberta). Passive air samplers were deployed on altitudinal transects (800–2740 above sea level) from Golden, British Columbia, to Banff National Park. Loewen et al. (2008) noted that the amount of 8:2 and 10:2 FTOHs (<2.0 ng/sampler) increased with increasing altitude. Lake water concentrations of PFOA along the elevation transect were below 0.001  $\mu\text{g/L}$ . No clear trend was evident between altitude and PFOA concentrations in lake water.

Stock et al. (2007) took air samples on Cornwallis Island, Nunavut, where mean values of total concentrations of FTOHs ranged from 2.8 (10:2 FTOH) and 14  $\text{pg/m}^3$  (8:2 FTOH). PFOA was also measured in particulates at a mean concentration of 1.4  $\text{pg/m}^3$ .

Shoeib et al. (2006) took twenty high-volume air samples during a crossing of the North Atlantic and Canadian Archipelago in July 2005 (Gothenburg, Sweden to Barrow, Alaska via the North Atlantic and Canadian Archipelago). The highest concentrations (sum of gas- and particle-phases) of FTOHs were for 8:2 FTOH at 5.8–26  $\text{pg}/\text{m}^3$ , followed by 10:2 FTOH at 1.9–17  $\text{pg}/\text{m}^3$  and 6:2 FTOH at below detection to 6.0  $\text{pg}/\text{m}^3$ . For comparison purposes, Shoeib et al. (2006) also collected air samples at a semi-urban site in Toronto in March 2006 where the mean 8:2 FTOH concentration in Toronto was 41  $\text{pg}/\text{m}^3$ . Dreyer et al. (2009) conducted high volume air sampling in the Atlantic Ocean, the Southern Ocean and the Baltic Sea. PFOA was detected in the particle fraction with a maximum concentration of 6  $\text{pg}/\text{m}^3$ . 6:2 FTOH and 8:2 FTOH were dominant in the gas-phase fraction. The concentrations of 8:2 FTOH were between 1.8 and 130  $\text{pg}/\text{m}^3$ . The sum of all the FTOHs (4:2 FTOH, 6:2 FTOH, 8:2 FTOH, 10:2 FTOH and 12:2 FTOH) ranged between 0.3–47  $\text{pg}/\text{m}^3$ .

### *Water*

Moody et al. (2002) measured PFOA concentrations in surface waters in Etobicoke Creek, a tributary to Lake Ontario, after an accidental release of aqueous fire-fighting foam. The malfunction released 22 000 L of fire retardant foam and 450 000 L of water from the sprinkler system into storm sewers leading to Spring Creek (approximate travel distance of 1.8 km) and subsequently to Etobicoke Creek, which empties into Lake Ontario. Background concentrations were also measured at an upstream site. Results indicated downstream PFOA concentrations up to 11.3  $\mu\text{g}/\text{L}$ . PFOA was also detectable at the upstream site at lower concentrations (ND–0.033  $\mu\text{g}/\text{L}$ ).

Scott et al. (2009) sampled 38 rivers (upstream and downstream of populated areas) across Canada for PFCs during 2001 to 2008. Concentrations of PFOA ranged from 4.4  $\times 10^{-5}$  to 0.0099  $\mu\text{g}/\text{L}$ . The maximum concentrations of PFOA occurred from Lake Erie's tributaries through to the St. Lawrence River. Most sites downstream of urban areas had higher concentrations than upstream sites. Background sites, such as glacial meltwater from British Columbia, had lower concentrations of PFOA.

Boulanger et al. (2004) reported PFOA concentrations in Lake Erie and Lake Ontario waters. Samples were acquired at a depth of approximately 4 m at four locations in both Lake Erie and Lake Ontario. Sampling sites were selected to sample urban-influenced and remote locations, as well as to provide a sample from eastern, central and western portions of each lake. Results indicated concentrations of 0.021–0.047  $\mu\text{g}/\text{L}$  in Lake Erie and 0.015–0.070  $\mu\text{g}/\text{L}$  in Lake Ontario. However, the study did not clearly delineate which samples were from remote or urban-influenced areas. Muir and Scott (2003) measured PFOA concentrations in Lake Superior, Lake Huron and Lake Ontario (exact locations not provided). Results ranged from 0.0015 to 0.0018  $\mu\text{g}/\text{L}$  in Lake Huron and from <0.000 01 to 0.0007  $\mu\text{g}/\text{L}$  in Lake Superior. Lake Ontario, at depths of 70–213 m, had PFOA concentrations ranging from 0.0023 to 0.011  $\mu\text{g}/\text{L}$ . The highest concentration of 0.011  $\mu\text{g}/\text{L}$  was sampled at a depth of 213 m. In a study by Furdui et al. (2005), measurements of PFOA were attempted in Lake Ontario, Lake Erie, Lake Huron and the North Channel (along the north shore of Lake Huron) using a method eliminating the extraction/concentration steps. With this method, PFOA was measured only in Lake

Ontario and Lake Erie, with concentrations ranging from 0.002 to 0.007 µg/L. Scott et al. (2003, 2006b) showed the presence of PFOA in the tributaries of Lake Ontario and Lake Erie. The PFOA concentrations in six Lake Ontario tributaries (Welland Canal, Trent River, Black River, Don River, Genessee River and Oswego River) ranged from 0.0015 to 0.025 µg/L. The four Lake Erie tributaries (Grand River, Stoney Creek, Sandusk Creek and Talbot Creek) had a concentration range of 0.0016–0.0093 µg/L. Tributary water from urban areas on Lake Ontario had maximum PFOA concentrations of 0.02 µg/L (Myers et al. 2009).

In 2001, PFOA was measured in precipitation in three remote areas (Turkey Lakes, Ontario; Kejimikujik, Nova Scotia; and Chapais, Quebec), with concentrations ranging from <0.0005 – 0.0031 µg/L (Scott et al. 2006b). Rainwater samples collected in Winnipeg, Manitoba, did not detect PFOA (method detection limit [MDL] of 0.0072 µg/L) (Loewen et al. 2005). Loewen et al. (2005) suggested that this may have been due to insufficient atmospheric concentrations of PFOA and a relatively high MDL. Scott et al. (2006a) measured PFOA in precipitation across Canada from 2002 to 2004. In 2002, Kejimikujik (remote site) had PFOA concentrations ranging from <0.0001 to 0.0031 µg/L. In 2002, Algoma, Ontario (remote site), had PFOA concentrations ranging from <0.0001 to 0.0061 µg/L. In 2003–2004, two urban sites in Ontario (Egbert and north Toronto) had PFOA concentrations ranging from 0.0007 to 0.0111 µg/L. In 2002, Saturna Island, British Columbia (rural site), had PFOA concentrations ranging from <0.0001 to 0.002 µg/L.

Stock et al. (2007) measured lake water samples from three Arctic lakes (Amituk, Resolute, and Char) on Cornwallis Island, Nunavut, in 2003–2005. Concentrations of PFOA ranged from 0.0009 to 0.014 µg/L. Ahrens et al. (2009) measured PFOA along the longitudinal gradient from Las Palmas (Spain) to St. John's, Newfoundland, and along the latitudinal gradient from the Bay of Biscay to the South Atlantic Ocean in the spring and fall of 2007. PFOA was not detected above the MDL of 0.0012 µg/L in the particulate phase or the deep water samples at 200 m and 3800 m. PFOA concentrations ranged from 0.000 004 0 to 0.000 229 µg/L at 11 m, 2 m and directly at the surface. In addition, Ahrens et al. (2009) noted that the concentrations of PFOA and perfluorononanoic acid (PFNA) were positively correlated, indicating that the sources of both compounds are related. Ahrens et al. (2010b) collected surface water samples from November 2 to December 30, 2008 along the latitudinal gradient from the North Sea (northern Europe) and Antarctica. PFOA was detected in 79% of the dissolved phase samples ranging in concentration from  $< 5.2 \times 10^{-6}$  to 0.000223 µg/L. PFOA was not detected in the particulate phase. Del Vento et al. (2009) measured up to 0.000448 µg/L PFOA in seawater and  $3.4 \times 10^{-5}$  – 0.002282 µg/L PFOA in snow from the Amundsen Gulf.

PFOA was also the major fluorinated contaminant detected in oceanic waters from the Pacific and Atlantic oceans and from several coastal seawaters from Asian sites (Japan, Hong Kong, China and Korea) (Yamashita et al. 2005). PFOA was detected at concentrations ranging from 0.000 001 5 to 0.000 192 µg/L, followed by PFOS at  $1.1 \times 10^{-6}$ –0.0577 µg/L. Yamashita et al. (2005) also found that deep seawater samples

collected at depths greater than 1000 m in the Pacific Ocean and the Sulu Sea contained trace levels (values not provided) of PFOA. PFOA was also observed in the North Sea (estuary of the river Elbe, German Bight, southern and eastern North Sea) at concentrations ranging from 0.003 to 0.02 µg/L (Caliebe et al. 2004). In the open sea, PFOA was detected at 0.0005 µg/L (Caliebe et al. 2004). Dissolved PFOA was also detected in Tokyo Bay, with concentrations ranging from 0.007 to 0.0182 µg/L (Masunaga and Odaka 2005). Concentrations of PFOA in brine and sea-ice were in the same range as the snow concentrations.

#### *Sediment*

Stock et al. (2007) measured PFOA in sediment core samples taken in three remote Canadian Arctic lakes (i.e., Resolute, Char and Amituk) on Cornwallis Island, Nunavut in 2003. Core samples taken at Char Lake had PFOA concentrations up to 0.0017 µg/g dry weight (g-dw). Core samples taken at Resolute Lake had PFOA concentrations ranging from 0.0023–0.00095 µg/g-dw. Suspended sediment samples were taken from Niagara-on-the-Lake in the Niagara River and measured for PFOA. PFOA concentrations increased slightly from <0.0001 to <0.0003 µg/g-dw from 1980 to 2002 (Lucaciu et al. 2005). Open lake sediment from Lake Ontario had maximum PFOA concentration of 0.0066 µg/g (Myers et al. 2009).

#### *Soil, Groundwater and Vegetation*

There have been no reported measurements of PFOA in soils or groundwater in Canada to date.

PFOA was measured in soils collected in Dalton, Georgia, USA, at levels ranging from 0.055 to 0.174 µg/g (Ellington et al. 2005). PFOA has been detected in groundwater from sites associated with military fire-fighting training activities in the United States (Florida, Nevada and Missouri), where aqueous film-forming foams have been used (Schultz et al. 2004). Concentrations ranged from ND to 6570 µg/L. The West Virginia Department of Environmental Protection (2003) measured concentrations of PFOA in groundwater samples from drinking water wells, where the concentrations ranged from ND (< 0.01 µg/L) to 23.6 µg/L. Murakami et al. (2009) measured PFOA in groundwater and springwater samples from 0 to 33 m below ground in the Tokyo (Japan) metropolitan area from September to November 2006. The concentration of PFOA ranged from 0.000 47 to 0.06 µg/L.

#### *Biota*

Studies from Canada have found the conjugate base of PFOA in a wide variety of wildlife. Martin et al. (2004b) measured PFOA in the whole body of a wide variety of biotic species from Lake Ontario, including benthic and pelagic invertebrates and various fish species. The concentration range was 0.001–0.09 µg/g-ww, with the highest concentration being found in the benthic invertebrate *Diporeia hoyi* in Lake Ontario (Martin et al. 2004b). This data from Lake Ontario shows that the benthic invertebrate, *Diporeia hoyi*, had higher concentrations of PFOA than any other organism in Lake Ontario (i.e., 90 µg/kg) (including the top-predator lake trout), indicating that sediments may be a reservoir for PFOA in this system (Martin et al. 2004b). This does not

necessarily mean that PFOA partitions strongly into aquatic sediments; it is more likely that PFOA precursors partition to the sediments and subsequently release PFOA upon bacterial or abiotic processing (Martin et al. 2004b; Stock et al. 2007).

Following a spill of fire-fighting foam in Etobicoke Creek, Moody et al. (2002) measured PFOA in the liver of common shiners (*Notropis cornuta*) at concentrations ranging from 0.006 to 0.091 µg/g-ww. Forty-six lake trout whole-body homogenates were analyzed in 2001 from all five of the Great Lakes (Furdui et al. 2007). PFOA concentrations ranged from 0.0007 µg/g-ww (Lake Erie) to 0.0024 µg/g-ww (Lake Michigan) (Furdui et al. 2007).

Martin et al. (2004a) also showed the presence of PFOA in polar bear liver (0.0029–0.013 µg/g-ww), whereas PFOA concentrations in other Arctic animals were below the detection limit (i.e., <0.002 µg/g). In Nunavut, trace levels of PFOA were measured in the liver of Arctic char (*Salvelinus alpinus*) (ND), burbot (*Lota lota*) (ND–0.0265 µg/g-ww), caribou (*Rangifer tarandus*) (ND–0.0122 µg/g-ww), ringed seal (ND–0.0087 µg/g-ww) and walrus (ND–0.0058 µg/g-ww) (Ostertag et al. 2009). Powley et al. (2008) did not detect PFOA in samples of zooplankton (*Calanis hyperboreus*, *Themisto libellula*, Chaetognatha), Arctic cod (*Boreogadus saida*), the blubber, blood or liver of ringed seal (*Phoca hispida*) and the blubber, blood or liver of bearded seal (*Erignathus barbatus*) taken near Banks Island (eastern edge of the Beaufort Sea in the Northwest Territories). However, the sample sizes were small, ranging from 1 to 5. The limit of detection used in this study was 0.0002 µg/g.

Studies in the United States have found the conjugate base of PFOA in a wide variety of biotic samples, including fish, clams, oysters, birds, mink and otters. In general, concentration ranges were from below the limit of detection to 1.9345 µg/g-ww—higher than most concentrations measured in Canadian biota—found at a Guntersville, Alabama, outfall location in gar liver (Giesy and Newsted 2001). In the common cormorants (*Phalacrocorax carbo*), concentrations were observed up to 0.450 µg/g-ww (Kannan et al. 2002). However, it was noted by Kannan et al. (2002) that for this colony of cormorants, the highest value (0.450 µg/g-ww) appeared to qualify as an outlier, as the concentration was 4.5 times greater than the standard deviation of the mean. In benthic algae collected at the Raisin River, the St. Clair River and Calumet River, PFOA could not be detected (detection limit 0.2 ng/g-ww; Kannan et al. 2005a). PFOA was found to be one of the dominant PFCs (in addition to PFOS) in plasma of immature loggerhead sea turtles (*Caretta caretta*) (0.000493–0.00814 µg/mL) and immature Kemp's Ridley sea turtles (*Lepidochelys kempii*) (0.002 77–0.004 25 µg/mL) captured in offshore waters of South Carolina, Georgia and Florida (Keller et al. 2005). Since sea turtles in the pelagic juvenile stage feed in areas distant from continental influences, the detection of PFCs in these turtles may indicate contamination of an ocean basin (Keller et al. 2005). Keller et al. (2005) also found that PFOA concentrations were not significantly different between species, sexes, ages or geographical locations. However, given that the captured turtles were juveniles, sex and age differences would not be expected.

Studies in Japan, China, Taiwan and Korea have found the conjugate base of PFOA in a wide variety of biota. Tseng et al (2006) found PFOA ranging in concentrations from 0.12 to 0.34  $\mu\text{g/g}$  in oysters (*Crassostrea gigas*), Japanese seaperch (*Lateolabrax japonicus*), and tilapia (*Oreochromis* sp.). Nakayama et al. (2008) did not detect PFOA (limit of quantification was 0.005  $\mu\text{g/g-ww}$ ) in the livers of wild common cormorants (*Phalacrocorax carbo*) from Lake Biwa in Japan. Concentrations of PFOA were measured in egg yolks of the little egret (*Egretta garzetta*), little ringed plover (*Charadrius dubius*) and vinous-throated parrotbill (*Paradoxornis webbiana*) collected around Lake Shihwa, Korea (Yoo et al. 2008). PFOA concentrations ranged from <0.0008 to 0.0543  $\mu\text{g/g-ww}$ . Wang et al. (2008) measured concentrations of PFOA in waterbird eggs (black-crowned night herons [*Nycticorax nycticorax*], great egrets [*Ardea alba*] and little egrets [*Egretta garzetta*]) in South China where PFOA concentrations ranged from <0.000 001 to 0.000 952  $\mu\text{g/g-ww}$ .

Male wild rats (*Rattus norvegicus*) collected in Japan (i.e., at a WWTP, a port, two industrial areas, a seafood market/port, a marketplace, and two landfill sites) (Yeung et al. 2009a) had whole-blood PFOA concentrations from 0.00006 to 0.00657  $\mu\text{g/mL}$ . PFOA was detected in the serum of captive giant panda (*Ailuropoda melanoleuca*) and red panda (*Ailurus fulgens*) in China (Dai et al. 2006). Serum concentrations ranged from 0.00033 to 0.00820  $\mu\text{g/mL}$  for the red panda and from 0.00032 to 0.00156  $\mu\text{g/mL}$  for the giant panda. PFOA was measured in serum of the Chinese Amur tiger (*Panthera tigris altaica*) (Li et al. 2008b) found in northeastern China, far eastern Russia and North Korea. PFOA was found at concentrations of 0.00004–0.00018  $\mu\text{g/mL}$ . In another study, PFOA was analyzed in the serum of captive Bengal tigers (*Panthera tigris tigris*) and African lions (*Panthera leo*) from Harbin Wildlife Park, China (Li et al. 2008a). PFOA concentrations were found to be higher in the African lion than in the Bengal tiger, suggesting different exposure uptakes or metabolic capabilities between the two species. In the Bengal tigers, PFOA ranged in concentration from ND to 0.000 097 8  $\mu\text{g/mL}$  and in the African lions, PFOA concentrations ranged from 0.000 286 to 0.001 04  $\mu\text{g/mL}$ .

Holmström and Berger (2008) did not detect PFOA in the adult liver, adult kidney, adult muscle, chick liver and egg of the common guillemot (*Uria aalge*) from the island of Stora Karlsö in the Baltic Sea. Additionally, PFOA was not detected in herring collected 150 km from Stora Karlsö (herring comprises a large part of the common guillemot diet). PFOA was not detected in the liver of the northern fulmar (*Fulmarus glacialis*) along the coast of Svalbard and Bjørnøya in the Barents Sea (Norwegian Arctic) (Knudsen et al. 2007). Whole-blood concentrations of PFOA were measured in waterfowl from the Gulf of Gdansk, Baltic Sea—common scoter (*Melanitta nigra*); common eider (*Somateria mollissima*); red-throated loon (*Gavia stellata*); razorbill (*Alca torda*); and long-tailed duck (*Clangula hyemalis*). Concentrations ranged from 0.00005 to 0.0018  $\mu\text{g/mL}$  (Gulkowska et al. 2005). The study also measured whole-blood PFOA concentrations in cod, which ranged from 0.00005 to 0.0007  $\mu\text{g/mL}$ . PFOA was detected in beaver liver collected from Poland at concentrations of 0.000 28–0.000 29  $\mu\text{g/g-ww}$  (Taniyasu et al. 2005).

PFOA was not detectable in fish, birds or marine mammals from Greenland and the Faroe Islands, except for polar bear liver ( $<0.012 \mu\text{g/g-ww}$ ) and ringed seal liver ( $<0.012 \mu\text{g/g-ww}$ ); however, these values were below the limit of quantification (Bossi et al. 2005). Livers were collected from 35 polar bears from two known subpopulations in northern and western Alaska (Southern Beaufort Sea subpopulation, from Icy Cape to east of Paulatuk in Canada; and Chukchi/Bering Sea subpopulation, near Russia and western Alaska) between 1993 and 2002 (Kannan et al. 2005b). Adult male polar bears from the Southern Beaufort Sea subpopulation had PFOA concentrations ranging from 0.0013 to 0.013  $\mu\text{g/g-ww}$ . Adult male polar bears from the Chukchi/Bering Sea subpopulation had PFOA concentrations ranging from 0.001 to 0.0042  $\mu\text{g/g-ww}$  (Kannan et al. 2005b). The authors also indicated that since lipid normalization of concentrations did not reduce the data variability within a population, the data were analyzed on a wet weight basis. The authors also found a lack of significant age, sex or subpopulation differences for PFOA.

PFOA was not observed in liver, blubber, muscle or spleen tissues in harbour seals (*Phoca vitulina*) from the Dutch Wadden Sea (detection limit was 0.062  $\mu\text{g/g-ww}$ ) (Van de Vijver et al. 2005). PFOA was measured in the liver and serum of the Baikal seal (*Pusa sibirica*) from Lake Baikal, eastern Siberia, Russia (Ishibashi et al. 2008b). In male and female Baikal seal liver, the concentration of PFOA ranged between  $<0.0015$  and 0.0039  $\mu\text{g/g-ww}$ . In male and female Baikal seal serum, PFOA concentrations ranged between  $<0.00033$  and 0.0019  $\mu\text{g/g-ww}$  (Ishibashi et al. 2008b).

PFOA was detected in the plasma (0.0006–0.163  $\mu\text{g/g-ww}$ ) of bottlenose dolphin populations of Delaware Bay (Delaware), Charleston (South Carolina), Indian River Lagoon (Florida) and Bermuda (Houde et al. 2005). Significant age and location interactions were noted for PFOA concentrations in plasma. PFOA concentrations in plasma significantly decreased with age in dolphins from the Charleston and Indian River Lagoon areas. PFOA was also measured in plasma, milk and urine from wild bottlenose dolphins from Sarasota Bay, Florida (Houde et al. 2006). The concentration of PFOA in plasma ranged from 0.0018 to 0.0068  $\mu\text{g/g-ww}$ , the concentration in milk was 0.0013  $\mu\text{g/g-ww}$  and the concentration in urine was below the MDL (0.00006  $\mu\text{g/g-ww}$ ). The concentration of PFOA significantly decreased with blubber thickness (a biological parameter related to body condition and contaminant storage). PFOA was measured in liver samples of Indo-Pacific humpback dolphins (*Sousa chinensis*) and of finless porpoises (*Neophocaena phocaenoides*) stranded in Hong Kong between 2003 and 2007 (Yeung et al. 2009b). PFOA concentrations in the humpback dolphins ranged from 0.000243 to 0.00832  $\mu\text{g/g-ww}$ . PFOA was detected in finless porpoises at concentrations ranging from  $<0.00025$  to 0.000859  $\mu\text{g/g-ww}$ . PFOA was also detected in Franciscana dolphin (*Pontoporia blainvillei*) and subantarctic fur seal (*Arctocephalus tropicalis*) collected from southern Brazil (Leonel et al. 2008). Concentrations were less than 0.0002  $\mu\text{g/g}$  for both species. PFOA and 8:2 telomer acid have been detected in the urine of bottlenose dolphins from populations located off the coasts of Florida and South Carolina (Houde et al. 2005). This study also found that PFOA concentrations in plasma in dolphins from the Charleston, South Carolina, and Indian River Lagoon, Florida, areas decreased with age.

### *Temporal and Geographical Trends*

Temporal trends in PFOA concentrations were not found in archived common guillemot (*Uria aalge*) eggs in the Baltic Sea, Iceland, the Faroe Islands, Sweden and Norway, as PFOA was not detected (Holmström et al. 2005; Löfstrand et al. 2008). Temporal trends in PFOA concentrations were not found in archived peregrine falcon (*Falco peregrinus*) eggs from 1974 to 2007, as PFOA was not detected. It should be noted that due to the low breeding success in the first 20 years, only a few eggs were collected and no eggs were collected between 1987 and 1991. Therefore, all eggs up to 1999 were analyzed individually. Eggs were pooled from the year 2000 and onward (Holmström et al. 2010).

However, Verreault et al. (2007) examined freshly laid whole eggs of two herring gull colonies (Røst and Hørnøya) in northern Norway and found that PFOA concentrations increased significantly between 1983 and 1993 for the Røst colony but not for Hørnøya colony. There was also an increase post-1993 in both colonies. It was noted that the eggs from the Røst colony had significantly higher PFOA concentrations compared with the Hørnøya colony in 1993 and 2003. Temporal trends were not found in liver samples in thick-billed murres (*Uria lomvia*) and northern fulmars (*Fulmaris glacialis*) from Prince Leopold Island in the Canadian Arctic (Butt et al. 2007a). Temporal trends in PFOA concentrations were also not found in lake trout collected between 1979 and 2004 from Lake Ontario (Furdui et al. 2008) and in two Canadian Arctic ringed seal (*Phoca hispida*) populations sampled from 1992 to 2005 (Butt et al. 2007b). O'Connell et al. (2010) analyzed 163 juvenile loggerhead turtle (*Caretta caretta*) plasma and serum for spatial and temporal trends of PFCs. The turtles were captured within 8.4 km of the nearest shore from Charleston (South Carolina), Cape Canaveral (Florida), Core Sound (North Carolina), Chesapeake Bay (Maryland) and Florida Bay (Florida). PFOA plasma/serum concentrations ranged from  $< 7.6 \times 10^{-5}$  to 0.000993  $\mu\text{g/g}$ . Spatially, Florida Bay turtles accumulated more PFOA compared to other PFCAs, suggesting local sources for turtles residing in Florida Bay. Temporal trends were examined over a nine-year period in loggerheads captured near Charleston; concentrations of PFOA did not change significantly through time.

However, temporal trends in PFOA concentrations were found in polar bears from Canada's Baffin Island, which showed an increase in PFOA contamination in their livers from 1972 to 2002 (Smithwick et al. 2006). PFOA doubling time in liver tissue was calculated to be  $7.3 \pm 2.8$  years for Baffin Island polar bears and  $13.9 \pm 14.2$  years for Barrow, Alaska, polar bears. Smithwick et al. (2006) noted that the sex and age of polar bears were not significantly correlated with PFOA concentrations. Dietz et al. (2008) subsampled liver tissue of 128 subadult (3- to 5-year-old) polar bears (collected from central East Greenland) from 19 sampling years within the period 1984–2006 for PFCs, including PFOA. The authors found annual increases of 2.3% for PFOA.

PFOA was measured in liver tissue from 80 adult female sea otters (*Enhydra lutris*) found freshly dead and beached along the California coast. Concentrations of PFOA in liver, ranging from  $< 5 \times 10^{-6}$  to 0.000147  $\mu\text{g/g-ww}$ , increased from 1992 to 2002 for these adult female sea otters (Kannan et al. 2006) However, PFOA was not found in the

adult male sea otters (detection limit of 0.005 µg/g). The reason for this lack of detection is not known (Kannan et al. 2006).

## Ecological Effects Assessment

### *Aquatic Organisms*

The most sensitive pelagic organism was found to be the freshwater alga, *Pseudokirchneriella subcapitata*. The 96-hour LOEC based on both growth rate and cell count was 2.0 mg/L (Ward et al. 1995b, d).

Several toxicity tests on the freshwater alga *Pseudokirchneriella subcapitata* were conducted (Elnabarawy 1981; Ward et al. 1995b, d, 1996c, e, h; Boudreau 2002; Thompson et al. 2004), and the 96-hour median effective concentration (EC<sub>50</sub>) values were determined to range from 4.9 to >3330 mg/L based on growth rate and from 2.9 to 1980 mg/L based on cell count. The 96-hour no-observed-effect concentrations (NOECs) ranged from 1.0 to 500 mg/L based on growth rate and from 0.99 to 210 mg/L based on cell count. Similarly, the 96-hour LOECs ranged from 2.0 to 1000 mg/L based on growth rate and from 2.0 to 430 mg/L based on cell count. A 14-day EC<sub>50</sub> value for this freshwater alga was determined to be 43 mg/L (Elnabarawy, 1981). Toxicity studies with this freshwater alga were conducted using both commercial mixtures of the ammonium and tetrabutylammonium salts of PFOA and high-purity PFOA, which may account for the large ranges observed. Another toxicity test (Boudreau 2002) was conducted using high-purity PFOA and the freshwater alga *Chlorella vulgaris*. This study determined a 96-hour IC<sub>50</sub> value (based on growth rate) of 116 mg/L. This rate indicates that there may be little difference in the sensitivities of the two freshwater algal species. Liu et al. (2008) used flow cytometric measurements to investigate the effects of PFOA on the membrane systems of the freshwater alga, *Scenedesmus obliquus*. PFOA did not inhibit algal growth at the maximum test concentration of 0.000 002 M (0.83 mg/L). However, the mitochondrial membrane potential was affected, and exposure to PFOA at a concentration of between 0.000 001 (0.41 mg/L) and 0.000 002 M (0.83 mg/L) caused an increase in the permeability of the membrane. This suggests damage to the mitochondrial function and membrane permeability at a concentration that did not result in the inhibition of algal growth.

Six Microtox toxicity tests were conducted on the bacterium, *Photobacterium phosphoreum*, using commercial mixtures of the ammonium and tetrabutylammonium salts of PFOA (3M Company 1987a, 1990a, 1996a, b, c; Beach 1995a). The 30-minute EC<sub>50</sub> values (based on rate of bioluminescence) ranged from 260 to 3150 mg/L. It is unclear why this range is so large; however, it may be a result of the lack of characterization of the commercial mixtures and their impurities.

One toxicity test (Boudreau 2002), using high-purity PFOA and the aquatic macrophyte, *Lemna gibba*, determined a 7-day IC<sub>50</sub> value (based on growth rate) of 80 mg/L.

Several toxicity tests have been conducted on the water flea, *Daphnia magna*, using commercial mixtures of PFOA, the ammonium and tetrabutylammonium salts of PFOA

and high-purity PFOA (3M Company 1982, 1984, 1987b; Ward and Boeri 1990; Ward et al. 1995e, 1996a, d, g; Boudreau 2002; CIT 2003). The 48-hour median lethal concentration (LC<sub>50</sub>) values ranged from 77 to 1550 mg/L, whereas the 48-hour EC<sub>50</sub> values (based on immobilization) ranged from 34 to 1200 mg/L. It is unclear why this range is so large. It may be a result of the lack of characterization of the commercial mixtures and their impurities, or, as suggested by Ward et al. (1996a), it may be due to inconsistencies in diet. The 48-hour NOECs (based on immobilization) ranged from 13 to 730 mg/L, whereas 21-day NOECs (based on survival and/or reproduction or length of parent) ranged from 13 to 89 mg/L. One study determined the 21-day EC<sub>50</sub> value (based on reproductive capacity) to be 39.6 mg/L (CIT 2003). A single toxicity study (Boudreau 2002), conducted using high-purity PFOA and the water flea, *Daphnia pulicaria*, determined the 48-hour LC<sub>50</sub> value and 48-hour EC<sub>50</sub> value (based on immobilization) to be 277 mg/L and 204 mg/L, respectively. These results indicate that there may be little difference in the sensitivities in the two *Daphnia* species. Kim et al. (2009) conducted acute toxicity, reproduction and embryo development tests in *Daphnia magna*. PFOA showed a 48-hr EC<sub>50</sub> at 253.5 mg/L. The NOEC was 100 mg/L. PFOA caused reduction of fecundity at 10 mg/L and induced embryo lethality (arrested egg development) and neonate deformities (curved or unextended spines and undeveloped second antenna) at 125 mg/L.

Li (2008) conducted toxicity tests on the freshwater planarian (*Dugesia japonica*), freshwater snail (*Physa acuta*), water flea (*Daphnia magna*) and green neon shrimp (*Neocaridina denticulata*). The 96-hour LC<sub>50</sub> for the freshwater planarian ranged from 318 to 357 mg/L, and the NOEC was 150 mg/L; for the freshwater snail, the 96-hour LC<sub>50</sub> ranged from 635 to 711 mg/L, and the NOEC was 250 mg/L. For *Daphnia magna*, the 48-hour LC<sub>50</sub> ranged from 166 to 198 mg/L, and the NOEC was 125 mg/L; and for the green neon shrimp, the 96-hour LC<sub>50</sub> ranged from 418 to 494 mg/L, and the NOEC was 250 mg/L.

Several toxicity tests have been conducted on the fathead minnow using commercial mixtures of both PFOA and the ammonium and tetrabutylammonium salts of PFOA (3M Company 1977, 1985a, 1987c; Elnabarawy 1980; Ward et al. 1995a, c, 1996b, f, i, j). The 96-hour LC<sub>50</sub> values ranged from 70 to 2470 mg/L, and the 96-hour NOEC values (based on mortality) ranged from 110 to 830 mg/L. It is unclear why this range is so large; however, this may be a result of the lack of characterization of the commercial mixtures and their impurities. Studies were conducted to investigate the toxicity of the ammonium salt with bluegill (3M Company 1978a, b), and the 96-hour LC<sub>50</sub> values were >420 and 569 mg/L.

Two studies have also been conducted that examined the toxicity of the sodium salt of PFOA (high purity) on pelagic communities as a whole, using microcosms consisting of a community of zooplankton and mixed with large invertebrates for a study period of 35 days (Sanderson et al. 2003, 2004). Results of these studies determined both individual and community LOEC values to range from 10 to 70 mg/L. Another study has been conducted that examined the toxicity of the sodium salt of PFOA to the aquatic macrophytes *Myriophyllum sibiricum* and *M. spicatum* using 12 000-L outdoor

microcosms over a period of 35 days (Hanson et al. 2005). The treatments applied were 0.3, 1, 30 and 100 mg/L. The endpoints monitored included growth, biomass, root number, primary root lengths and number of nodes. The results indicated that the two species of *Myriophyllum* were similar in their sensitivity to PFOA. The NOECs for *Myriophyllum* spp. were greater than or equal to 23.9 mg/L (Hanson et al. 2005).

#### *Avian Organisms*

O'Brien et al. (2009) reported that linear PFOA that had been injected into the air cell of white leghorn chicken eggs had no effect on embryonic pipping success at concentrations up to 10 µg/g ww of embryo, and PFOA accumulated in the liver of these embryos 2.9–4.5 times higher than the initial whole-egg concentration. Yeung et al. (2009c) exposed one-day old male chickens to a mixture of PFOS, PFOA and perfluorodecanoate (PFDA) at doses between 0.1 mg/kg body weight and 1.0 mg/kg body weight for three weeks. It was concluded that exposure to a mixture of PFOS/PFOA/PFDA at 1.0 mg/kg body weight had no adverse effect on juvenile chickens. The half-life for PFOA was 3.9 days at both doses.

#### *Bacterial Organisms*

Toxicity tests of PFOA and its salts have been conducted with mixed-liquor activated sludge (obtained from the Metro WWTP in St. Paul, Minnesota). It should be noted, however, that the bacteria in activated sludge were selected for their ability to thrive on anthropogenic chemicals, and, as such, toxicity tests using them may underestimate toxicity. In total, five toxicity tests were conducted on mixed-liquor activated sludge using commercial mixtures of the ammonium and tetrabutylammonium salts of PFOA (3M Company 1980a, 1990b, 1996d; Beach 1995b). The 3-hour EC<sub>50</sub> values (based on respiration inhibition) ranged from >1000 to >3320 mg/L. In addition, the 7-minute NOEC (based on respiration inhibition) was determined to be 1000 mg/L (3M Company 1980a).

#### *Benthic Invertebrates*

In a study by MacDonald et al. (2004), the toxicity of high-purity PFOA to the aquatic midge *Chironomus tentans* was investigated. No toxicity was observed at any of the concentrations tested; as such, the 10-day NOEC value (based on survival and growth) was determined to be 100 mg/L.

#### *Soil-Dwelling Organisms*

According to Tominaga et al. (2004), the soil-dwelling nematode *Caenorhabditis elegans* has been shown to be a suitable test organism, showing both lethal and sublethal effects, in the ecotoxicological assessments of liquid and soil media. Tominaga et al. (2004) examined acute lethal toxicity and multi-generational sublethal toxicity (fecundity and reproduction) using PFOA concentrations of 0 mM (mmol/L) (0 mg/L), 0.01 mM (4.14 mg/L), 0.1 mM (41.4 mg/L), 0.5 mM (207 mg/L), 1.0 mM (414.07 mg/L) and 5.0 mM (2100 mg/L) for 48 hours. All concentrations up to 0.1 mM (41.4 mg/L) showed no acute lethality until 48 hours. Acute lethality appeared at concentrations greater than 0.5 mM (207 mg/L) and did not depend on the incubation time. EC<sub>50</sub>s were calculated for 1 hour (3.85 mM or 1590 mg/L), 2 hours (2.80 mM or 1160 mg/L), 3 hours (2.70 mM or 1120

mg/L), 4 hours (2.65 mM or 1100 mg/L), 24 hours (2.75 mM or 1140 mg/L) and 48 hours (2.35 mM or 973 mg/L) (Tominaga et al. 2004). In the multi-generational test, generation-response and concentration-response relationships were not observed for PFOA.

#### *Terrestrial Plants*

Li (2008) conducted seed germination and 5-day root elongation toxicity tests on lettuce (*Lactuca sativa*), cucumber (*Cucumis sativus*) and pakchoi (*Brassica rapa chinensis*). PFOA had no effect on cucumber seed germination, with both LC<sub>50</sub> and NOEC values greater than 2000 mg/L. The LC<sub>50</sub> and NOEC values for lettuce seed germination were 1734 and 1000 mg/L, respectively. The LC<sub>50</sub> and NOEC values for pakchoi seed germination were 579 and 250 mg/L, respectively. The EC<sub>50</sub> for root elongation for the three species ranged from 263 to 1254 mg/L. PFOA almost completely inhibited lettuce and pakchoi root growth at or above 1000 mg/L. NOECs for root elongation for the three species ranged from <62.5 to 250 mg/L.

Stahl et al. (2009) studied the soil-to-plant carryover of a mixture of PFOA/PFOS on spring wheat, oats, potatoes, maize, and perennial ryegrass. Concentrations ranged from 0.25 to 50 mg/kg of PFOA/PFOS as an aqueous solution. PFOA concentrations were higher than PFOS in all plants except for potatoes with uptake/storage more intensive in the vegetative portion than the storage organ. Visible abnormalities were noted at concentrations > 10 mg/kg. At 25 – 50 mg/kg PFOA/PFOS, necrosis was observed in both oats and potatoes, a yellowing of the ryegrass leaves, and diminished growth for spring wheat.

#### *Terrestrial Mammals*

Butenhoff et al. (2002) conducted a 26-week cynomolgus monkey oral gavage study for which the lowest-observed-adverse-effect level (LOAEL) was 3 mg/kg body weight (kg-bw) per day for males for serum levels showing reversible liver effects and relative liver weight increases without histopathological effects. This study reported a mean liver concentration of PFOA of 15.8 µg/g at week 27 for the 3 mg/kg-bw per day treatment group (i.e., at the LOAEL). Other mammalian studies can be found in the human health assessment section of this document.

#### *Other Effects*

Liu et al. (2007a) used freshwater male tilapia (*Oreochromis niloticus*) as the *in vitro* model to detect the induction of vitellogenin. Vitellogenin is an egg yolk precursor protein expressed in females of fish, amphibians, reptiles (including birds), insects and the platypus. In the presence of substances that affect endocrine function, males can also express the vitellogenin gene. Cultured male tilapia hepatocytes were exposed to PFOA, 4:2 FTOH, 6:2 FTOH and 8:2 FTOH for 48 hours. A dose-dependent induction of vitellogenin was observed in PFOA- and 6:2 FTOH-treated cells, whereas vitellogenin remained unchanged for 4:2 FTOH and 8:2 FTOH. The estimated 48-hour EC<sub>50</sub> values

were  $2.9 \times 10^{-5}$  M (12 mg/L) for PFOA and  $2.8 \times 10^{-5}$  M (12.9 mg/L) for 6:2 FTOH. In the time course study, vitellogenin induction took place at 48 hours (PFOA), 72 hours (4:2 FTOH), 12 hours (6:2 FTOH) and 72 hours (8:2 FTOH) and increased further after 96 hours of exposure. Co-exposure to a mixture of individual PFCs and 17 $\beta$ -estradiol for 48 hours significantly inhibited 17 $\beta$ -estradiol-induced hepatocellular vitellogenin production in a dose-dependent manner, except for 4:2 FTOH. The estimated 48-hour median inhibitory concentration (IC<sub>50</sub>) values were  $5.1 \times 10^{-7}$  M (0.21 mg/L) for PFOA,  $1.1 \times 10^{-6}$  M (0.51 mg/L) for 6:2 FTOH and  $7.5 \times 10^{-7}$  M (0.35 mg/L) for 8:2 FTOH. In order to further investigate the estrogenic mechanism, the hepatocytes were co-exposed to a mixture of PFOA and 6:2 FTOH plus the known estrogen receptor inhibitor tamoxifen for 48 hours. The overall results demonstrated that PFOA and FTOHs have estrogenic activities and that exposure to a combination of 17 $\beta$ -estradiol and PFOA or FTOHs produces anti-estrogenic effects. The results of the estrogen receptor inhibition assay further suggested that the estrogenic effect of PFOA and FTOHs may be mediated by the estrogen receptor pathway in primary cultured tilapia hepatocytes.

Wei et al. (2008a) assessed the effects of PFOA on male and female rare minnows (*Gobiocypris rarus*) at concentrations of 3, 10 and 30 mg/L for 28 days. Exposure to PFOA at 3 mg/L elicited moderate hepatocellular hypertrophy in the livers of both male and female fish. Male rare minnows exposed to PFOA at 10 mg/L showed eosinophilic hyaline droplets in the cytoplasm of the hepatocytes; female rare minnows displayed more eosinophilic hyaline droplets in the cytoplasm of the hepatocytes, hepatocellular hypertrophy and vacuolar degeneration. Rare minnows exposed to PFOA at 30 mg/L showed severe hepatic histopathological changes and disruption of mitochondrial functions. The inhibition of the thyroid hormone biosynthesis genes and the induction of estrogen-responsive genes may indicate a role in endocrine function. Wei et al. (2008b) further identified the potential protein biomarkers for PFOA exposure in the livers of the rare minnows at 3, 10 and 30 mg/L for 28 days, finding the abundance of 34 and 48 protein spots altered in males and females, respectively. These proteins were involved in intracellular fatty acid transport, oxidative stress, macromolecule catabolism, the cell cycle, maintenance of intracellular Ca<sup>2+</sup> homeostasis and mitochondrial function. Wei et al. (2007) studied the *in vivo* effects of waterborne PFOA on the expression of hepatic estrogen-responsive genes, vitellogenin, and estrogen receptor and on the gonadal development in freshwater rare minnow (*Gobiocypris rarus*). The study showed mature females exposed to 3, 10, and 30 mg/L PFOA for 28 d had degenerating vitellogenic-stage oocytes (atresia) in the ovaries. In males exposed to 10 mg/L PFOA, primary growth-stage oocytes (pre-vitellogenic oocytes) developed in some testes. The number of sperm and various stages of germ cells within the spermatogenic cycle in the 10 and 30 mg/L PFOA treatments were lower than those in control males. PFOA increased hepatic vitellogenin concentration and induced testis-ova gonads in mature male rare minnows at 10 and 30 mg/L for 28 days. Wei et al. (2007) showed that PFOA can disrupt the activity of estrogen by inducing hepatic estrogen-responsive genes in males, although the mechanism of development of testes-ova in rare minnows by PFOA exposure is not known.

Stevenson et al. (2006) examined the toxicity of PFOA with respect to the multixenobiotic resistance mechanism in the marine mussel, *Mytilus californianus*. This mechanism acts as a cellular first line of defence against broad classes of xenobiotics exporting moderately hydrophobic chemicals from cells via adenosine triphosphate (ATP)–dependent, transmembrane transport proteins. The most studied transporter is the P-glycoprotein, which is a fragile defence mechanism and can be compromised by some xenobiotics. This increased sensitivity, referred to as chemosensitization, arises from the ability of the P-glycoprotein to recognize and bind to multiple xenobiotic substrates, resulting in the saturation of the binding capacity. Non-toxic substances can also be chemosensitizers and cause adverse effects on organisms by allowing normally excluded toxic substances to accumulate in the cell. Stevenson et al. (2006) found that PFOA at 50  $\mu\text{M}$  (20 mg/L) significantly inhibited the P-glycoprotein in *Mytilus californianus* and thus is a chemosensitizer for that organism. The study also showed that this inhibition was reversible once the marine mussel was removed from contamination and placed in clean seawater.

Ishibashi et al. (2008b) showed that PFOA activates the mammalian peroxisome proliferator–activated receptor  $\alpha$  (PPAR $\alpha$ ) in the livers of Baikal seals—the first reported identification of PPAR $\alpha$  complementary deoxyribonucleic acid (DNA) in an aquatic wildlife species. PPAR is a member of the ligand-activated nuclear hormone receptor superfamily. PPAR $\alpha$  plays a critical physiological role as a lipid sensor and a regulator of lipid metabolism. The lowest-observed-effect concentration (LOEC) for PFOA was 62.5  $\mu\text{M}$  (25.9 mg/L). Yang (2010) exposed male Japanese medaka (*Oryzias latipes*) to 10, 50 and 100 mg/L PFOA for 7 days. There were no impacts on survival, relative liver and gonad size, and condition factor at any concentration. However, PFOA induced inhibition of catalase activity at high doses with no changes of superoxide dismutase or glutathione peroxidase activities in the liver, suggesting that PFOA may induce peroxisomal fatty acid oxidation and impose oxidative stress through the alteration of cellular oxidative homeostasis in the liver. PFOA also increased the messenger ribonucleic acid (mRNA) levels of pro-inflammatory cytokines, suggesting that it may be involved in inflammation and tissue injury. The effects on peroxisome proliferation and cytokine expression suggest that chronic exposure to PFOA can be carcinogenic in the Japanese medaka: peroxisome proliferation is a key carcinogenic mechanism and chronic inflammation is associated with an increased risk of cancer in rodents.

The potential impact of exposure to PFCs on liver lesions was investigated in East Greenland polar bears (Sonne et al. 2008). Liver parameters examined included mononuclear cell infiltrations, lipid granulomas, steatosis, Ito cells and bile duct hyperplasia/portal fibrosis. The population consisted of 28 females and 29 males harvested by local hunters between 1999 and 2002. Liver samples were analyzed for PFOS, perfluorononanoic acid, perfluoroundecanoic acid, perfluorodecanoic acid, perfluorotetradecanoic acid, PFOA, perfluorooctanesulfonamide, perfluorodecanoate and perfluorohexanesulfonate. In 23 cases, the concentration of PFOA was below the detection limit (0.0012  $\mu\text{g/g-ww}$ ). Liver samples were also analyzed for several perfluorinated compounds, including C9, C10, C11, C12 and C13 PFCAs. Sixty-five

percent of the polar bears had total PFA concentrations above 1  $\mu\text{g/g-ww}$ . In female bears, the total PFA concentration ranged from 0.256 to 2.77  $\mu\text{g/g-ww}$ ; in male bears, the total PFA concentration ranged from 0.114 to 3.052  $\mu\text{g/g-ww}$ . All PFA compounds in the analysis were summed, so a direct cause–effect correlation with a particular perfluorinated compound, such as PFOA, cannot be determined. East Greenland polar bears are also contaminated with other substances, such as organochlorines (PCBs, dichlorodiphenyltrichloroethane [DDT]) and mercury, which may function as confounding synergistic co-factors in the development of the lesions. The authors concluded that the statistical analysis did not answer the question of whether chronic exposure to PFCs is associated with liver lesions in polar bears; however, these lesions were similar to those produced by PFCs under laboratory conditions (Sonne et al. 2008).

The effect of PFOA on immune function and clinical blood parameters has been examined in bottlenose dolphins and sea turtles from Florida, Georgia and South Carolina. It should be noted that a direct cause–effect relationship cannot be clearly established, as there may be other co-occurring contaminants. The results revealed that there may be increases in indicators of inflammation and immunity in bottlenose dolphin blood parameters in relation to PFOA, suggesting that PFOA may alter biomarkers of health in marine mammals (Peden-Adams et al. 2004a). Examples of biomarkers analyzed in bottlenose dolphins include absolute numbers of lymphocytes, serum triglyceride, serum total protein, serum albumin, serum cortisol, C-reactive protein, lysozyme activity and B-cell proliferation (Peden-Adams et al. 2004a). Serum triglyceride exhibited stronger relationships to PFOA in females than in males. Lipopolysaccharide-induced lymphocyte proliferation (B-cell proliferation) had positive but weak correlations with PFOA in male bottlenose dolphins, and a strong correlation was observed between PFOA and lysozyme activity (a measurement of innate immunity) in the same species. However, in another study by Flanary et al. (2010), no correlations were found between any perfluorinated compound, including PFOA, and blood chemistry parameters (e.g. cholesterol, creatinine, albumin, total serum ion, etc.) for the northern fur seal (*Callorhinus ursinus*).

Low levels of PFAs may also alter biomarkers of health in loggerhead sea turtles (Peden-Adams et al. 2004b). Examples of biomarkers analyzed in loggerhead sea turtles include plasma total protein, plasma globulin, T-cell proliferation, plasma lysozyme activity and B-cell proliferation (Peden-Adams et al. 2004b).

### **Characterization of Ecological Risk**

The approach taken in this ecological screening assessment is to examine relevant scientific and technical information and develop conclusions based on multiple lines of evidence approach, including consideration of persistence, exposure, trends, toxicity, bioaccumulation and widespread occurrence in the environment.

Assessment endpoint organisms have been selected based on analysis of exposure pathways. For each endpoint organism, a conservative (reasonable worst-case) predicted environmental concentration (PEC) and a predicted no-effect concentration (PNEC) are

determined. The PNEC is arrived at by selecting the lowest critical toxicity value (CTV) for the type of organism of interest and dividing it by an assessment factor appropriate for the data point. A risk quotient (PEC/PNEC) is calculated for each type of endpoint in order to estimate potential ecological risk in Canada. However, there is also uncertainty regarding the risk that PFOA may pose now or in the future. Typically, quantitative risk estimates (i.e., risk quotients or probabilistic analyses) are important lines of evidence when evaluating a substance's potential to cause environmental harm. However, when risks for persistent and bioaccumulative substances such as PFOA are estimated using such quantitative methods, they are highly uncertain and are likely to be underestimated. Given that long-term risks associated with persistent and bioaccumulative substances cannot at present be reliably predicted, quantitative risk estimates have limited relevance. Furthermore, since accumulations of such substances may be widespread and are difficult to reverse, a conservative response to uncertainty is justified.

### *Mammalian Wildlife*

Butenhoff et al. (2002) conducted a 26-week cynomolgus monkey oral gavage study for which the LOAEL was 3 mg/kg body weight (kg-bw) per day for males for serum levels showing reversible liver effects and relative liver weight increases without histopathological effects. This study reported a mean liver concentration of PFOA of 15.8 µg/g at week 27 for the 3 mg/kg-bw per day treatment group (i.e., at the LOAEL). This value was selected as the CTV. This CTV was divided by an assessment factor of 100 to give a PNEC of 0.158 µg/g or 158 µg/kg. The assessment factor was used to account for laboratory to field extrapolation, intra- and interspecies variation, the fact that the substance is persistent and has the potential to accumulate and biomagnify in terrestrial and marine mammals, and extrapolation from an LOAEL to a no-observed-adverse-effect level (NOAEL). The datum selected for the PEC is the highest liver PFOA concentration in polar bear—i.e., 13 µg/kg-ww, from Sanikiluaq, Nunavut, Canada (Martin et al. 2004a).

The risk quotient (PEC/PNEC) for Canadian mammalian wildlife is 0.08 (13/158). The risk quotient is less than 1, indicating low likelihood of risk from exposures at current concentrations in the environment.

### *Pelagic Organisms*

Current Canadian surface water measurements include those of Etobicoke Creek (Toronto, Ontario), relating to a spill of aqueous fire-fighting foam (Moody et al. 2002), and water measurements in Lake Ontario (Boulanger et al. 2004). These data were selected for the PECs in Canada under three scenarios:

- 1) spill conditions (11.3 µg/L; downstream of spill over 150 days);
- 2) a creek in a densely populated region (0.033 µg/L; upstream of spill over 150 days); and

- 3) a lake in a densely populated region (highest background concentration 0.070 µg/L; Lake Ontario).

The spill condition is an extreme worst-case PEC. The upstream conditions in Etobicoke Creek may be considered a high-density urban scenario for general surface waters in Canada owing to the population density surrounding Etobicoke Creek, storm sewer inputs along its length and the reasonably low natural flow of the creek, which causes minimal dilution of the anthropogenic inputs. Nonetheless, higher concentrations were measured in Lake Ontario. The maximum observed PFOA concentration in each scenario was selected as the PEC:

- 1) spill (PEC = 11.3 µg/L);
- 2) receiving creek (PEC = 0.033 µg/L); and
- 3) receiving lake (PEC = 0.070 µg/L).

Most of the available toxicity data are for freshwater pelagic organisms, given that PFOA is expected to partition primarily to the aquatic environment. The organism that was most sensitive to PFOA, as determined from single-species tests, was the freshwater alga *Pseudokirchneriella subcapitata* (96-hour LOEC for growth rate and cell count of 2.0 mg/L) (Ward et al. 1995b, 1995d). This 2.0 mg/L value is selected as the CTV for pelagic organisms. This CTV is divided by an assessment factor of 100 to account for laboratory to field extrapolation, extrapolation from an LOAEL to an NOAEL, and intra- and interspecies variation, to give a PNEC of 0.02 mg/L or 20 µg/L. The risk quotients (PEC/PNEC) for pelagic organisms are as follows:

- 1) spill condition is 0.56 (11.3/20).
- 2) receiving creek conditions is 0.002 (0.033/20).
- 3) receiving lake conditions is 0.004 (0.07/20).

These risk quotients indicate low likelihood of risk to pelagic organisms from exposures at current concentrations in the environment.

Wei et al. (2007) showed that female rare minnows (*Gobiocypris rarus*) exposed to 3, 10, and 30 mg/L PFOA for 28 d had degenerating vitellogenic-stage oocytes in the ovaries. The value of 3 mg/L was selected as the CTV. This CTV is divided by an assessment factor of 100 to account for laboratory to field extrapolation, extrapolation from an LOAEL to an NOAEL, and intra- and interspecies variation, to give a PNEC of 0.03 mg/L or 30 µg/L. The risk quotients (PEC/PNEC) for pelagic organisms under:

- 1) receiving creek conditions is 0.001(0.033/30)
- 2) receiving lake conditions is 0.002 (0.07/30)

These risk quotients indicate a low likelihood of risk from exposures at current concentrations in the environment.

The values derived as risk quotients for PFOA are summarized in Table 6.

**Table 6. Summary of values derived as risk quotients for PFOA**

Endpoint organism	CTV	PNEC	PEC	Scenario	Risk quotient (PEC/PNEC)
	(µg/L) <sup>1</sup>				
Freshwater alga	2000 <sup>2</sup>	20 <sup>3</sup>	11.3 <sup>4</sup>	Extreme worst – case (spill condition)	0.6
Freshwater alga (urban creek)	2000 <sup>2</sup>	20 <sup>3</sup>	0.033 <sup>5</sup>	High-density urban scenario (receiving creek)	0.002
Freshwater alga (Lake Ontario)	2000 <sup>2</sup>	20 <sup>3</sup>	0.07 <sup>6</sup>	High-density urban scenario (receiving lake)	0.004
Canadian Arctic polar bear (liver)	15.8 mg/kg <sup>7</sup>	158 µg/kg <sup>8</sup>	13 µg/kg <sup>9</sup>	---	0.08
Male and female rare minnows	3 mg/L <sup>10</sup>	0.03 mg/L <sup>3</sup>	0.033–0.07 <sup>5 and 6</sup>	receiving creek and lake	0.001 – 0.002

<sup>1</sup> Unless otherwise indicated.

<sup>2</sup> The 96 h LOEC for growth rate and cell count in freshwater algae (*Pseudokirchneriella subcapitata*) (Ward et al. 1995a, b).

<sup>3</sup> Assessment factor 100 to account for laboratory to field extrapolation, and intra- and interspecies variation

<sup>4</sup> Highest PFOA concentration observed downstream in the Etobicoke Creek following a spill of aqueous fire-fighting foam.

<sup>5</sup> Highest PFOA concentration observed upstream in the Etobicoke Creek following a spill of aqueous fire-fighting foam (representing the background concentration in the creek independent of the spill).

<sup>6</sup> Highest PFOA concentration observed from Lake Ontario (Boulanger et al. 2004).

<sup>7</sup> Liver concentration at the LOAEL from a 26-week cynomolgus monkey PFOA feeding study (Butenhoff et al. 2002).

<sup>8</sup> Assessment factor of 100 to account for laboratory to field extrapolation, potential effects caused by additional stressors, intra- and interspecies variation and extrapolation from an LOAEL to an NOAEL. No NOAEL (or no-observed-effect level [NOEL]) could be determined in the Butenhoff et al. (2002) study. The effective NOEL was below 3 mg/kg-bw per day. The cause of death at the low dose level (3 mg/kg-bw per day) could not be ascertained (i.e., it may or may not have been related to treatment and may indicate a large intraspecies variation), as the tumours in rodents are thought to be peroxisome proliferative induced (not a genotoxic type) and the increased liver weights at these low doses may be indicative of possible tumour induction in a chronic exposure scenario.

<sup>9</sup> The highest liver PFOA concentration for polar bear from Sanikiluaq, Nunavut, Canada (Martin et al. 2004a).

<sup>10</sup> The lowest concentration causing vitellogenin induction in the livers of male and female rare minnows (Wei et al. 2007).

In summary, the risk quotients for pelagic organisms indicate a low likelihood of risk from exposures at current concentrations in the aquatic environment. The risk quotient for Canadian mammalian wildlife (i.e., polar bears) is less than 1; however, due to the persistence of the substance, its tendency to accumulate and biomagnify in a variety of terrestrial and marine mammals, its hepatotoxicity, and the upward temporal trend of PFOA concentrations in polar bears and some other species, PFOA concentrations in polar bears may approach exposures resulting in harm.

## Uncertainties in Evaluation of Ecological Risk

While certain data gaps and uncertainties exist, there is, nonetheless, a substantial body of information on PFOA and its precursors. For example, while the mechanism of transport of PFOA and its precursors to the Arctic is not clear, they appear to be mobile in some form, as PFOA has been measured in biota throughout the Canadian Arctic, far from known sources. Environmental pathways of PFOA to biota are not well understood, as there are relatively few monitoring data on concentrations of various precursors in air, water, effluents and sediments in Canada. While mechanisms of toxic action of PFOA are not well understood, a range of toxicological effects, including vitellogenin induction, hepatotoxicity and feminization of male fish, have been reported in a variety of species. There is limited information on the toxicology of PFOA precursors, the potential for combined or synergistic effects with PFOA, and the toxicology and potential for combined or synergistic effects of PFOA with other perfluoroalkyl acids. In addition, analytical results from individual laboratories may not be directly comparable, according to studies by van Leeuwen et al. (2006), indicating variability in analytical results between individual laboratories.

## Potential to Cause Harm to Human Health

### Exposure Assessment

PFOA has been detected in a number of locations in Canada: in house dust in Ottawa, Ontario with a mean level of 106 ng/g (n=67; range 2.29 to 1234 ng/g; median 19.72 ng/g - Kubwabo et al. 2005); in tap water in Calgary, Alberta, and Vancouver, British Columbia, at 0.2 ng/L (one sample per location - Lien et al. 2006); in surface waters from US and Canadian locations in Lake Ontario and Lake Erie at levels ranging from 13 to 50 ng/L (mean of 8 samples from 4 locations in Lake Ontario: 42.5ng/L; mean of 8 samples from 4 locations in Lake Erie: 35.6 ng/L - Boulanger et al. 2004; median of 13 samples on Lake Ontario: 21 ng/L; median of 3 samples in Lake Erie: 15 ng/L – Sinclair et al. 2006); in lake water at 5 locations in the Arctic with means of 0.9 to 14 ng/L (range 0.5 to 16 ng/L – Stock et al. 2007); and in indoor air and dryer lint (Shoeib et al. 2011). PFOA contamination has also been detected in fish and water at airport sites in Canada where fire-fighting foams have been released (Moody et al. 2002; 2008 email from Transport Canada, to Bureau of Risk and Impact Assessment, Health Canada; unreferenced).

Similarly, FTOHs have been detected in a number of locations in Canada: in house dust in Ottawa, Ontario (n=59; mean 8:2FTOH: 55 ng/g – Shoeib et al. 2005), and in the air over rural and urban sites in Ontario and Manitoba (total FTOHs in Toronto, Ontario: range 113 to 213 pg/m<sup>3</sup>, mean 165 pg/m<sup>3</sup>; Winnipeg, Manitoba: range <MDL-18 pg/m<sup>3</sup>, mean 11 pg/m<sup>3</sup>; Long Point, Ontario: <MDL to 52 pg/m<sup>3</sup>, mean 26 pg/m<sup>3</sup>; n=3 samples per location -Stock et al. 2004; 8:2FTOH in Toronto, Ontario: range 9-123 pg/m<sup>3</sup>, mean 55 pg/m<sup>3</sup>; n=4; Long Point, Ontario: range 25-40 pg/m<sup>3</sup>, mean 32 pg/m<sup>3</sup>; n=2 – Martin

et al. 2002) and in the Arctic (total FTOHs: mean 28 pg/m<sup>3</sup>; range for 8:2FTOH <LOD to 20 pg/m<sup>3</sup> – Stock et al. 2007; 8:2 FTOH: range 5.8 to 26 pg/m<sup>3</sup>; n=20 – Shoeib et al. 2006).

In 3 of 54 composite food samples collected for the Canadian Total Diet Study from 1992 to 2004, PFOA was detectable, with the highest level quantified (3.6 ng/g) in a sample of microwave popcorn (Tittlemier et al. 2007). PFOA was also found in several species of fish (both raw and cooked samples; maximum level detected 1.59 ng/g) purchased at markets in Ontario in 2006 (Del Gobbo et al. 2008) and in some native foods (seal, duck and caribou; maximum level detected 0.8 ng/g) collected in Nunavut in 1997–1998 (Ostertag et al. 2009).

PFOA was detected in the packaging materials and in the vapours produced from the microwave cooking of both tested brands of prepackaged microwave popcorn, and 8:2 FTOH was found in the packaging and vapours of one of two brands of microwave popcorn. Neither PFOA nor 8:2 FTOH was detected in the packaging materials or vapours of plain popcorn kernels cooked in a polyethylene bag (Sinclair et al. 2007). In studies that analyzed products purchased at US retail stores, PFOA was detected in new polytetrafluoroethylene-treated cookware following heating to normal cooking temperatures (Begley et al. 2005) and in water boiled in two of four new non-stick pans (Sinclair et al. 2007). PFOA and 8:2 FTOH were detected in off-gassing from all four tested brands of new non-stick cooking pans heated at normal cooking temperatures (Sinclair et al. 2007). PFOA was also detected in cooking oil following heating under normal cooking conditions in new non-stick pans in a study in Italy (Bononi and Tateo 2007). Other studies have reported no detectable PFOA following extraction of new treated cookware (Powley et al. 2005; Washburn et al. 2005; Bradley et al. 2007). Extracts from some fluorochemical-treated articles (apparel, carpet and upholstery) were found to contain PFOA (Washburn et al. 2005).

PFOA was detected in 44 of 45 samples of human breast milk from Massachusetts, with concentrations ranging from <0.0301 to 0.161 µg/mL (Tao et al. 2008), and cord blood of newborns in Canada was found to contain PFOA in three studies (Tittlemeier et al. 2004; Monroy et al. 2008; Beesoon 2011), indicating potential exposures *in utero* and through breast milk.

The available data suggest that Canadians are exposed to PFOA and its precursors present in the environment, including via air, drinking water and food; and from the use of consumer products, such as new non-stick cookware and PFC-treated apparel and materials such as carpets and upholstery. In general, the levels of PFOA observed in Canada in ambient air, food and drinking water are comparable to those measured elsewhere, including the United States, Europe and Asia (Fromme et al. 2009). However, in other countries, industrial sources not present in Canada have led to localized PFOA concentrations in drinking water that are much higher than the levels reported in Canada (e.g., Little Hocking, Ohio, mean concentration of 3.5 µg/L; Emmett et al. 2006a).

A quantitative estimate of exposure to PFOA based on levels in environmental media and through use of consumer products was not derived, as biomonitoring data—which aggregate exposure from all sources—were available. However, such estimates of total daily intake of PFOA have been published recently. Trudel et al. (2008) estimated the exposure of the general population in North America to PFOA from air, food, drinking water, dust and consumer products. The exposure estimates for low-, intermediate- and high-exposure scenarios ranged from 1 to 130 ng/kg-bw per day for all age groups. Diet was found to be the major source of exposure for the low- and intermediate-exposure scenarios, whereas consumer products (oral exposure to treated carpet and migration from treated paper into food, and inhalation during the consumer use of spray treatment products on clothing) were the major contributors in high-exposure scenarios. This study did not consider contributions from exposure to PFOA precursors. In another study, Fromme et al. (2009) estimated exposure to PFOA for the general population using data from North America, Europe and Japan. The upper bound of exposure was estimated to be 12.6 ng/kg-bw per day and was mainly due to dietary consumption. Exposure to FTOHs contributed less than 1% of the exposure to PFOA. This study did not look specifically at consumer product scenarios.

Biomonitoring data form the basis of this exposure assessment for PFOA, as blood levels represent aggregate exposure from all routes and sources, including exposure to precursors of PFOA. PFOA has been identified in blood samples from non-occupationally exposed populations worldwide, including in adults, children and newborns in Canada. The widespread detection of PFOA in human blood indicates that humans are environmentally exposed to PFOA and/or precursor compounds that degrade to PFOA. Once in the body, PFOA can bind to certain proteins (Han et al. 2003, 2005), but there is no evidence that it is modified by metabolism, conjugation or defluorination (Vanden Heuvel et al. 1991). PFOA has a relatively long half-life in humans, in the range of 2–4 years (Olsen et al. 2007; Bartell et al. 2010; Brede et al. 2010).

PFOA has been measured in the blood of non-occupationally exposed adults, children, and newborns in several studies, at levels ranging from < 0.0001 µg/mL up to 0.0561 µg/mL, presented in Table 7. Canadian biomonitoring data are consistent with data from the United States. Serum and plasma PFOA levels in children and the elderly are comparable with those in adults. However, based on data from a German study, infants aged 6 months appear to be the highest-exposed age group. In the study, PFOA levels were measured at two time points in maternal blood (n ~ 40 and 38), 6 months after delivery (n = 47), cord blood (n = 33) and in blood of infants at 6 (n = 40) and 19 months (n = 24) after birth, and monthly in breast milk samples. Concentrations in maternal serum ranged from 0.7 to 8.7 µg/L. In cord serum, the values ranged from 0.5 to 4.2 µg/L. The median results from serum at 6 and 19 months of age were 6.9 and 4.6 µg/L, respectively. In breast milk, PFOA was detected only in some samples. Authors suggest the an increase in concentrations of PFOA during the first months of an infant's life is due to breastfeeding, since breast milk contains measurable levels of PFOA (Fromme et al. 2010).

**Table 7. Representative PFOA biomonitoring studies from Canada, the United States and Germany**

Population description	n	AM, GM or median concentration (µg/mL)	Range (µg/mL)	95th percentile (µg/mL)	Reference
<b>Canadian data</b>					
Plasma in Canadians aged 20 to 79 years, collected in Canadian Health Measures Survey (CHMS) 2007-2009	2880	GM 0.00252	< LOD (0.0003) - max not reported	0.00550	Health Canada 2010
Plasma in Inuit children aged 12 to 54 months, collected in Northern Contaminants Program 2006-2008	86	GM 0.00162	0.00046–0.01100	NA	Turgeon-O'Brien et al. 2010
Pooled serum in pregnant women in Alberta, collected in 2005	50 599	weighted mean 0.0026 µg/g serum	0.0017–0.0038 µg/g serum	NA	Alberta Health and Wellness 2008
Maternal and cord serum samples from 152 women and their babies in Vancouver, British Columbia, collected in Chemicals, Health and Pregnancy Study (ChirP) 2006–2008	mothers 152	AM 0.0018 maternal at 15 weeks' gestation	< LOD (0.0005)–0.0046 maternal	NA	Webster 2011; Beesoon 2011 (unpublished results)
	infants 20	AM 0.0011 cord	0.0005–0.0024 cord		
Maternal and cord serum samples from women and their 105 babies in Hamilton, Ontario, collected in 2004–2005	mothers 101	AM 0.00254 24–28 weeks gestation	0.00133–0.00314	NA	Monroy et al. 2008
		AM 0.00224 at delivery			
	infants 105	AM 0.00194 cord	0.00109–0.00237 cord		
Maternal and cord plasma samples from 23 pooled plasma samples representing 560 individual donors from northern populations in four geographic regions in the Canadian Arctic, collected 1994–2001	mothers 10 pools	AM 0.0022 maternal	0.00048–0.00546	NA	Tittlemier et al. 2004
	infants 13 pools	AM 0.0034 cord			
<b>United States and German data</b>					
Serum from Americans aged 12 years or older; U.S. National Health and Nutrition Examination Survey (NHANES) 2007–2008	2100	GM 0.0041	< LOD (0.0001)–0.0772	0.0097	U.S. CDC 2011
Serum from residents of Seattle aged 65–96	238	GM 0.0042	< LOQ (0.0014)–0.0167	0.0097	Olsen et al. 2004a
Serum from children aged 2–12 from 23 states, collected in 1994–1995	598	GM 0.0049	< LOQ (0.0029)–0.0561	0.010	Olsen et al. 2004b

Population description	n	AM, GM or median concentration (µg/mL)	Range (µg/mL)	95th percentile (µg/mL)	Reference
Serum from pooled samples of children aged 3–5 yrs (21 individuals per pool) and of children aged 6–11 yrs (57 individuals per pool), collected in NHANES 2001–2002	12 pools (ages 3-5)	N/A	0.0058–0.0084	NA	Kato et al. 2009
	12 pools (ages 6-11)		0.0059–0.0082		
Cord serum samples from infants born in Baltimore, Maryland, in 2004–2005	299	Median 0.0016	0.0003–0.0071	0.0034	Apelberg et al. 2007a
Serum from German women at delivery and 6 months after, and their infants at birth (cord blood) and at 6 and 19 months, collected in 2007–2008	mothers 38	Median 0.0019 at delivery	0.0007–0.0087	0.0052	Fromme et al. 2010
	mothers 47	Median 0.0015 after 6 months		0.0039	
	infants 33	Median 0.0014 cord	0.0005–0.0042 cord	0.0037	
	infants 40	Median 0.0069 6 months	0.00096–0.0269 6 months	0.0195	
	infants 24	Median 0.0046 19 months	Not reported	0.0114	

Abbreviations: AM arithmetic mean; GM geometric mean; LOD limit of detection; LOQ limit of quantification; NA not available

Confidence in the measure of exposure (i.e., levels of PFOA in blood) is high, as the data cover all of Canada, all age groups from infants to seniors, and includes vulnerable populations such as pregnant women, nursing infants and people living in northern Canada. Levels in Canadians, as reported in the CHMS, are comparable to those reported in the United States from NHANES. The use of biomonitoring data accounts for multiple sources of exposure and eliminates the need to calculate upper-bound estimates of exposure from environmental sources and consumer products and household materials.

### Health Effects Assessment

Most of the relevant toxicity studies in laboratory animals have been conducted on the ammonium salt of PFOA (APFO); studies are also available on the anion (PFO), the sodium salt (PFOA-Na) and on PFOA itself. PFOA and its salts are expected to dissociate rapidly in biological media to form the PFO anion, and the toxicological effects of exposure to PFOA, APFO and PFOA-Na are similar. Therefore, PFOA and its salts are considered to be biologically equivalent in this report. Toxicological data on individual precursors of PFOA were not reviewed as the approach for this assessment was to consider these compounds in terms of their contribution to exposure to total PFOA. A summary of the toxicological database for PFOA and its salts is provided in Appendix 2. The studies considered critical to the screening assessment are those with the lowest administered doses and those that reported the lowest serum levels of PFOA associated with effects.

A short-term (14-day) oral toxicity study with APFO in rats and mice identified an LOAEL of 0.3 mg/kg-bw per day. This dose was associated with a mean serum PFOA level of 13 µg/mL and increased liver weight in male mice; and a mean serum PFOA level of 20 µg/mL and altered lipid parameters in male rats. This dose was the lowest tested; thus, no NOAEL was obtained (Loveless et al. 2006).

In a subchronic (13-week) oral toxicity study in male rats, no effects, including histopathological changes in the liver, were observed at 0.06 mg/kg-bw per day. At the next dose (0.64 mg/kg-bw per day), increased liver weight and hepatic hypertrophy were observed. These effects were not observed after an 8-week recovery period. Corresponding serum PFOA concentrations at the NOAEL and LOAEL were 7.1 and 41.2 µg/mL, respectively, at the end of the 13-week exposure period (Palazzolo 1993; Perkins et al. 2004).

Liver effects were also observed in a 14-day inhalation study in male rats. Reversible liver weight increase, reversible increases in serum enzyme activities and microscopic liver pathology, including necrosis (not reversible), occurred at exposure levels of 8 mg/m<sup>3</sup> and above, but not at 1 mg/m<sup>3</sup>. These exposures were calculated as equivalent to doses of 2.48 and 0.31 mg/kg-bw per day, respectively<sup>3</sup> (corresponding serum PFOA levels were 47 and 13 µg/mL, respectively, at the end of the 14-day exposure period) (Haskell Laboratory 1981a; Kennedy et al. 1986).

In a 26-week oral subchronic toxicity study in male monkeys, the lowest tested APFO dose of 3 mg/kg-bw per day resulted in increased liver weight (Thomford 2001b; Butenhoff et al. 2002). The average serum PFOA level based on biweekly measurements was 77 µg/mL.

In a developmental toxicity study in mice, the oral administration of APFO at 1 mg/kg-bw per day on days 1–17 of gestation resulted in increased liver weight in the dams, alterations in fetal ossification and early puberty in male pups. The mean serum PFOA level in the dams at the LOAEL of 1 mg/kg-bw per day was 21.9 µg/mL. As this was the lowest tested dose, no NOAEL was determined (Lau et al. 2006). During the preparation of this final screening assessment, Macon et al. (2011) published a study investigating low-dose effects of PFOA in mice. The study reported significantly lower mammary gland developmental scores in offspring of CD-1 mice on PND 21 when dams were exposed to 0.01 mg/kg-bw per day through oral gavage during GD 10–17; serum PFOA was 16.5 ± 2.1 ng/ml. Authors reported a sensitivity of mammary glands to PFOA in CD-1 mice and that further research is needed to determine if the sensitivity is attributed to timing of exposure, mouse strain, or if there are other mechanisms underlying the apparent sensitivity in CD-1 mice. There is insufficient information to determine if these mammary gland effects are permanent and therefore adverse at low-dose levels.

Two chronic toxicity studies in laboratory animals were identified. In the first chronic toxicity study, CD rats were given APFO at 0, 30 or 300 ppm in the diet for 2 years (0,

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<sup>3</sup> Doses were calculated using the following reference values: rat inhalation rate = 0.11 m<sup>3</sup>/day; rat body weight = 0.35 kg (Health Canada 1994).

1.3 or 14.2 mg/kg-bw per day for males; 1, 1.6 or 16.1 mg/kg-bw per day for females). An LOAEL of 1.3 mg/kg-bw per day was determined based on significant increases in serum liver parameters (alanine aminotransferase [ALT], alkaline phosphatase [AP] and albumin) in males. No evidence of carcinogenic activity was seen in the females, but the males showed an increase in testicular Leydig cell adenomas. This increase was significant ( $p \leq 0.05$ ) in the high-dose group (14.2 mg/kg-bw per day) (Sibinski 1987). In the second study, male CD rats were given only one dietary dose level of APFO (300 ppm; 13.6 mg/kg-bw per day) for 2 years. The exposed males had significantly higher incidences of adenomas of the liver, hyperplasia and adenomas in Leydig cells and hyperplasia and adenomas in pancreatic acinar cells (Biegel et al. 2001). Serum PFOA levels were not reported in either of the chronic studies.

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, several Ames bacterial mutation assays, and three *in vitro* chromosomal aberration tests (two in hamster cells and one in human cells) (see Appendix 2 for specific compound details and references). Positive results were obtained in one chromosome damage test in hamster cells and one micronucleus assay in human cells *in vitro*. PFOA caused oxidative DNA damage in human hepatoma cells in culture and in the liver of rats treated by the oral or intraperitoneal route. The genotoxicity database indicates that PFOA compounds are not mutagenic.

In rodents, PFOA triggers a peroxisome proliferation response, which is mediated by PPAR $\alpha$ . Activation of PPAR $\alpha$  causes changes in liver and affects lipid metabolism and transport and other biochemical processes. The triad of benign tumours observed in PFOA-exposed male rats (liver, testicular Leydig cell and pancreatic acinar cell adenomas) is typical of PPAR agonists, including clofibrate, 2,2-dichloro-1,1,1-trifluoroethane (HCFC 123) and pirinixic acid (WY-14,643) (Cook et al. 1999; Kennedy et al. 2004). It has been proposed that the activation of hepatic PPAR $\alpha$ , rather than direct genotoxic action, is the critical event in the induction of these tumours. The confidence in the PPAR $\alpha$  mode of action is high for liver tumours, moderate for Leydig cell tumours (LCTs) and low for pancreatic acinar cell tumours (PACTs) (reviewed in Klaunig et al. 2003).

PFOA has been shown to activate PPAR $\alpha$  *in vitro* and causes hepatic peroxisome proliferation *in vivo*. Temporal and dose–response data support a PPAR $\alpha$  mode of action for rat liver tumours. In the chronic dietary study by Biegel et al. (2001), PFOA caused an increase in liver weight and peroxisome proliferation in the liver of treated rats at every time point studied, starting at 1 month of treatment, and the first occurrence of liver tumours was after 12 months. In a 14-day study in male rats, Liu et al. (1996) determined an NOEL of 0.2 mg/kg-bw per day and a LOEL of 2 mg/kg-bw per day for increased liver weight and hepatic peroxisome proliferation (measured by hepatic  $\beta$ -oxidation), key endpoints in liver tumour initiation. Evidence of liver carcinogenicity was observed at 13.6 mg/kg-bw per day in the chronic study by Biegel et al. (2001), but not at 1.3 mg/kg-bw per day in the chronic toxicity study by Sibinski (1987), which is in agreement with the dose–response relationship for early key events. In a subchronic study in monkeys,

there was no increase in peroxisome proliferation in response to PFOA, although liver effects, including liver weight increases, were observed (Butenhoff et al. 2002).

PFOA did not induce peroxisome proliferation or cell proliferation in male rat Leydig cells (Biegel et al. 2001), suggesting a mechanism for tumour induction other than direct PPAR activation in the testes. It has been proposed that PFOA-induced LCTs in the male rat are the result of an increase in serum estradiol due to hepatic PPAR $\alpha$  activation and subsequent changes in activities of enzymes involved in steroid biosynthesis. Studies have shown that treatment with PFOA causes increased hepatic aromatase activity and serum estradiol levels (Liu et al. 1996; Biegel et al. 2001). In a 14-day study in male rats, Liu et al. (1996) demonstrated that hepatic aromatase activity and serum estradiol were increased only at doses that caused hepatic peroxisome proliferation. An NOEL of 0.2 mg/kg-bw per day and a LOEL of 2 mg/kg-bw per day for increased hepatic aromatase activity and serum estradiol were determined. In the chronic toxicity study by Sibinski (1987), LCTs were increased significantly at the high dose of 14.2 mg/kg-bw per day but not at the low dose of 1.3 mg/kg-bw per day. PFOA caused an increase in serum estradiol in exposed rats at 1, 3, 6, 9 and 12 months, prior to the first occurrence of LCTs, in the chronic dietary study by Biegel et al. (2001). Thus, the proposed PPAR $\alpha$  mode of action is consistent with dose–response and temporal associations with increased serum estradiol. Within the testis, estradiol modulates growth factor expression, which could lead to hyperplasia and adenomas (Biegel et al. 1995). PFOA and other PPAR $\alpha$  agonists, including bezafibrate, monoethylhexyl phthalate (MEHP) and WY-14,643, have also been shown to inhibit testosterone production in Leydig cells *in vitro* (Klaunig et al. 2003), although serum testosterone was not decreased in the 2-year rat bioassay with PFOA (Biegel et al. 2001). In non-human primates, treatment with PFOA did not cause an increase in serum estrogen or a decrease in serum testosterone, and no abnormal histopathology was noted in the testes in the 26-week study (Butenhoff et al. 2002).

A hepatic PPAR-mediated pathway may also be involved in the induction of PACTs in male rats, although the confidence in this mode of action is lower than for liver tumours or LCTs (reviewed in Klaunig et al. 2003). *In vivo* mechanistic evidence is mainly indirect, from other PPAR-agonists that have been demonstrated to cause rat PACTs. Pancreatic acinar cell (PAC) hypertrophy, hyperplasia and adenomas in rat have been shown to be modified by steroid hormones, including estradiol and cholecystokinin. PFOA exposure could cause reduced bile flow or changes in bile composition resulting from downstream effects of hepatic PPAR $\alpha$  activation. This may, in turn, cause an increase in cholecystokinin (CCK) levels and stimulation of the PACs. Although no mechanistic data are available for PFOA itself, decreased bile flow and bile acid concentration as well as a sustained increase in plasma CCK occurred in rats treated with the PPAR $\alpha$  agonist WY-14,643. These changes were observed as early as 3 months, earlier than the time point at which PACTs were first observed. PFOA-treated rats had increased pancreatic cell proliferation at 15, 18 and 21 months, and acinar hyperplasia was significantly increased in the chronic dietary study by Biegel et al (2001). No abnormal histopathology was noted in the pancreas of PFOA-treated monkeys in the 26-week study (Butenhoff et al. 2002).

In a draft risk assessment, the US EPA stated that “there is strong evidence to conclude that the liver toxicity and liver adenomas that are observed in rats following exposure to PFOA result from a PPAR $\alpha$ -agonist mode of action,” which is unlikely to occur in humans. They also conclude that although the LCTs and PACTs may be relevant to humans, they probably do not represent a significant cancer hazard due to quantitative differences in receptor expression and other toxicodynamic factors (US EPA 2005). However, the Science Advisory Board reviewed the US EPA’s risk assessment and concluded that there may be other modes of action for liver tumours and that as the modes of action for LCTs and PACTs are unknown, they should be considered relevant to humans (US EPA 2006b).

Recent studies in mice lacking expression of the PPAR $\alpha$  gene (PPAR $\alpha$ -null) suggest that some of the effects associated with exposure to PFOA are independent of the peroxisome proliferation pathway. Developmental effects, such as delayed eye opening, deficits in postnatal weight gain and reduced postnatal survival, were observed in wild-type but not PPAR $\alpha$ -null mice, suggesting that these effects are dependent on PPAR $\alpha$  expression. However, early pregnancy losses were observed in both strains of mice, indicating involvement of pathways other than peroxisome proliferation (Abbott et al. 2007). Yang et al. (2002) noted that reductions in spleen weight and number of splenocytes in wild-type mice treated with PFOA in the diet for 7 days did not occur in treated PPAR $\alpha$ -null mice. PFOA-exposed mice also had reduced thymus weight and number of thymocytes, effects that were attenuated in the PPAR $\alpha$ -null mice. However, significant liver weight increase occurred in both wild-type and PPAR $\alpha$ -null mice. Gene profiling studies also suggest that PFOA can alter mouse liver genes independent of PPAR $\alpha$  (Rosen et al. 2008a, b); however, the toxicological relevance of this is not known.

Available epidemiological studies on the adverse health effects of exposure to PFOA include cross-sectional general population studies, studies in populations exposed to higher levels of PFOA through contaminated drinking water, and occupational exposure studies. Recently, two studies (one cross-sectional study in the United States and one cohort study in Denmark) have given limited suggestions of a weak association between gestational exposure to PFOA and reduced birth weight (Apelberg et al. 2007b; Fei et al. 2007). However, the magnitude of the effect was small, given normal variations in the parameters measured, and all of the children were within the normal range of variation. No associations between maternal serum PFOA levels and birth weight were observed in other general population studies in Canada (Monroy et al. 2008; Hamm et al. 2009), Japan (Washino et al. 2009) or a US community with a mean serum PFOA level 10 times higher than that of the general US population (Stein et al. 2009).

Several studies on occupationally exposed workers (Olsen et al. 2003; Sakr et al. 2007a, 2007b; Costa et al. 2009) and on highly exposed community residents (Steenland et al. 2009; Frisbee et al. 2010) have observed a positive association between serum PFOA and total cholesterol and other lipid parameters. Similar findings have been reported in a recent cross-sectional study on the general population of the United States (Nelson et al. 2010). In contrast, other occupational epidemiology studies (Olsen et al. 2000; Olsen and

Zobel 2007) and highly exposed community studies (Emmett et al. 2006b) do not provide evidence of a significant association between serum PFOA and cholesterol.

The overall weight of evidence does not support causal relationships between PFOA and observed adverse health effects, due to numerous confounding factors including exposure to multiple chemicals. A recent review on the epidemiologic evidence of health effects of PFOA also suggests that the available epidemiological data are insufficient to make conclusions regarding the role of PFOA for any of the health effects observed (Steenland et al. 2010a).

Confidence in the effects assessment for PFOA is moderate to high, as the toxicological database covers a wide range of endpoints and life stages, several species and both sexes.

### **Characterization of Risk to Human Health**

The available data are sufficient to derive margins of exposure (MOEs) based on comparisons of serum PFOA levels in laboratory animals at the critical effect levels with serum or plasma PFOA levels in humans from biomonitoring studies. The MOEs between the serum PFOA levels associated with the most sensitive effects in laboratory animals and the plasma PFOA levels in adult Canadians range from approximately 5100 to 30 600 for geometric means and from 2300 to 14 000 for 95th percentiles. For Inuit children (12–54 months), MOEs for the geometric mean and maximum values range from 8000 to 47 500 and 1200 to 7000, respectively. For nursing infants, MOEs for the median and 95<sup>th</sup> percentile values range from 1880 to 11 000 and 660 to 3900, respectively (Table 8).

**Table 8. Margins of exposure**

Critical study and effect (reference)	Critical effect level (mg/kg-bw per day)	PFOA dose metric at critical effect (serum PFOA in µg/mL)	Human exposure to PFOA – serum or plasma (µg/mL)	MOE <sup>1</sup>
Increased liver weight in male mice given APFO by gavage for 14 days  (Loveless et al. 2006)	LOAEL = 0.3	13	Canadians 20–79 years <sup>2</sup> GM – 0.00252	5159
			Canadians 20–79 years <sup>2</sup> 95 <sup>th</sup> percentile <sup>3</sup> – 0.00550	2364
			Inuit children 12–54 months <sup>3</sup> GM – 0.00162	8024
			Inuit children 12–54 months <sup>3</sup> Maximum – 0.01100	1182
			6-month infants, Germany <sup>4</sup> Median – 0.0069	1884
			6-month infants, Germany <sup>4</sup> 95 <sup>th</sup> percentile – 0.0195	667
Changes in lipid parameters in male rats given APFO by gavage for 14 days  (Loveless et al. 2006)	LOAEL = 0.3	20	Canadians 20–79 years <sup>2</sup> GM – 0.00252	7937
			Canadians 20–79 years <sup>2</sup> 95 <sup>th</sup> percentile – 0.00550	3636
			Inuit children 12–54 months <sup>3</sup> GM – 0.00162	12 346
			Inuit children 12–54 months <sup>3</sup> Maximum – 0.01100	1818
			6-month infants, Germany <sup>4</sup> Median – 0.0069	2899
			6-month infants, Germany <sup>4</sup> 95 <sup>th</sup> percentile – 0.0195	1026
Increased liver weight in mouse dams, alterations in fetal ossification and early puberty in male pups, following dosing of dams with APFO by gavage on days 1–17 of pregnancy  (Lau et al. 2006)	LOAEL = 1	21.9	Canadians 20–79 years <sup>2</sup> GM – 0.00252	8690
			Canadians 20–79 years <sup>2</sup> 95 <sup>th</sup> percentile – 0.00550	3982
			Inuit children 12–54 months <sup>3</sup> GM – 0.00162	13 519
			Inuit children 12–54 months <sup>3</sup> Maximum – 0.01100	1991
			6-month infants, Germany <sup>4</sup> Median – 0.0069	3174
			6-month infants, Germany <sup>4</sup> 95 <sup>th</sup> percentile – 0.0195	1123
Increased liver weight in male monkeys dosed with APFO by	LOAEL = 3	77	Canadians 20–79 years <sup>2</sup> GM – 0.00252	30 556
			Canadians 20–79 years <sup>2</sup> 95 <sup>th</sup> percentile – 0.00550	14 000

Critical study and effect (reference)	Critical effect level (mg/kg-bw per day)	PFOA dose metric at critical effect (serum PFOA in µg/mL)	Human exposure to PFOA – serum or plasma (µg/mL)	MOE <sup>1</sup>
gavage for 26 weeks (Thomford 2001b; Butenhoff et al. 2002)			Inuit children 12–54 months <sup>3</sup> GM – 0.00162	47 531
			Inuit children 12–54 months <sup>3</sup> Maximum – 0.01100	7000
			6-month infants, Germany <sup>4</sup> Median – 0.0069	11159
			6-month infants, Germany <sup>4</sup> 95 <sup>th</sup> percentile – 0.0195	3949

<sup>1</sup> MOE was calculated as the ratio of the serum PFOA level associated with the critical effect to the serum PFOA level in humans.

<sup>2</sup> Canadian Health Measures Survey, Health Canada 2010

<sup>3</sup> Northern Contaminants Program, Turgeon-O'Brien et al. 2010. 95th percentile values were not reported, therefore MOEs are based on maximum values.

<sup>4</sup> Fromme et al. 2010

The experimental animal studies that were used for generation of MOEs were those with the lowest administered doses and serum PFOA levels associated with effects. A 14-day oral study in mice and rats (Loveless et al. 2006) had the lowest LOAEL (0.3 mg/kg-bw per day) identified in critical studies, and MOEs were calculated based on the serum PFOA levels in mice and rats associated with this dose. Although no NOAEL was determined in the critical study, there is supporting evidence from other studies, such as a 13-week oral rat study and a 14-day rat inhalation study, in which no effects were observed at 0.06 and 0.31 mg/kg-bw per day, respectively (Haskell Laboratory 1981a; Kennedy et al. 1986; Palazzolo 1993; Perkins et al. 2004).

MOEs were also calculated based on serum levels in mice dosed at the LOAEL for developmental toxicity (1 mg/kg-bw per day) (Lau et al. 2006). Although no NOAEL was determined in this study, in a follow-up study designed to examine the mechanism of action of PFOA-induced developmental effects, an NOAEL for developmental toxicity of 0.3 mg/kg-bw per day was determined, based on decreased neonatal survival at 0.6 mg/kg-bw per day and delayed eye opening at 1 mg/kg-bw per day. As serum PFOA levels were not measured until 22 days post-partum, effect levels from this study were not used for determining an MOE (Abbott et al. 2007). In Macon et al. 2011, significantly lower mammary gland developmental scores in offspring of CD-1 mice on PND 21 were observed when dams were exposed to 0.01 mg/kg-bw/day. This study was not considered appropriate for use in risk characterization, due to evidence of strain sensitivity, lack of repeatability of the endpoint at low exposure levels, lack of understanding of the mechanism of action, and the relevance of this endpoint for humans. Furthermore, the current study does not provide sufficient evidence that these effects are permanent and therefore adverse.

A 26-week toxicity study in monkeys was also selected for MOE estimation, as primates are considered to be a better surrogate for humans than are rodents (Thomford 2001b; Butenhoff et al. 2002). The steady-state serum PFOA level of monkeys dosed at the LOAEL of 3 mg/kg-bw per day was used for the calculations. No NOAEL was determined in this study.

The use of serum levels for the MOE calculations significantly reduces uncertainties associated with interspecies and intraspecies differences in pharmacokinetics. In laboratory animals, PFOA distributes primarily to the serum and liver (Vanden Heuvel et al. 1991; Butenhoff et al. 2004a; Hundley et al. 2006; Kudo et al. 2007). Data on PFOA tissue distribution in humans are limited, but it is assumed that the pattern would be similar to that observed in experimental animals (including male rats, male and female mice and non-human primates) (Hundley et al. 2006). PFOA has been detected in human post-mortem liver samples in two studies (Olsen et al. 2003b; Maestri et al. 2006). Since data on PFOA levels in human tissues are limited, the availability of data on PFOA concentrations in blood (serum or plasma) makes it the most appropriate measure of internal exposure. Due to the long half-life of PFOA and its lack of metabolism, human adult blood levels of PFOA represent cumulative (lifetime) exposure to PFOA and any contributions from its precursors. Blood levels of PFOA are comparable in children, adults and the elderly. Although the critical toxicology studies in experimental animals were conducted over less than lifetime exposure durations, pharmacokinetic data indicate that the reported serum PFOA levels would represent steady state (Vanden Heuvel et al. 1991; Butenhoff et al. 2004a; Lau et al. 2006).

Where an MOE is estimated on the basis of effects in rodents, the possible role of peroxisome proliferation should be acknowledged. Rats and mice are sensitive to the effects of peroxisome proliferators, whereas monkeys and humans are relatively non-responsive at similar doses (reviewed in Klaunig et al. 2003; Kennedy et al. 2004). As humans are generally less susceptible than rodents to peroxisome proliferators, MOEs based on peroxisome proliferation-dependent effects in rodents would be conservative. As the margins were calculated based on the most sensitive effects and species, they are considered protective of both PPAR-dependent and PPAR-independent effects.

APFO has induced tumours in exposed rats, but PFOA compounds have not been tested for carcinogenic potential in any other laboratory animal species. The PPAR-agonist mode of action proposed for rat liver, testes and pancreatic tumours may not be relevant for humans, but human relevance has not been definitively determined according to established frameworks (Meek et al. 2003; Boobis et al. 2006).

PFOA has been shown to activate the human PPAR $\alpha$  in cell culture *in vitro* (Takacs and Abbott 2007; Wolf et al. 2008) but not male rat Leydig cells (Biegel et al. 2001). PPAR $\alpha$  activation has a wide range of effects, including regulating the expression of genes involved in cell growth and survival. In fact, some PPAR $\alpha$  ligands have been shown to possess anti-tumorigenic properties, such as suppression of growth of several types of human cancer cells *in vitro* and inhibition of carcinogenesis *in vivo* (reviewed in Pozzi and Capdevila 2008), making PPAR $\alpha$  a potential target for cancer therapy. It should also

be noted that other PPAR $\alpha$  ligands, such as fibrates, which cause a high incidence of tumours in rodents, are commonly used therapeutically in humans, with no evidence of carcinogenicity in epidemiological studies (reviewed in Peters et al. 2005).

Although the modes of action for tumour induction have not been demonstrated conclusively and the relevance of the rat tumours to carcinogenicity in humans is uncertain, the genotoxicity database indicates that PFOA is not directly mutagenic. Thus, as the tumours observed in male rats are not considered to have resulted from direct interaction with genetic material, a threshold approach is used to characterize risk to human health. The MOEs generated for non-neoplastic effects are protective with respect to the increased incidence of benign tumours observed in the chronic studies of PFOA in rats, since a) the tumours were observed only at PFOA doses higher than those that induced non-neoplastic effects, b) the genotoxicity database indicates that PFOA is not mutagenic, c) rat liver tumours are likely induced via a mode of action that is not relevant to humans and d) there were no PFOA-related effects in non-human primates that have been associated with the development of pancreatic or testicular tumours in rats.

### **Uncertainties in Evaluation of Risk to Human Health**

The use of blood (serum or plasma) levels reduces the uncertainty associated with a determination of the upper-bound estimate of human intake of PFOA, owing to the limited available data on levels of PFOA and precursors in air, foodstuffs, drinking water and breast milk and resulting from contact with household materials treated with perfluorinated substances. Moreover, the levels of PFOA in human blood provide a measure of aggregate exposure from multiple sources and exposure routes. The use of blood levels also significantly reduces uncertainties associated with interspecies and intraspecies differences in pharmacokinetics.

Use of 95th percentile serum or plasma values is conservative. Furthermore, measures have recently been taken to reduce global facility emissions and product content of PFOA and related chemicals, including in Canada (US EPA 2006c; EPA 2009). Although two older biomonitoring studies in the United States have shown declining serum PFOA levels from before the reduction measures were instituted (Calafat et al. 2007; Olsen et al. 2008), more recent data from NHANES demonstrate stable PFOA serum levels over the period from 2003 to 2008 (U.S. CDC 2011). Recent Canadian data exhibit a similar trend of stable levels over the period from 2004 to 2009 (see Table 7). The MOEs presented in Table 8 are based on serum and plasma levels from 1994 to 2009. PFOA levels in Canadians, as reported in the CHMS, are comparable to levels in the United States, as reported in the most recent NHANES data. There remains a gap in biomonitoring data for Canadian infants and children from birth to 2 years. Data from nursing infants have shown that this age group may represent the most highly exposed subpopulation (Fromme et al. 2010).

Uncertainty remains regarding the mode of action for tumour induction; however, as the database for genotoxicity suggests that PFOA is not mutagenic, the MOEs based on non-

neoplastic effects in the most sensitive species are considered protective of any potential carcinogenic effects in humans.

There is some uncertainty regarding the effects of PFOA at low doses, including mammary gland development; additional studies are required to further investigate these early findings.

## Conclusion

The assessment is based on a weight-of-evidence approach regarding the persistence, bioaccumulation, temporal trends in some species (i.e., the polar bear), long-range transport and the widespread occurrence and concentrations of PFOA in the environment and biota (including remote areas of Canada).

Based on the information presented in this screening assessment, it is concluded that PFOA, its salts and its precursors are entering 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. In addition, it is concluded that PFOA and its salts are extremely persistent and meet the criteria for persistence as set out in the *Persistence and Bioaccumulation Regulations*. PFOA and its salts do not meet the criteria for bioaccumulation as set out in the *Persistence and Bioaccumulation Regulations*. Nevertheless, the weight of evidence is sufficient to conclude that PFOA and its salts accumulate and biomagnify in terrestrial and marine mammals

Based on a comparison of upper-bound levels of PFOA in the blood (plasma or serum) of humans with serum levels that are associated with the development of adverse effects in laboratory animals, it is considered that the resulting margins of exposure (Table 8) are adequately protective of human health. It is concluded that PFOA and its salts are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Precursors of PFOA that can degrade to PFOA in the environment were not individually assessed. The approach for the assessment included the contribution of precursors to total PFOA which is the moiety of toxicological concern, as they can degrade to PFOA in the environment.

It is therefore concluded that PFOA, its salts and its precursors meet one or more of the criteria set out in section 64 of CEPA 1999.

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## Appendix 1: Summary of health effects information for PFOA

Endpoint	Lowest effect levels <sup>1</sup> /results
Acute toxicity: oral	<b>Lowest oral LD<sub>50</sub> (female rat) = 430 mg/kg-bw [APFO]</b> (IRDC 1978)  [Additional studies: Biosearch Inc. 1976 [PFOA]; Griffith and Long 1980 [APFO]; Haskell Laboratory 1981b [APFO]; Glaza 1990 [not specified], 1997 [APFO]]
Acute toxicity: dermal	<b>Lowest dermal LD<sub>50</sub> (rabbit) = &gt;100 and &lt;1000 mg/kg-bw [APFO, 24 h, covered]</b> (Riker Laboratories Inc. 1979)  [Additional studies: Haskell Laboratory 1979b [APFO]; Kennedy 1985 [APFO]; Glaza 1995 [PFOA-Na]]
Acute toxicity: inhalation	<b>Lowest inhalation LC<sub>50</sub> (male rat) = 980 mg/m<sup>3</sup> [APFO, 4 h]</b> (Kennedy et al. 1986)  [Additional studies: Haskell Laboratory 1969 [APFO]; Griffith and Long 1980 [APFO]]
Short-term repeated-dose toxicity: oral	<b>Lowest oral LOAEL = 0.3 mg/kg-bw per day</b> based on a marked dose-related increase in relative liver weight in mice (serum PFOA concentration 13 µg/mL) and altered lipid parameters in rats (serum PFOA concentration 20 µg/mL) (no NOAEL). Groups of 10 male mice and rats were dosed by gavage with APFO at 0, 0.3, 1, 3, 10 or 30 mg/kg-bw per day for 14 days (Loveless et al. 2006).  [Additional studies: Christopher and Marias 1977 [APFO]; Metrick and Marias 1977 [APFO]; Griffith and Long 1980 [APFO]; Kojo et al. 1986 [PFO or PFOA, unclear]; Kennedy 1987 [APFO]; Kawashima et al. 1989 [PFOA]; Cook et al. 1992 [APFO]; Sohlenius et al. 1992 [PFO, unspecified salt]; Permadi et al. 1993 [PFOA]; Biegel et al. 1995 [APFO]; Henwood 1997 [APFO]; Kudo et al. 1999 [PFO or PFOA, unclear]; Q. Yang et al. 2000 [PFOA], 2001 [PFOA]; Thomford 2001a [APFO]; Loveless et al. 2006 [APFO]; C. Yang et al. 2008 [PFOA]; Macon et al. 2011 [APFO]]
Short-term repeated-dose toxicity: inhalation	<b>Lowest inhalation LOAEC = 8 mg/m<sup>3</sup></b> (2.48 mg/kg-bw per day, mean serum PFOA concentration 47 µg/mL), based on liver cytoplasmic hypertrophy, degeneration and/or necrosis, increased liver weight, and elevated AP in rats (NOAEC = 1 mg/m <sup>3</sup> , equating to 0.31 mg/kg-bw per day, serum PFOA concentration 13 µg/mL). Male rats were exposed to APFO at 0, 1, 8 or 84 mg/m <sup>3</sup> for 6 h/day, 5 days/week, for 2 weeks (Haskell Laboratory 1981a; Kennedy et al. 1986).  [Additional studies: Haskell Laboratory 1979a [APFO]]
Short-term repeated-dose toxicity: dermal	<b>Lowest dermal LOAEL = 20 mg/kg-bw per day</b> based on increases in liver weight and aspartate aminotransferase (AST)/ALT in rats (no NOAEL). Rats were exposed to APFO at 0, 20, 200 or 2000 mg/kg-bw per day for 6 h/day (covered), 5 days/week, for 2 weeks (Haskell Laboratory 1980; Kennedy 1985).  [Additional studies: Riker Laboratories Inc. 1979 [APFO]; McDonald

Endpoint	Lowest effect levels <sup>1</sup> /results
Subchronic toxicity: oral (rodent)	<p data-bbox="516 233 683 260">1997 [APFO]]</p> <p data-bbox="516 266 1356 495"><b>Lowest oral LOAEL = 0.64 mg/kg-bw per day</b> (mean serum PFOA concentration 41.2 µg/mL) based on transiently increased liver weight, hypertrophy and raised palmitoyl coenzyme A oxidase in rats (NOAEL = 0.06 mg/kg-bw per day, serum PFOA concentration 7.1 µg/mL). Male rats were dosed with APFO at 0, 1, 10, 30 or 100 ppm in the diet for 13 weeks (0, 0.06, 0.64, 1.94 or 6.5 mg/kg-bw per day) (Palazzolo 1993; Perkins et al. 2004).</p> <p data-bbox="516 533 1349 596">[Additional studies: Goldenthal 1978a [APFO]; Griffith and Long 1980 [APFO]]</p>
Subchronic toxicity: oral (primate)	<p data-bbox="516 602 1341 831"><b>Lowest oral LOAEL = 3 mg/kg-bw per day</b> based on increased liver weight in male cynomolgus monkeys dosed with APFO by gavage (capsule) 7 days/week for 26 weeks (serum PFOA concentration 77 µg/mL) (no NOAEL). Groups of six male cynomolgus monkeys were initially dosed at 0, 3, 10 or 30 mg/kg-bw per day. The high-dose animals received no APFO on days 12–21 and resumed dosing on day 22 at 20 mg/kg-bw per day (Thomford 2001b; Butenhoff et al. 2002).</p> <p data-bbox="516 869 1354 999">The liver weight data were subsequently modelled (Butenhoff et al. 2004c) to estimate the lower 95% confidence limit of a benchmark dose associated with a 10% increase in liver weight (LBMD<sub>10</sub>) and the associated serum concentration (LBMIC<sub>10</sub>):</p> <p data-bbox="516 1037 1321 1064">LBMD<sub>10</sub> = 3.9 mg/kg-bw per day [APFO] (LBMIC<sub>10</sub> was 23 µg/mL)</p> <p data-bbox="516 1102 1349 1165">[Additional studies: Goldenthal 1978b [APFO]; Griffith and Long 1980 [APFO]]</p>

Endpoint	Lowest effect levels <sup>1</sup> /results			
Carcinogenicity/ chronic toxicity	<p><b>Non-neoplastic effects:</b>  <b>Lowest oral LOAEL = 1.3 mg/kg-bw per day</b> in male rats and <b>1.6 mg/kg-bw per day</b> in female rats, based on dose-related increases in serum ALT, AP and albumin in males and females; and ataxia and a slight increase in ovarian tubular hyperplasia in females (no NOAEL). CD rats (five per dose per sex) 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/day for females).</p> <p><b>Carcinogenicity:</b>            No evidence of carcinogenic activity was seen in the females. In males, there was an increased incidence of testicular Leydig cell adenomas (0/49, 2/50 and 7/50 in control, low-dose and high-dose groups, respectively), significant (<math>p \leq 0.05</math>) at the high dose (Sibinski 1987).</p> <p><b>Additional studies:</b>  <b>Oral LOAEL = 13.6 mg/kg-bw per day</b> based on increased incidences of Leydig cell hyperplasia and adenomas, liver adenomas, and pancreatic acinar cell hyperplasia and adenoma in male rats (no NOAEL). Male CD rats were given APFO at 0 or 300 ppm in the diet (0 or 13.6 mg/kg-bw per day) for 2 years (Biegel et al. 2001).</p>			
		Control (ad libitum)	Control (pair-fed)	Dosed group (300 ppm)
	Leydig hyperplasia	11/80	26/78	35/76*
	Acinar hyperplasia	14/80	8/79	30/76*
	Leydig adenoma	0/80	2/78	8/76*
	Acinar adenoma	0/80	1/79	7/76*
	Hepatic adenoma	2/80	1/79	10/76*
	Acinar carcinoma	0/80	0/79	1/76
	Hepatic carcinoma	0/80	2/79	0/76
* $p \leq 0.05$				
Genotoxicity and related endpoints: <i>in vitro</i>	<p><b>Negative:</b></p> <p>Bacteria, mutation, with and without S9 [PFOA-Na] (Lawlor 1995) [Additional studies: Kennedy 1976 [not specified]; Litton Bionetics Inc. 1978 [APFO]; Lawlor 1996 [APFO]]</p> <p>Mammalian cells, chromosomal aberration, with and without S9 [APFO] (Murli 1996a) [Additional studies: Murli 1996c [APFO]; 1996f [PFOA-Na]]</p>			

Endpoint	Lowest effect levels <sup>1</sup> /results
	<p><b>Positive:</b></p> <p>Mammalian (CHO) cells, chromosomal aberration [PFOA-Na] (Murli 1996d)</p> <p>Mammalian (human hepatoma) cells, micronuclei and oxidative DNA damage [PFOA] (Yao and Zhong 2005)</p>
Genotoxicity and related endpoints: <i>in vivo</i>	<p><b>Negative:</b></p> <p>Mouse (male/female) bone marrow micronucleus [PFOA-Na], up to 5 g/kg-bw; acute oral gavage (Murli 1995)</p> <p>[Additional studies: Murli 1996b [APFO]; 1996e [APFO]]</p> <p><b>Positive:</b></p> <p>Rat (male), oxidative DNA damage, increase in 8-hydroxy-deoxyguanosine in liver DNA but not kidney DNA [PFOA]; 0.02% in diet for 2 weeks or 100 mg/kg-bw by a single intraperitoneal injection (Takagi et al. 1991)</p>
Developmental toxicity: oral	<p><b>Oral LOAEL = 1 mg/kg-bw per day</b> (mean serum PFOA level 21.9 µg/mL in dams) based on maternal toxicity (increased liver weight) and fetal toxicity (reduced ossification, early puberty in males) in mice (no NOAEL). Pregnant CD-1 mice were given APFO by gavage at 0, 1, 3, 5, 10, 20 or 40 mg/kg-bw on days 1–17 of gestation (Lau et al. 2006).</p> <p>[Additional studies: Gortner 1981 [APFO], 1982 [APFO]; Staples et al. 1984 [APFO]; Mylchreest 2003 [APFO]; Abbott et al. 2007 [APFO]; White et al. 2007 [APFO]; Wolf et al. 2007 [APFO]; Hines et al. 2009 [APFO]; Macon et al. 2011 [APFO]]</p>
Developmental toxicity: inhalation	<p><b>Inhalation LOAEC = 10 mg/m<sup>3</sup></b> (equivalent to 3.1 mg/kg-bw per day) in rats, based on maternal toxicity (unkempt appearance, lower weight gain, increased liver weight) and fetal toxicity (lower body weight) (NOAEC = 1 mg/m<sup>3</sup>). Pregnant rats were exposed to APFO at 0, 0.1, 1 or 10 mg/m<sup>3</sup> for 6 h/day (whole-body exposure) on days 6–15 of gestation (Staples et al. 1984).</p>
Reproductive toxicity	<p><b>Oral LOAEL = 1 mg/kg-bw per day</b> in rats, based on parental toxicity (kidney and liver weight increases) in F<sub>0</sub> and F<sub>1</sub> males (NOAEL for reproductive parameters = 30 mg/kg-bw per day). Sprague-Dawley rats (60 rats per sex per group) were dosed with APFO by gavage at 0, 1, 3, 10 or 30 mg/kg-bw per day. F<sub>0</sub> exposed from cohabitation to 6 weeks post-weaning of F<sub>1</sub>; F<sub>1</sub> exposed from weaning to weaning of F<sub>2</sub> (York 2002; Butenhoff et al. 2004a, b).</p>
Epidemiological studies (general population exposure)	<p>Random selection of 1400 women and their infants from the Danish National Birth Cohort. Maternal PFOA serum levels were inversely associated with birth weight and length. There were no associations between maternal PFOA and early childhood developmental milestones at 6 and 18 months. In 1240 women with planned pregnancies, increased maternal serum PFOA early in gestation was associated with increased time to pregnancy (mean maternal serum PFOA = 0.0056 µg/mL; lowest</p>

Endpoint	Lowest effect levels <sup>1</sup> /results
	<p>[reference] quartile: maternal PFOA <math>\leq 0.003\ 91\ \mu\text{g}/\text{mL}</math>) (Fei et al. 2007, 2008a, b, 2009)</p> <p>In a cross-sectional study of 293 newborn cord blood samples in Baltimore, Maryland, there was a small negative association of cord blood PFOA level with birth weight (mean cord serum PFOA = <math>0.0016\ \mu\text{g}/\text{mL}</math>) (Apelberg et al. 2007b).</p> <p>In a study of 101 pregnant women and their infants in Hamilton, Ontario, there was no association between maternal or cord serum PFOA and birth weight (mean maternal serum PFOA = <math>0.002\ 54\ \mu\text{g}/\text{mL}</math> at 24–28 weeks' gestation and <math>0.002\ 24\ \mu\text{g}/\text{mL}</math> at delivery; mean cord serum PFOA = <math>0.001\ 94\ \mu\text{g}/\text{mL}</math>) (Monroy et al. 2008).</p> <p>In a retrospective cohort study of 428 women in Japan, there was no association between maternal serum PFOA levels and birth weight (mean maternal serum PFOA = <math>0.0014\ \mu\text{g}/\text{mL}</math>) (Washino et al. 2009).</p> <p>In a study of 252 pregnant women and their babies in Alberta, there was no association between maternal serum PFOA and fetal weight (median maternal serum PFOA = <math>0.0015\ \mu\text{g}/\text{mL}</math>) (Hamm et al. 2009).</p> <p>In a study of 105 Danish men from the general population, men with a high level of combined serum PFOS and PFOA had lower sperm concentrations (Joensen et al. 2009).</p> <p>In a cross-sectional study of 860 adults from the general population of the U.S., there was a positive association between serum PFOA and total cholesterol and non-high-density cholesterol (Nelson et al. 2010).</p> <p>In a cross-sectional study of 860 adults from the general population of the U.S., when adjusted for confounders, there was an association between serum PFOA and liver enzymes (Lin et al. 2010).</p> <p>In a cross-sectional study of 3974 adults from the general population of the U.S., there was a positive association between serum PFOA and thyroid disease (Melzer et al. 2010).</p> <p>In a prospective cohort study of 713 Danish people, there was no association of plasma PFOA levels and incidence rate of prostate, bladder, pancreatic and liver cancers (Eriksen et al. 2009).</p>
Epidemiological studies (populations with greater exposure to PFOA through contaminated drinking water)	<p>In a cross-sectional study of 1555 singleton births in Ohio, a subset of 380 of the mothers lived in a county where drinking water was known to be contaminated with PFOA (mean drinking water concentration 2002–2005: <math>6.78\ \mu\text{g}/\text{L}</math>). There was no difference in mean birth weight or in the incidence of low birth weight in the highly exposed group compared with those in surrounding counties with levels of PFOA in drinking water of approximately 20–1000 times lower (Nolan et al 2009a). In a follow-up study, the investigators reported no association between</p>

Endpoint	Lowest effect levels <sup>1</sup> /results
	<p>elevated exposure to PFOA (as determined by living in an area serviced by contaminated drinking water) and congenital anomalies (Nolan et al. 2009b). Serum levels of PFOA were not measured in these studies; however, a previous study of a population in this drinking water area reported a median serum PFOA concentration of 0.354 µg/mL (Emmett et al. 2006b; see above).</p> <p>In a cross-sectional study of 1845 pregnancies in communities in Ohio and West Virginia served by drinking water contaminated with PFOA, serum PFOA was measured up to 5 years following the birth, and health outcomes were self-reported. There was no association between maternal serum PFOA level and birth weight (mean serum PFOA level: 0.048 µg/mL; median serum PFOA level: 0.0212 µg/mL) (Stein et al. 2009).</p> <p>In a cross-sectional general population study of 371 subjects in Ohio in a county where the drinking water contained PFOA at a mean level of 3.5 µg/L for the previous 3 years, there were no significant relationships between serum PFOA concentration and liver or renal function tests, cholesterol levels or other hematological parameters (median serum PFOA concentration: 0.354 µg/mL) (Emmett et al. 2006b).</p> <p>In a cross-sectional study of 54 468 adults living in Ohio and West Virginia served by drinking water contaminated with PFOA (C8 Health Project), the self-reported age-adjusted prevalence of diabetes was similar to state-wide levels for Ohio and West Virginia. Odds ratios for type II diabetes were &lt;1 for all serum PFOA levels above the lowest (reference) decile, including when analysis was restricted to those who had lived in contaminated water districts for at least 20 years and with at least 10 years of exposure before diagnosis (mean serum PFOA level: 0.0868 µg/mL; median serum PFOA level: 0.0281 µg/mL; lowest [reference] decile: serum PFOA &lt;0.0079 µg/mL) (MacNeil et al. 2009).</p> <p>In a cross-sectional study of 46 294 adults living in Ohio and West Virginia served by drinking water contaminated with PFOA (C8 Health Project), there were positive trends between increased serum PFOA and total cholesterol, LDL-cholesterol and triglycerides. The odds ratio for high cholesterol increased for each quartile, up to 1.4. There was no association between serum PFOA levels and HDL-cholesterol (mean serum PFOA level: 0.080 µg/mL; median serum PFOA level: 0.027 µg/mL; lowest [reference] quartile: serum PFOA &lt;0.0131 µg/mL; highest quartile: ≥0.067 µg/mL) (Steenland et al. 2009).</p> <p>In a cross-sectional study of 46 294 children and adolescents living in the Mid-Ohio River Valley served by drinking water contaminated with PFOA (C8 Health Project), there was a significant positive association between serum PFOA and total cholesterol and LDL-cholesterol (Frisbee et al. 2010).</p> <p>In a cross-sectional study of 54 951 adult community residents in</p>

Endpoint	Lowest effect levels <sup>1</sup> /results
	Ohio and West Virginia, exposed through contaminated drinking water (C8 Health Project), there was a significant positive association between serum PFOA uric acid (hyperuricemia) (Steenland et al. 2010b).
Epidemiological studies (occupational exposure)	<p><b>Liver enzymes, hormones, lipids and other serum parameters:</b></p> <p>In a cross-sectional and longitudinal (3–6 years) examination of medical records for 263 workers in fluorochemical production, no significant relationships were noted between serum PFOA and hematological, thyroid or liver parameters. There were positive associations between serum PFOA and total cholesterol and triglycerides (mean serum PFOA level: 1.78 µg/mL; range: 0.04–12.7 µg/mL) (Olsen et al. 2003a).</p> <p>In two small cross-sectional studies (111 and 80 workers in PFOA production), serum PFOA levels were not significantly associated with serum estradiol or testosterone in either study (serum PFOA: up to 115 µg/mL) (Olsen et al. 1998).</p> <p>Annual medical surveillance of 53 male workers in PFOA production (exposed for 0.5–32.5 years) and 107 unexposed controls was carried out. Over 30 years, there was no clinical evidence of any specific disease in exposed workers, and all biochemical parameters tested were within normal range. In 2007, total cholesterol was significantly greater in 34 exposed workers compared with 34 controls matched by age and other factors. Multivariate analysis on 56 subjects who had serum PFOA assessed concurrently with biochemical parameters over the last 6 years showed that total cholesterol was weakly but significantly correlated with serum PFOA (serum PFOA analyzed 2000–2007; in 2007, median serum PFOA in currently exposed workers: 5.71 µg/mL; median in formerly exposed workers: 4.43 µg/mL) (Costa et al. 2009).</p> <p>Medical surveillance data on male workers involved in PFOA production in 1993 (<i>n</i> = 111), 1995 (<i>n</i> = 80) and 1997 (<i>n</i> = 74) (only 17 subjects were common for the 3 surveillance years) indicated that serum cholecystokinin levels were negatively associated with serum PFOA levels. There were no associations with serum PFOA and liver enzymes or lipids (serum PFOA levels: means for each year 5.0–6.8 µg/mL, overall range up to 114.1 µg/mL) (Olsen et al. 2000).</p> <p>In a cross-sectional study in 1025 workers in fluoropolymer production, using multivariate linear regression, serum PFOA was significantly positively associated with cholesterol, very low density lipoprotein (VLDL), LDL and gamma glutamyl aminotransferase (GGT), and in men, with serum estradiol and testosterone. There was no association of serum PFOA with HDL, triglycerides, AST, ALT or bilirubin (serum PFOA levels ranged from 0.0046 to 9.55 µg/mL; mean 0.428 µg/mL) (Sakr et al. 2007a).</p> <p>Medical surveillance data and serum PFOA measurements were</p>

Endpoint	Lowest effect levels <sup>1</sup> /results
	<p>collected for up to 25 years for 454 workers in fluoropolymer production. A linear mixed effects model was used. Serum PFOA was positively associated with total cholesterol and AST and negatively associated with total bilirubin. There was no association of serum PFOA with triglycerides, LDL, HDL, GGT, ALT or AP (serum PFOA levels ranged from 0 to 22.66 µg/mL; mean 1.13 µg/mL over 23-year study period) (Sakr et al. 2007b).</p> <p><b>Mortality and cancer:</b></p> <p>A retrospective cohort mortality study of 2083 employees at a fluorochemical production facility was conducted. The exposure of the cohort members to fluorochemicals was grouped as high, low or non-exposed based on biomonitoring for PFOS. The overall mortality rate was less than expected in the general population. There were two deaths due to liver cancer in the high- and low-exposure groups (SMR 3.08) and three deaths due to bladder cancer, all in the high-exposure group (SMR 12.77) (Alexander et al. 2003). PFOA was not manufactured at this site, but workers showed occupational levels of serum PFOA along with six other perfluorochemicals (serum PFOA: geometric mean 0.899 µg/mL) (Olsen et al. 2003c).</p> <p>A retrospective cohort mortality analysis of 6027 workers at a West Virginia fluoropolymer manufacturing plant was done. The SMRs were derived based on comparison with the US population, state population and a regional employee population. Most SMRs were less than or equal to 1. The only statistically significant elevation in mortality was for diabetes mortality compared with the regional employee population (SMR = 1.97). There was also a non-significant elevation for ischemic heart disease (IHD) mortality compared with the regional employee population (SMR = 1.09). The numbers of deaths due to liver, pancreatic and testicular cancers (8, 11 and 1, respectively) were less than expected for the US population (Leonard et al. 2008). PFOA in serum of workers had previously been measured at this facility and was found to be detectable regardless of job description. In 1025 workers, serum PFOA levels ranged from 0.0046 to 9.55 µg/mL (mean 0.428 µg/mL) (Sakr et al. 2007a; see above).</p> <p>A mortality study conducted on a cohort of 4747 employees exposed to APFO at DuPont plant concluded that there was no increased IHD mortality risk for APFO exposed workers (Sakr et al. 2009).</p> <p>A mortality study was conducted on a cohort of 3993 employees in APFO production. Jobs were classified as “definite” or “probable” APFO exposure or non-exposed. Previously collected data on serum PFOA levels for various areas of the plant were used to estimate cumulative exposure. SMRs for the general population of Minnesota were ≤1 for most causes of death, including liver cancer, liver cirrhosis, pancreatic cancer, IHD and all heart disease. There were no deaths from testicular cancer (no SMR estimated). The SMRs for subjects in jobs</p>

<b>Endpoint</b>	<b>Lowest effect levels<sup>1</sup>/results</b>
	with definite exposure were >1 for prostate cancer and cerebrovascular disease (SMRs of 2.1 and 1.6, respectively). Comparing the highest and lowest cumulative exposure categories gave an increased risk for prostate cancer and cerebrovascular disease (hazard ratios [HRs] of 6.6 and 4.6, respectively). The SMR for subjects in jobs with probable exposure was 2.0 for diabetes, and the HR compared with the low-exposure group was 3.7. There were no deaths from diabetes in the definite exposure group (Lundin et al. 2009).

<sup>1</sup>LC<sub>50</sub>, median lethal concentration; LD<sub>50</sub>, median lethal dose; LOAEC, lowest-observed-adverse-effect concentration; LOAEL, lowest-observed-adverse-effect level; NOAEC, no-observed-adverse-effect concentration; NOAEL, no-observed-adverse-effect level.