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DRAFT State of Per- and Polyfluoroalkyl Substances (PFAS) Report

Environment and Climate Change Canada
Health Canada

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Contents

Executive Summary

Per- and polyfluoroalkyl substances (PFAS) are a class of over 4700 human-made substances. These substances have a wide range of uses in products available to consumers, industrial applications, and other specialized applications. The widespread use of these substances and their extreme persistence in the environment, propensity for accumulation, and mobility has led to PFAS being commonly detected in the environment and humans. Despite data having largely been generated on a limited suite of well-studied PFAS, there is a growing body of evidence that exposure to other PFAS can lead to adverse effects on the environment and human health. Cumulative effects from co-exposure to multiple PFAS may also occur.

This report provides a qualitative assessment of the fate, sources, occurrence, and potential impacts of PFAS on the environment and human health to inform decision-making on PFAS in Canada.

The common chemical characteristic of PFAS is their perfluoroalkyl moiety, which is extremely stable in the environment, to the extent that PFAS have often been termed “forever chemicals.” Simple PFAS are highly persistent, whereas more complex molecules transform into stable PFAS. In this report, PFAS refers to the broad chemical definition by the Organisation for Economic Co-operation and Development (OECD), which—with a few noted exceptions—includes any chemical with at least a perfluorinated methyl group ($–CF_3$) or a perfluorinated methylene group ($–CF_2–$). This definition captures substances with a wide range of structures and properties, from discrete chemicals such as perfluorocarboxylic acids, perfluorosulfonic acids, and fluorotelomer alcohols, to side-chain fluorinated polymers and high molecular weight fluoropolymers. Some PFAS on the market also possess structural attributes other than perfluoroalkyl chains (e.g., inclusion of ether linkages or chlorine atoms in the fluorinated hydrocarbon chains).

The desirable properties of PFAS (including their oil and water repellency, high chemical, physical and thermal resistance to degradation, and low surface tension) has led to their use in a wide range of products available to consumers and in industrial applications. Some typical uses of PFAS include surfactants, lubricants, and repellents (for dirt, water, and grease). PFAS can also be found in certain firefighting foams (i.e., aqueous film-forming foams [AFFF]), textiles (e.g., carpets, furniture, and clothing), cosmetics, and food packaging materials.

There are many potential sources of PFAS in Canada that can lead to human exposure and releases to the environment. Humans can be exposed to PFAS from various sources such as food and food packaging, cosmetics, products available to consumers, ambient air, indoor air and dust, and drinking water. Furthermore, PFAS-impacted contaminated sites represent “hot spot” areas across Canada where Canadians and the environment may be exposed to elevated concentrations of PFAS. Such sites include those associated with the use of AFFF, typically released during activities associated with fighting fuel fires, including training activities and maintenance of firefighting equipment at airports and military facilities. As it is not possible to separate PFAS-containing waste from the general waste stream, PFAS-containing products can be found in municipal solid waste (MSW) landfills or are destined for MSW incineration. Composting of PFAS-containing food packaging, releases into wastewater treatment systems, and the application of biosolids to land provide additional routes of entry for PFAS into the environment. It should be noted that PFAS contamination is present throughout Canada and is not limited to a few sources or areas.

Once PFAS are released into the environment, their physical and chemical properties influence their fate and behaviour. Neutral PFAS (e.g., fluorotelomer alcohols) may be more volatile and therefore more likely to be found in the atmosphere. Fluorotelomer alcohols as well as other polyfluoroalkyl substances and some side-chain fluorinated polymers can undergo transformation to form other more stable PFAS that are extremely persistent in the environment under ambient conditions. Ionic PFAS (which are predominantly ionized at environmental pH) such as perfluorocarboxylic acids and perfluorosulfonic acids are water soluble and non-volatile, and thus partition predominantly to water where they can mobilize. Some shorter-chain PFAS, adopted in place of prohibited long-chain PFAS, have proven to be even more mobile on a local scale, potentially leading to transfer to food crops and drinking water. Some PFAS are also capable of undergoing long-range transport in the atmosphere (i.e., for neutral, volatile PFAS) or in global ocean currents (i.e., for ionic PFAS), as evidenced by their widespread distribution around the world, including in remote regions. Experience with contaminated sites management has also indicated that PFAS are very challenging to remove from environmental media, and it is not possible to remove them from the broader environment.

Globally, PFAS can be found in virtually all environmental compartments, including air, surface and groundwater, oceans and soils as well as in wastewater influent and effluent, landfill leachate, sewage sludge, and contaminated sites. While the highest reported concentrations are typically in proximity to known sources of release, PFAS are also routinely reported in locations far removed from these sources. Similarly, although the highest concentrations of PFAS in organisms have been noted in proximity to known releases, their ubiquitous presence has been noted in tissue samples collected from organisms worldwide. While the number of PFAS that have been examined in studies to date has been limited, studies have increasingly noted the frequent detection of a range of PFAS. Monitoring and research activities in Canada are being conducted to better understand trends in PFAS occurrence in Canadian ecosystems and wildlife. Thus far, these activities have confirmed the ubiquitous presence of PFAS throughout Canada.

Depending on the substance's physical and chemical properties, certain PFAS have been found to bioaccumulate in biota. PFAS have also been reported to significantly biomagnify (i.e., to accumulate to increasingly higher levels up the food chain) in air-breathing organisms (e.g., mammals, birds), which can increase the likelihood of adverse effects being observed. Ecotoxic effects such as immunotoxicity and neurotoxicity as well as effects on growth, reproduction, and development, have been reported in the literature, although there are still significant data gaps for certain species, subgroups of PFAS, and types of effects studied.

Currently, only a small number of PFAS are monitored in human biomonitoring surveys. Certain PFAS have been found in the blood (plasma or serum) of the general population in Canada and internationally. PFAS can also be transferred through the placenta, and infants and children can be exposed to PFAS though ingestion of human milk. A number of subpopulations were identified as having potential for greater exposure to PFAS. Northern Indigenous communities (as measured in adults, including pregnant women) as well as Indigenous youth and children in other parts of Canada were found to have elevated levels of certain PFAS. Firefighters internationally were also found to have elevated levels of certain PFAS. Canadian firefighters and people living in the vicinity of sites contaminated with PFAS (e.g., associated with the use of AFFF) may also be disproportionately exposed to higher levels of PFAS, although specific Canadian biomonitoring information was not available for these subpopulations.

In humans, some well-studied PFAS can be readily absorbed in the body and bind to proteins in the blood. These PFAS can then be distributed through the bloodstream and accumulate in well perfused tissues (e.g., liver and kidneys). Some of the studied PFAS have been shown to be eliminated very slowly from the human body. Toxicological (*in vitro* and *in vivo*) and human epidemiological information is only available for a limited number of PFAS. On the basis of these studies, it is evident that exposure to PFAS has the potential to cause effects of concern to human health. Furthermore, recent information on well-studied PFAS, particularly perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), shows negative effects on human health at lower levels than in previous studies. Effects commonly reported in animal studies include effects on the liver, kidney, thyroid, immune system, nervous system, metabolism and bodyweight, and reproduction and development. Outcomes of human epidemiological studies involve similar organs/systems/endpoints.

Although the vast majority of toxicology and epidemiology studies have focused on the effects from exposure to a single PFAS, biota and humans typically experience exposure to many PFAS at a given time, as can be seen from environmental sampling and biomonitoring data. A limited number of studies have evaluated the interactive effect of multiple PFAS on different endpoints; however, given the vast number and ubiquity of PFAS, it is reasonable to assume that cumulative effects may occur. The Government of Canada has been actively studying the ecological and human health effects associated with exposure to PFAS, including the use of new approach methods to characterize multiple PFAS in biological and environmental media at the same time. These studies confirm the environmental presence of PFAS mixtures that include many substances that are not targeted in typical monitoring and surveillance studies. In addition to specific initiatives, there are ongoing environmental and human monitoring and surveillance programs to address subpopulations that may be more susceptible or highly exposed, including pregnant women and children, Indigenous and northern communities in Canada, and firefighters.

Canada has acted to address PFAS for which early evidence had indicated potential concerns for the environment or human health. A limited number of subgroups of PFAS are subject to risk management controls in Canada. The manufacture, use, sale, offer for sale, and import of PFOS, PFOA, long-chain perfluorocarboxylic acids, and their salts and precursors are prohibited under the *Prohibition of Certain Toxic Substances Regulations, 2012*, with a limited number of exemptions. Proposed regulations that would repeal and replace the *Prohibition of Certain Toxic Substances Regulations, 2012*, were also published in May 2022, which propose to further restrict these groups of substances by removing or providing time limits for most remaining exemptions. Some PFAS notified under the *New Substances Notification Regulations (Chemicals and Polymers)* have also been subject to prohibitions, ministerial conditions, and significant new activity provisions under the *Canadian Environmental Protection Act, 1999* (CEPA). It has been observed that shorter-chain PFAS have been used as substitutes for long-chain PFAS (carbon chain length of 8 or more) following the implementation of regulatory restrictions on the latter.

Other domestic activities that target PFAS include water and soil guidelines developed for the protection of human health and the environment by the Government of Canada or through the Canadian Council of Ministers of the Environment (CCME), reducing risks from known federal contaminated sites through the *Federal Contaminated Sites Action Plan* and reducing the anthropogenic release of chemicals of mutual concern into the Great Lakes under the *Great Lakes Water Quality Agreement*. Regulations for the import, export, and manufacture of certain ozone-

depleting substances and concerning halocarbon alternatives are also set out under the *Ozone-Depleting Substances and Halocarbon Alternatives Regulations*.

The Government of Canada works with other governments internationally on initiatives that address PFAS, including through the OECD and the Stockholm Convention on Persistent Organic Pollutants. For example, Canada has successfully nominated long-chain perfluorocarboxylic acids, their salts, and related compounds for addition to the Stockholm Convention.

Given the significant data gaps for most PFAS and the complexity and magnitude of the group, continuing to assess and manage risks of individual PFAS or small groups of PFAS is impractical and does not address the broader concern posed by these substances. Complexities include the nature of their physical and chemical properties, unique environmental fate and behaviour characteristics, and co-exposure to multiple PFAS in biota and humans. Generating data and applying a quantitative risk analysis and management approach would take an extremely long time; meanwhile, exposures to the environment and humans would continue to increase, and new PFAS would continue to be created or used in Canada.

The broad use of PFAS and their consequent ubiquitous presence in the environment have resulted in continuous environmental and human exposure to multiple PFAS, with well-studied PFAS demonstrating the potential to affect multiple systems and organs in both humans and wildlife. Certain PFAS may potentially bioaccumulate and biomagnify in food webs to an extent that can cause adverse effects in biota at low environmental concentrations; recent information on well-studied PFAS, particularly PFOA and PFOS, also shows negative human health effects at lower levels than indicated by previous studies. As a result of the extreme persistence of PFAS, their potential for bioaccumulation in organisms and biomagnification through the food chain, their ability to move locally and over long ranges, and the difficulty of their removal from the broader environment, environmental concentrations and uptake by biota and humans will increase in the absence of intervention. Additionally, the potential for cumulative exposure and effects are important considerations as most wildlife and human exposures involve an unknown mixture of PFAS.

Despite uncertainties associated with understanding the characteristics of substances across the range of PFAS structures from toxicological, epidemiological and monitoring datasets that are focused on a limited number of PFAS, there is a growing body of evidence suggesting that concerns identified for well-studied PFAS are more broadly applicable than previously believed. Similarly, while the specific hazards associated with mixtures of PFAS are largely unknown, there are many potential sources of PFAS that can lead to exposure and it is reasonable to assume that cumulative effects may occur from exposure to multiple PFAS.

Consistent with application of precautionary assumptions that are protective of human health and the environment when addressing gaps in information, it is necessary to anticipate that hazardous properties identified for PFAS that have been well studied may also be inherent in other substances in the class, and that combined exposure to multiple PFAS increases the likelihood of detrimental impacts.

Owing to the extreme persistence of these substances, impacts on the environment are expected to increase if entry to the environment continues. On the basis of what is known about well-studied PFAS and the potential for other PFAS to behave similarly, it is proposed that the class of PFAS meets the criterion under paragraph 64(*a*) of CEPA as these substances are entering or may enter

the environment in a quantity or concentration or under conditions that have or may have immediate or long-term harmful effects on the environment or its biological diversity. However, it is proposed to conclude that the class of PFAS does not meet the criterion under paragraph 64(*b*) of CEPA as these substances are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends.

Owing to the widespread use of PFAS combined with their ubiquitous presence in the environment, humans are continuously exposed to multiple PFAS, which have the potential to cause adverse effects of concern. On the basis of what is known about well-studied PFAS and the potential for other PFAS to behave similarly, and on the expectation that combined exposures to multiple PFAS increase the likelihood of detrimental impacts, it is proposed that the class of PFAS meets the criterion under paragraph 64(*c*) of CEPA as these substances are entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that the class of PFAS meets one or more of the criteria set out in section 64 of CEPA.

1 Introduction

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have developed a report on the class of per- and poly-fluoroalkyl substances (PFAS) to provide an overview of the sources, fate, occurrence, and potential impacts of PFAS on the environment and human health. This report and its proposed conclusion are intended to inform decision-making on PFAS as a class in Canada. This class of substances was considered a priority on the basis that scientific evidence to date indicates that the PFAS used to replace regulated PFAS (i.e., perfluorooctane sulfonate and its salts and precursors [PFOS], perfluorooctanoic acid and its salts and precursors [PFOA], and long-chain perfluorocarboxylic acids [LC-PFCAs] and their salts and precursors) may also be associated with environmental or human health effects.

PFAS are a large class of human-made substances that include a very broad range of chemicals from discrete fluorosurfactants to high molecular weight fluoropolymers, including larger precursors that can transform in the environment to produce simpler PFAS. Their unique properties have led to their use in a wide range of industrial processes and consumer products, such as surfactants and water and grease repellents. For example, these substances are used in certain firefighting foams, textiles (including carpets and clothing), cosmetics, and paper food packaging.

The common chemical characteristic of PFAS is the perfluoroalkyl moiety, which is extremely stable, rendering it resistant to environmental and metabolic transformation. As a result of this stability, PFAS have often been termed “forever chemicals” due to their long persistence in the environment. The extreme persistence of the fluorocarbon moiety, combined with the propensity for environmental accumulation and mobility of many PFAS, has resulted in the ubiquitous presence of PFAS globally, even in remote regions like the Arctic (Kwiatkowski et al. 2020). It has been argued that the ongoing release of these highly persistent substances will result in increased concentrations and increased probabilities of known and unknown effects (Cousins et al. 2020a).

The widespread use of these substances has led to the presence of certain PFAS in humans and nearly all environmental compartments, including ambient air, surface waters, groundwater, marine waters, and soil as well as in landfill leachates, wastewater influent and effluent, sewage sludge, and contaminated sites (e.g., ECHA 2022c). Globally, several groups of PFAS have been found in the environment near point sources, such as manufacturing plants and sites where firefighting foams have been used, including airports and military bases (e.g., Hu et al. 2016; Lanza et al. 2016). PFAS can also be released to the environment through consumer use and disposal of PFAS-containing products. Therefore, landfills and wastewater treatment facilities (including associated waste products such as biosolids) are potential PFAS sources (e.g., Gewurtz et al. 2013; Lakshminarasimman et al. 2021). Once in the environment, certain PFAS move readily through water and soil and can contaminate large areas (e.g., Bhavsar et al. 2016; CCME 2021a). Significant costs are associated with assessing and remediating contaminated soil and drinking water sources (Kwiatkowski et al. 2020). This is because PFAS (and especially the perfluoroalkyl moiety) do not readily break down, and treatment and

destruction technologies at commercial scales are still quite limited. Many PFAS have been shown to be transported long distances through the atmosphere, waterbodies, and within groundwater. Long-range transport of PFAS has resulted in these substances being found in the Arctic in air, ice, and both fresh and salt water as well as in wildlife such as polar bears, whales, seals, and birds (Muir et al. 2019). Certain PFAS have also been found in significantly higher concentrations in northern First Nations and Inuit communities compared with the rest of the Canadian population (e.g., Caron-Beaudoin et al. 2020; Garcia-Barrios et al. 2021).

In Canada, three well-defined subgroups of PFAS (i.e., PFOS, PFOA, and LC-PFCAs, and their salts and precursors) were assessed under Canada's Chemicals Management Plan (CMP) (EC 2006, 2012; EC, HC 2012). These groups were added to the List of Toxic Substances found in Schedule 1 of CEPA on the basis of risks to the environment due in large part to their persistence and bioaccumulation potential, and are regulated under the *Prohibition of Certain Toxic Substances Regulations, 2012* (PCTSR). This risk management measure addresses 94 PFAS on the Domestic Substances List (DSL)[1] (Canada 1999). Given that these subgroups are defined using a description of the fluorinated moiety, the risk management measures also apply to any PFAS meeting the description, even those not known to be used in commerce in Canada. Approximately 100 PFAS, notified under the *New Substances Notification Regulations (Chemicals and Polymers)* (NSNR), have also been subject to prohibitions, ministerial conditions, or significant new activity (SNAc) provisions under CEPA. Many of these actions under the NSNR have been rescinded and replaced by the introduction of other regulations, which cover the same substances and prevent risk to human health and/or the environment (e.g., the *Ozone-Depleting Substances and Halocarbon Alternatives Regulations* [ODSHAR]).

A quantitative risk analysis and management approach on discrete substances, subgroups, or groups of existing PFAS (i.e., with risk conclusions drawn and management actions taken for each substance/group) has been recognized as an inefficient way to manage the broad class of PFAS. Many scientists (Helsingør, Madrid, and Zürich Statements [Scheringer et al. 2014; Blum et al. 2015; Ritscher et al. 2018]) recommend a preventive and precautionary approach to this class of substances, with management actions undertaken on broad subgroups or on the class in its entirety despite a lack of scientific certainty regarding the majority of PFAS, which remain poorly studied. In addition, multilateral organizations and agreements, such as the Organisation for Economic Co-operation and Development (OECD) and the United Nation's Stockholm Convention on Persistent Organic Pollutants (POPs), have recognized the potential for regrettable substitution within the PFAS family. Many jurisdictions, including the European Union, have acted or committed to taking action on PFAS as a class.

In April 2021, the Government of Canada published a Notice of Intent, signalling an intent to move forward with activities to address PFAS as a class, including the publication of this State

[1] The Domestic Substances List (DSL) is an inventory of substances manufactured in or imported into Canada on a commercial scale. It was originally published in the *Canada Gazette*, Part II on May 4, 1994, and included approximately 23 000 substances deemed to have been in Canadian commerce between January 1984 and December 1986. The DSL is amended, on average, 12 times per year to add, update, or delete substances. It now contains more than 28 000 substances and can be accessed through Substances Search.

of PFAS Report summarizing relevant information on the class of PFAS (ECCC, HC 2021). This report is not a quantitative assessment of the risks of PFAS, but rather provides a qualitative assessment of the fate, sources, occurrence, and potential impacts of PFAS on the environment and human health, including the basis for a class-based approach and application of precaution, to inform decision-making on PFAS in Canada. It includes information collected through targeted literature searches, including information submitted by stakeholders in response to the *Notice of Intent to Address PFAS as a Class* (ECCC, HC 2021). The majority of relevant data were identified up to March 2022, with targeted data identified up to August 2022. This report has undergone external review and/or consultation. Comments on the report were received from Ms. Theresa Lopez, Ms. Jennifer Flippin, and Dr. Joan Garey at Tetra Tech.

1.1 Chemical scope

The class of PFAS encompasses a broad range of structures (e.g., ethers, polymers), including those with varying degrees of fluorination and chain length (Buck et al. 2011; ITRC 2020a; OECD 2021; Wang et al. 2017a). This is illustrated by the OECD list of approximately 4700 PFAS, compiled from public sources (OECD 2018a). Additionally, new PFAS are continually being invented and notified to Canada.

While certain chemical definitions have been proposed for PFAS, such as those found in reports by the Interstate Technology and Regulatory Council (ITRC 2020a), the Toxics Use Reduction Institute (TURI 2021), and the US EPA (2021a), the term has not benefited from a community-accepted definition. Under the auspices of the OECD/UNEP Global PFC Group, a document has been published to address PFAS terminology. This document uses the OECD (2021) definition for PFAS, defined as **"fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), i.e., with a few noted exceptions, any chemical with at least a perfluorinated methyl group ($–CF_3$) or a perfluorinated methylene group ($–CF_2–$) is a PFAS."**

This chemical definition captures substances with a wide range of structures, properties, and use patterns that may be subject to differences in regulatory oversight. The fluorocarbon moiety is frequently functionalized, commonly as carboxylic or sulfonic acids (e.g., PFOA or PFOS) or as fluorotelomer alcohols (FTOHs). These functionalized molecules may be used to chemically link the fluorocarbon moiety, with its unique properties, to more complex molecules, such as side-chain fluorinated polymers or sulfonamidoethanol compounds.

PFAS are sometimes classified on the basis of whether they are polymeric or non-polymeric (Buck et al. 2011). Polymeric PFAS include side-chain fluorinated polymers such as those produced using fluorotelomer acrylate monomers or perfluorinated sulfonamide side chain-, urethane-based co-polymers (Chu and Letcher 2014). For the former, the resulting polymer contains fluorinated side-chain components bonded via simple esters. Polyfluoropolyethers feature perfluorinated carbons or a series of perfluorinated carbons separated by oxygen atoms. The linkage chemistry between the per- or poly-fluorinated moiety within a polymer, including fluorinated side-chains, may provide an opportunity for transformation and the release of discrete, non-polymeric PFAS (ITRC 2021a).

A third polymer subgroup, fluoropolymers, have been described as those made by (co)polymerization of olefinic monomers, at least one of which contains F bound to one or both of the olefinic C atoms, to form a carbon-only polymer backbone with F atoms directly attached to it, such as polytetrafluoroethylene (Buck et al. 2011).

The OECD (2021) definition of PFAS is broader than the moiety approach used to compile the OECD list of PFAS in 2018; consequently, the number of individual PFAS exceeds the approximate 4700 PFAS originally identified using this new definition. For example, it includes certain drugs, pesticides, and many substances that are regulated in Canada under the ODSHAR, such as chlorofluorocarbons (CFCs), hydrochlorofluorocarbons (HCFCs), and hydrofluorocarbons (HFCs). Trifluoracetic acid, a transformation product formed in the atmosphere from some of the ODSHAR-regulated substances and hydrofluoroolefins (HFOs) (UNEP 2016), is also captured by the OECD definition.

This State of PFAS Report uses the 2021 OECD chemical definition of PFAS, given the concern with the stability of the fluorocarbon moiety, which results in persistence in the environment and resistance to transformation. For PFAS that experience some transformation, the fluorinated portion of the molecule is typically preserved, resulting in stable PFAS transformation products. While the scope of PFAS is based on a chemical definition, the OECD (2021) report notes that individual jurisdictions may need a working definition for PFAS, which may be established by combining the general definition of PFAS with additional considerations (e.g., specific properties or use areas). Such a working definition may be beneficial when contemplating regulatory or non-regulatory approaches to reduce exposure.

PFAS acronyms that are frequently used in this report are defined in Appendix A. This State of PFAS Report often refers to long-chain (LC) and short-chain (SC) PFAS, where long-chain refers to a carbon chain length of 8 (C8) or higher and short-chain refers to a carbon chain length of 7 (C7) or lower. Reports by other authors (e.g., the OECD) may refer to perfluorinated sulfonates with 6 (C6) or more fully fluorinated carbons (e.g., PFHxS) as long-chain PFAS; however, the definitions of short-chain and long-chain PFAS used in this report are consistent with other Government of Canada publications. Moreover, reference to perfluoroalkyl acids (PFAAs) includes the PFAAs (e.g., PFCAs, PFSAs, PFPAs, PFPiAs) and perfluoroalkylether acids (e.g., PFECAs, PFESAs) subgroups.

2 Uses and sources of exposure

KEY POINTS ON USES AND SOURCES OF EXPOSURE

- PFAS are used in many industrial sectors and are found in a wide range of products, including certain firefighting foams (i.e., AFFF), textiles (including carpets, furniture, and clothing), cosmetics, and food packaging materials.
- Some other uses of PFAS include solvents; processing aids; oil/water repellents in packaging; levelling agents in paints, ink, and adhesive formulations; and refrigerants / blowing agents.
- PFAS-impacted contaminated sites represent “hot spot” areas across Canada where Canadians and the environment may be exposed to elevated concentrations of PFAS and include sites associated with the use of firefighting foams.

- Food and food packaging, cosmetics, products available to consumers, ambient air, indoor air and dust, and drinking water as well as PFAS releases from municipal solid waste (MSW) landfills, MSW incineration, composting of PFAS-containing food packaging, wastewater treatment systems, and the application of biosolids to land are also potential sources of human and environmental exposure to PFAS.
- PFAS contamination is present throughout Canada and is not limited to a few sources and areas.

2.1 Uses of PFAS

PFAS possess a unique set of practical traits that are useful in a broad spectrum of applications, such as:

- oil and water repellency, which provides stain resistance, soil repellency, and non-stick properties;
- high resistance to chemical, physical, and thermal degradation (or for precursors, transformation to other stable PFAS); and
- low surface tension, resulting in the use of PFAS as surfactants and lubricants.

Due to their unique properties, PFAS are used in many industrial sectors and are found in a wide range of products, including certain firefighting foams, food packaging, non-stick cookware, drugs, cosmetics, textiles, vehicles, and electronics. A 2020 study (Glüge et al. 2020) identified more than 200 uses within 64 use categories for more than 1400 PFAS. Table 4 of that study presents in detail the known PFAS uses, functions, and the related sectors. Furthermore, fluoropolymers have uses in a variety of applications including medical devices, mechanical parts, and chemical processing equipment (Henry et al. 2018).

PFAS are commonly used in aqueous film-forming foam (AFFF). AFFF is a synthetic mixture that may contain hydrocarbon-based surfactants and fluorinated surfactants with the ability to rapidly extinguish hydrocarbon fuel fires. Prior to the voluntary phaseout of its production in 2002, the most commonly used PFAS in firefighting foams was PFOS. In Canada, AFFF that contain certain regulated PFAS are prohibited under the PCTSR with a few exemptions (Canada 2012a). The regulations currently allow the use of AFFF that contains residual levels of PFOS (up to a maximum concentration of 10 ppm), the use and import of AFFF contaminated with PFOS in a military vessel or military firefighting vehicle returning from a foreign military operation, and the import, use, sale, and offer for sale of AFFF that contains PFOA and/or LC-PFCAs used in firefighting. These exemptions accommodate the transition to alternatives to PFOA and/or LC-PFCAs and the residual levels of PFOS that remain in firefighting equipment from historical use of the substance. These regulations are currently being revised, and the proposed *Prohibition of Certain Toxic Substances Regulations, 2022* would further restrict these exemptions (Canada 2022a). Certain shorter length PFAS have been used as replacements for regulated PFAS in this application. PFAS releases from AFFF have led to contaminated sites in Canada, which is further discussed in section 2.3.

In Canada, although there are regulations in place prohibiting PFOS, PFOA, LC-PFCAs, their salts, and their precursors, these regulations currently include a limited number of exemptions

such as manufactured items. As a result, these substances may remain in circulation (refer to section 8.1.1 for additional information on risk management under CEPA). Furthermore, longer-chain PFAS are often produced as impurities during the manufacturing process of shorter-chain length replacements, and they may still be present in the effluents of manufacturing plants and in finished products (Prevedouros et al. 2006).

Eight different Canadian surveys to gather information on commercial activity in Canada, issued pursuant to section 71 of CEPA since the year 2000, have included a total of 269 PFAS, with a number of these PFAS being included in more than one survey (Canada 2005a, 2005b, 2012b, 2015, 2017, 2018, 2020a). Of the 269 PFAS that have been surveyed, responses were received for 87 PFAS from 27 different companies in 150 reports submitted to the various surveys. Most of these surveys were conducted more than 10 years ago; only 54 different PFAS have been surveyed in the past 10 years. Of the 269 PFAS surveyed, 169 have been prohibited by the PCTSR, 2012 since they were last surveyed. As a result, the data gathered via these surveys is not considered further in this report.

Only very limited information on the type and concentrations of PFAS used in consumer products sold in Canada is available (Beesoon et al. 2012; Kim et al. 2015).

2.1.1 Uses notified to the Government of Canada

Knowledge of the many uses of PFAS in Canada has been informed by New Substances Notifications received under the NSNR of CEPA, Cosmetic Notifications received under the *Cosmetic Regulations* of the *Food and Drugs Act* (F&DA), and voluntary submissions received by Health Canada that are related to food packaging materials (FPMs).

2.1.1.1 New Substances Notification Regulations (NSNR)

Approximately 270 new PFAS have been notified to Canada under the NSNR since 1994 (half of which are polymers). Of the 270 PFAS, 28 have been identified as intended to be manufactured in Canada, albeit with limitations (e.g., identified as contained site-limited intermediates, contained for export only, subject to the ODSHAR, or subject to the SNAc provisions of CEPA). New substances that are imported into or manufactured in Canada are subject to notification requirements tiered to annual import/manufacture quantity. Notification requires substance-specific information such as identity, use, hazard, and ecotoxicity information in order to assess the potential for risk to humans and the environment.

These New Substances Notifications have indicated a wide range of potential uses for chemical PFAS (Figure 1). Some typical uses notified for chemical PFAS include as processing aids (e.g., mould release agents for plastics); oil/water repellents in packaging, carpet, leather, fabric, and tile; levelling agents in paints, ink, and adhesive formulations; grease-proof coating for food packaging (i.e., food contact materials); refrigerants / blowing agents; firefighting foams (surfactants in AFFF); or as active ingredients in human and veterinary drug products. “Other” uses in Figure 1 include antistatic agents, colourants, electrolytes, cosmetic ingredients, tracers, and herbicide safeners. Polymers, which are not represented in Figure 1, were notified mostly with the intended use of anti-stain and water/oil repellency, with some intended uses as surfactants, processing aids, and levelling agents.

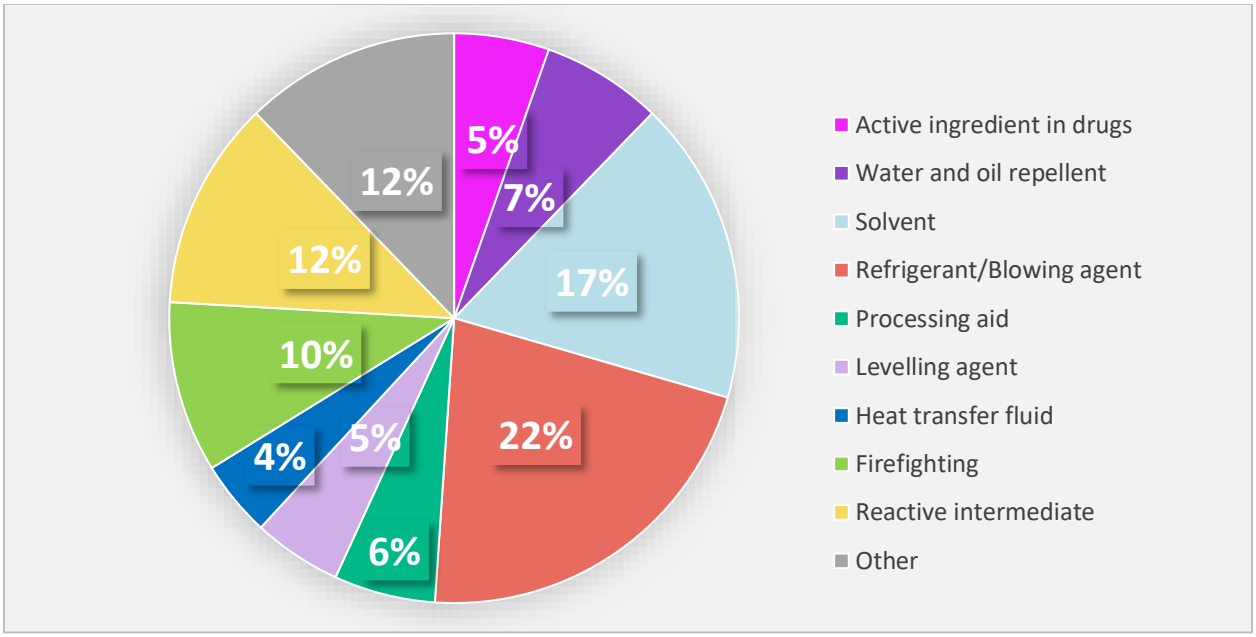


Figure 1. Uses of chemical PFAS notified under the NSNR since 1994. Percentage of total notified uses for notifications.

Approximately 90 PFAS notified under the NSNR have been added to the Domestic Substances List (DSL). Once a substance is added to the DSL, it may be used for any purpose unless it is subject to risk management measures.

Prior to 2016, many refrigerants and blowing agents notified under the NSNR were later added to the DSL with or without risk management measures; however, as of December 2016, these substances have been regulated under the ODSHAR (see section 8.1).

Although the intended uses notified by importers and manufacturers under the NSNR are largely industrial, some of the same PFAS may be used in other types of products, such as cosmetics. Despite the fact that few PFAS with a reported intended use in cosmetics have been notified under the NSNR, subsequent analysis has shown that 15 PFAS notified under the NSNR for industrial uses, including some not on the DSL, have also been notified for cosmetic use in Canada under the *Cosmetic Regulations* and are presently used in cosmetics. Therefore, PFAS that were reported to have industrial uses at the time of notification (such as an industrial foam stabilizer) may be subsequently used in non-industrial products that result in greater direct human exposure (such as cosmetics).

2.1.1.2 Cosmetics

PFAS are intentionally added to some cosmetics, such as foundations, moisturizers, lotions, and creams, to improve the penetration of other ingredients into the skin, enhance brightness, and increase the durability of makeup. Section 30 of the *Cosmetic Regulations* requires that all manufacturers and importers of cosmetics submit a Cosmetic Notification (CN) form to Health Canada, which includes a list of all the ingredients and, for each ingredient, its exact concentration or the concentration range (Canada 2019). Between 1993 and 2020, a total of 4775 CNs containing one or more PFAS were submitted to Health Canada. Approximately 90%

of these notifications were for leave-on products such as makeup and moisturizers, and are intended to be used on body, face, lips and eye areas. Most of these products (86.5%) contain listed PFAS at or below a concentration of 3%; in about 2.5% of the products, PFAS ingredients are notified above a concentration of 10%. A preliminary trend analysis of the CN data indicated that the annual number of notifications of PFAS-containing cosmetics increased between 1993 and 2017, reaching a maximum of 663 in 2017. Notifications then decreased to approximately 400 per year between 2018 and 2020. Health Canada typically receives between 50 000 and 60 000 CNs per year for cosmetics such as cleansers, conditioners, exfoliators, foundations, body creams, makeup products, and sunscreen. PFAS-containing CNs received each year represent less than 1% of the total CNs received by Health Canada annually.

As of July 2021, 71 unique PFAS ingredients have been notified in cosmetics in Canada. These PFAS ingredient names are notified using the International Nomenclature of Cosmetic Ingredients (INCI) naming convention. Among these, 10 (polytetrafluoroethylene [PTFE], perfluorodecalin, polyperfluoromethyl isopropyl ether**,** perfluorononyl dimethicone, trifluoroacetyl tripeptide-2, polyperfluoroethoxymethoxy difluoroethyl PEG Phosphate, perfluorohexylethyl triethoxysilane, methyl perfluorobutyl ether, tetradecyl aminobutyroylvalylaminobutyric urea trifluoroacetate, and methyl perfluoroisobutyl ether) were the most frequently notified PFAS ingredients. Given that PFOA and PFOS are prohibited substances under the PCTSR, they were not notified as cosmetic ingredients per se; however, cosmetics containing polymeric PFAS such as PTFE, FTOHs, and PAPs may be potential sources of PFOA, PFOS, and other PFAAs (Fujii et al. 2012).

The identification and measurement of PFAS in cosmetics is still an emerging area internationally. Using chromatographic methods, several research groups have investigated cosmetic products for specific PFAAs and their precursors (Danish EPA 2018; Whitehead et al. 2021). PFCA precursors, including 6:2 and 8:2 fluorotelomer compounds, were detected in cosmetics purchased in the United States and Canada (Whitehead et al. 2021). The concentration of individual PFAS varied widely in tested samples, ranging from low ppb to ppm. In addition, several researchers have studied the total fluorine and extractable organic fluorine content in cosmetic products using methods that do not identify/differentiate between different kinds of fluorine-containing substances and which may include non-PFAS (Fujii et al. 2013; Schultes et al. 2018; Whitehead et al. 2021). The results from these studies indicate that the sum of the concentrations of individually identified PFAS measured in cosmetics was substantially lower than their respective total fluorine content, in many cases accounting for only about 1% of the total fluorine. Consequently, the lack of mass balance observed in these studies indicates the presence of many unknown fluorinated substances in cosmetics, some of which may be PFAS. The availability of a wide spectrum of fluorinated ingredients and lack of analytical standards makes it challenging to screen for individual PFAS in cosmetics.

2.1.1.3 Food packaging

In Canada, all food packaging materials (FPMs), including domestic and imported materials, must comply with the safety provisions under Division 23 of the *Food and Drugs Regulations*. Division 23 prohibits the sale of food in a package that could transfer a chemical to the food that may be harmful to the health of the consumer. The responsibility to ensure that the materials

used in contact with foods are in compliance with regulatory requirements lies with the food seller (e.g., the food manufacturer, packager, or distributor). However, food packaging manufacturers are able to voluntarily seek the opinion of Health Canada regarding the acceptability, from a food safety perspective, of the FPMs that they wish to sell to the food industry.

To date, Health Canada has evaluated and issued Letters of No Objection concerning 21 polymeric PFAS (i.e., fluoropolymers, perfluoropolyether polymers, and side-chain fluorinated [co]polymers). These polymeric PFAS are typically used in food contact applications such as in non-stick cookware, gaskets, parts for food processing equipment, and paper/paperboard food packaging. These uses are consistent with the use of PFAS reported in food contact materials internationally (US FDA 2022a; European Commission 2020a; OECD 2020).

Given the existing risk management actions in Canada (see section 8.1.1), the United States, and Europe (OECD 2015, 2020; US EPA 2009), the presence of PFOS-based food packaging on the Canadian marketplace is not expected. The proposed amendments to the PCTSR will further restrict the import, use, sale, and offer for sale of manufactured items containing PFOA and LC-PFCAs in Canada (Canada 2022a).

In June 2022, the *Single-use Plastics Prohibition Regulations* was published in the *Canada Gazette*, Part II, prohibiting the manufacture, import, and sale of 6 categories of single-use plastics (Canada 2022b). It is possible that single-use plastic food takeout containers and straws may be replaced by paper alternatives that may contain PFAS treatments.

Additionally, since treated paper and paperboard may enter recycled paper feedstock, it is possible that untreated paper products made from recycled feedstock will contain detectable concentrations of PFAS. According to Curtzwiler et al. (2021), the PFCA (i.e., PFBA, PFHxA, PFOA, and PFDA) concentration threshold in recycled paper packaging materials, associated with functional performance gains, ranged from 30 ppm for PFDA to 1238 ppm for PFBA.

Due to the known use of polymeric PFAS in paper/paperboard food packaging, it is expected that PFAS will be detected in paper and paperboard food packaging on the retail market. For example, Schaider et al. (2017) found fluorine in 56% of dessert and bread wrappers, 38% of burger-contact papers (at levels of 60 ppm), and 20% of paperboard samples (average of 14 ppm) when sampling fast food packaging in larger cities in the United States. According to Trier et al. (2011), the surface coating of treated paper and board yielded concentrations ranging from 1 ppm to 100 ppm of certain polyfluorinated surfactants, which can be precursors of PFAS, whereas adding PFAS to pulp yielded 600 ppm to 9000 ppm (or 0.06% to 0.9% of the paper weight). These levels are consistent with those reported by Xu et al. (2013a) for tested perfluoroalkyl acids and polyfluoroalkyl phosphoric acids in food contact papers.

2.2 Occurrence in retail foods

PFAS have been reported at very low concentrations in various retail foods in Canada, the United States, Australia, New Zealand, and Europe (EFSA 2020; FSANZ 2021; Ostertag et al. 2009; Tittlemier et al. 2006, 2007; US FDA 2021a). The European Food Safety Authority (EFSA; 2020) indicates that the source of PFAS detected in retail foods (e.g., PFOS and LC-PFAS)

appears to primarily be from PFAS that have bioaccumulated through aquatic and terrestrial food chains, not direct migration from FPMs. The Food Standards Australia and New Zealand (FSANZ; 2017) also reports that PFSAs, PFCAs, and fluorotelomer sulphonates were not detected in various packaged foods in Australian supermarkets.

In collaboration with the Canadian Food Inspection Agency, Health Canada monitors the levels of PFAS in food. Tittlemier et al. (2007) reported that only 9 out of 54 composite samples (4 meat-containing, 3 fish and shellfish, 1 fast food, and 1 microwave popcorn) from the Canadian Total Diet Study (TDS) between 1992 and 2004 contained detectable levels of perfluorinated compounds. PFOS and PFOA were detected the most frequently (in all 9 composites), with concentrations ranging from 0.5 ppb to 4.5 ppb. Among this small data set, the consumption of beef contributed to more than 80% of the average total dietary PFAS exposure (i.e., total PFCA and PFOS).

Tittlemier et al. (2006) analyzed 151 TDS composite food samples from 1992 to 2004 for a series of perfluoroalkyl sulfonamides (FASA) including perfluorooctanesulfonamide (PFOSA) and a number of N-alkyl perfluorooctanesulfonamides, namely N-ethylperfluorooctanesulfonamide, N,N-diethylperfluorooctanesulfonamide, N-methylperfluorooctanesulfonamide, and N,N-dimethylperfluorooctanesulfonamide. At least one FASA was detected in a sample from each of the food groups tested (baked goods and candy, dairy, eggs, fast food, fish, meat, and foods to be prepared in packaging). The highest concentrations of the sum of FASA compounds analyzed in this study were found in fast food composites, ranging from less than the limits of detection (LOD) to 27.3 ppb.

Ostertag et al. (2009) reported the detection of 6:2 fluorotelomer unsaturated carboxylate (in cold cuts at 1.26 ppb), PFHpA (in cookies, cheese, pizza, and frozen beef dinner at ≤0.59 ppb), PFOA (in cookies, cheese, peppers, canned lunchmeats, and pizza at ≤0.77 ppb), PFNA (in cold cuts and cookies at ≤3.75 ppb), PFDA (in peppers at 1.02 ppb), and PFOS (in cheese at ≤1.14 ppb) in samples collected in 1998 from stores and restaurants in Whitehorse, Yukon Territory, Canada.

The CFIA has conducted targeted surveys for PFOS and PFOA in various foods (root vegetables, potato products, seafood products, frozen vegetables, flour and cereals) sampled from 2013 to 2016. None of the more than 3200 food samples had levels of PFOS or PFOA above the LOD of 0.25 ng/g (data are not publicly available).

In a 2020 assessment, the EFSA noted that more than 90% of the results for PFAS in foods analyzed as part of European dietary surveys, conducted from 2000 to 2016, were below the limit of quantification (LOQ) or LOD. In the surveys assessed by EFSA (2020), high concentrations (95th percentile >10 ppb) of PFAS were reported in edible offal from game animals and a number of fish species. According to EFSA, 4 PFAS (PFOA, PFNA, PFHxS, and PFOS) contributed a median of 46% (range of 33% to 56%) to the sum of all adult dietary exposures to PFAS. The relative median contributions were 9%, 2%, 4%, and 30% for PFOA, PFNA, PFHxS, and PFOS, respectively. Other PFAS that contributed more than 5% were PFBA

(16%) and PFHxA (15%). According to EFSA (2020), concentrations of PFOS and PFOA in food appear to be decreasing.

Food Standards Australia and New Zealand (FSANZ 2021) report that of the 30 PFAS analyzed in their 27th Australian Total Diet Study (covering years 2019–2020), PFOS was the only congener found to have detectable concentrations in the regional and national food samples analyzed. PFOS was detected in eggs, fish fillets (saltwater), liver or other offal (non-poultry), prawns (cooked), and canned tuna. PFOS was most frequently detected in liver or other offal at concentrations ranging from <0.05 ppb to 5.5 ppb. All other concentrations of PFOS detected were below 0.2 ppb. In the previous 24th Australian TDS (Phase 2, covering year 2011) of a smaller subset of food samples and analytes (i.e., PFOA and PFOS only), FSANZ (2016a) reported that PFOS was only detected in 2 of 50 samples (i.e., PFOS was detected in fish fillets and beef sausages at concentrations ≤1 ppb).

The US FDA has conducted analyses for PFAS in foods grown or produced in contaminated geographic areas as well as in foods from the general food supply (Genualdi et al. 2022; US FDA 2021a, 2022a; Young et al. 2012, 2013). PFAS occurrence data from the general food supply (US FDA 2021a) were obtained from the analysis of samples collected from the United States FDA's TDS, which included a wide variety of foods such as fruits and vegetables, bread, meats, fish, dairy products, processed foods, and baby foods, as well as from targeted surveys on bottled water (2016), seafood (2013), and milk (2012). The US FDA analyzed 4 sets of TDS samples for 16 PFAS (PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFBS, PFPeS, PFHxS, PFHpS, PFOS, ADONA, HFPO-DA, 11Cl-PF3OUdS, 6:2 Cl-PFESA [F53B]) and one set of TDS samples for 20 PFAS (PFUnDA, PFDoA, PFTrDA, and PFTeDA, in addition to the 16 PFAS analyzed in the other data sets; US FDA 2022b). In all 5 combined TDS data sets, only 10 of the 532 total samples analyzed had detectable levels of PFAS. PFOS was detected in ground turkey (85.7 ppt), tilapia (3 samples; 87, 83, and 28 ppt), pre-cooked shrimp (216 ppt), baked cod (98 ppt), protein powder (140 ppt), and frozen fish sticks/patties (33 ppt). PFNA was detected in samples of frozen fish stick/patties (50 ppt) and baked cod (2 samples; 233 ppt and 87 ppt). PFDA was detected in canned tuna (72 ppt) and baked cod (23 ppt). PFUnDA was detected in pre-cooked shrimp (233 ppt) and baked cod (151 ppt), and PFDoA was detected in pre-cooked shrimp (71 ppt). No other PFAS were detected in any other food sample from the TDS. The bottled water survey analyzed for PFOS and PFOA and none of the 30 samples had detectable levels of either PFAS (US FDA 2021a). In the seafood survey, 11 of 46 samples had detectable levels of at least one type of PFAS, and PFOS was the most widely detected (in 9 of 11 positives), with generally higher concentrations (0.97 ppb to 6.29 ppb) (Young et al. 2013). In the milk survey, 1 of 12 raw milk samples had detectable levels of PFAS, while none of the 49 retail milk samples did (Young et al. 2012). The lone sample with detectable PFAS (PFOS at 0.16 ppb) came from a dairy farm that had applied PFAS-containing biosolids to its fields. Although the United States FDA has not presented PFAS exposure estimates based on the above results, they have stated that these results do not suggest any need to avoid particular foods because of concerns regarding PFAS contamination (US FDA 2021b). The US FDA (2021b) has limited the assessment of human health risk to PFOA, PFNA, PFBS, PFHxS, and PFOS.

The US FDA also conducted a targeted survey in 2021–2022 for 20 PFAS in 8 types of seafood (primarily imported): tuna, salmon, tilapia, crab, shrimp, cod, pollock, and clam (US FDA 2022c). The US FDA determined that the levels of PFOA in the canned clam samples were likely a health concern. Subsequently, the two distributors of the canned clams in question initiated a voluntary product recall (US FDA 2022d).

A study by Ruffle et al. (2020) analyzed 70 samples of fish and shellfish commercially available in the United States for 26 PFAS compounds. Up to 10 PFAS were detected in 21 samples, with PFOS as the predominant compound found. Total PFAS concentrations were generally single digit or sub-ppb level (0.6 to 4.4 ppb) except for fish from the Great Lakes area, with higher levels reported in whitefish, walleye, and yellow perch (1.2 ppb to 21.6 ppb).

Although food-related PFAS occurrence data from Canada, Europe, Australia and New Zealand, and the United States are growing, the scope of existing data is still limited compared with the number of PFAS included under this broad class. Notably, targeted analysis and quantification in the varied and complex matrices of food present methodological challenges. Due to analytical limitations associated with measuring substances in complex food matrices, much of the occurrence data show a very high frequency of non-detect concentrations (i.e., below the LOD), rendering exposure estimates highly uncertain. EFSA (2020) recommended that improved analytical methods for a broader range of PFAS in a broader range of foods are needed in order to reduce the uncertainty in the dietary exposure assessment. In an effort to improve dietary exposure estimates, food research organizations, including the Food Research Division of Health Canada's Food Directorate, continue to work to develop occurrence data in various food matrices (e.g., fish, meat, fast foods) using methods that have recently been developed (Rawn et al. 2022a).

2.3 Sites contaminated with Aqueous Film-Forming Foams (AFFF)

PFAS-impacted contaminated sites where AFFF (aqueous film-forming foams) have been or are being used (e.g., firefighting training areas) represent "hot spot" areas where the environment may be exposed to PFAS. In addition, Canadians can also be exposed to PFAS through various environmental media as a result of AFFF use. PFAS contamination may pose risks to human health and the environment not only at the contaminated site (i.e., on-site), but also off-site due to the potential for significant migration in surface water and groundwater or by wind erosion or overspray of the AFFF product during use. PFAS have demonstrated the ability to travel long distances (greater than 2 km) in the subsurface (groundwater) and surface water, which can lead to a large area of impact from a single point source of PFAS (Bhavsar et al. 2016; CCME 2021a). An example of a contaminated site impacted by PFAS, an airport firefighting training area, is illustrated in the conceptual site model below in Figure 2 (HC 2021a). It highlights examples of potential human exposure pathways for a PFAS-impacted site as a result of historical AFFF use. Potential routes of exposure may include ingestion of impacted drinking water; consumption of country foods (e.g., fish, berries, edible vegetation); and/or direct contact with soil, surface water, groundwater, sediment, and/or other environmental media.

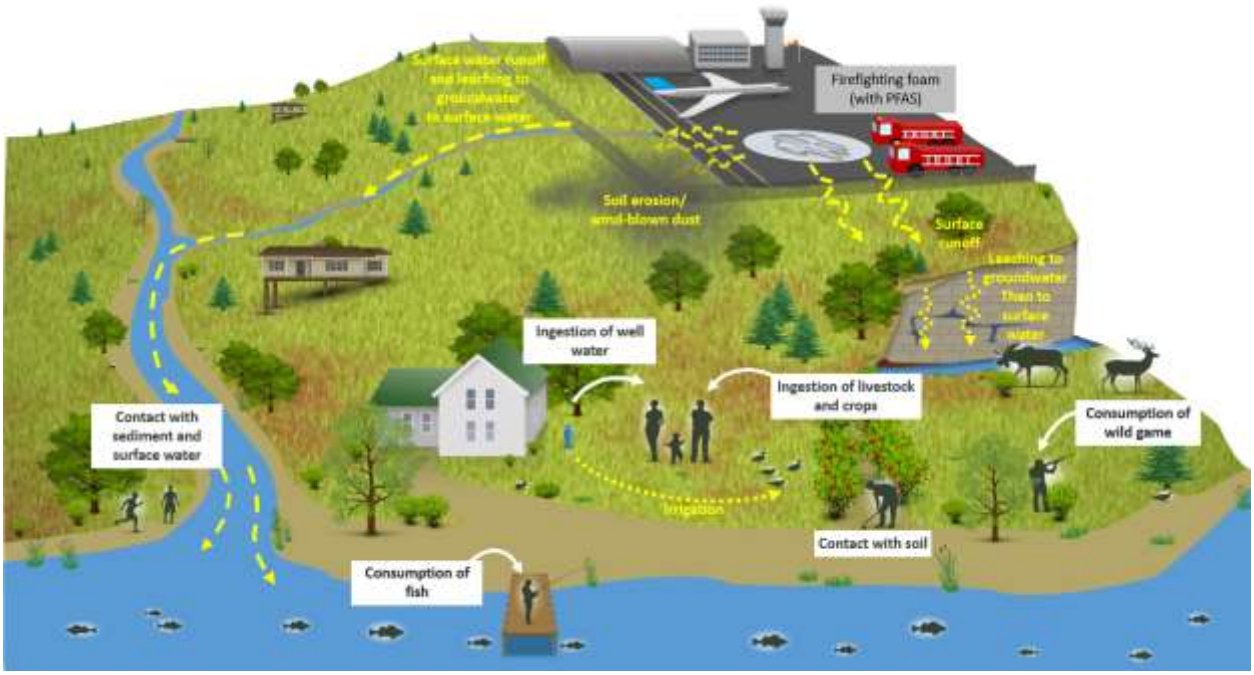


Figure 2. Conceptual site model for a PFAS-impacted contaminated site due to historical AFFF use, and associated human health exposure pathways to be assessed in a human health risk assessment.

Federal contaminated sites are located on land owned or leased by the federal government, or on land where the federal government has accepted responsibility for the contamination. There are over 100 federal contaminated sites with confirmed or suspected PFAS contamination. As shown in Figure 3, such sites exist in all provinces and territories. Most of these sites are associated with past and/or current use of AFFF, typically during activities associated with fighting fuel fires, including training activities and maintenance of firefighting equipment at airports and military facilities. Several PFAS (PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFBS, PFHxS, and PFOS) were detected in groundwater at former firefighting training areas in British Columbia, Alberta, Nova Scotia, and Ontario (Paterson et al. 2008; Environmental Sciences Group 2015). Other sources of PFAS at federal contaminated sites may include landfill leachate and land application of wastewater treatment biosolids, which are discussed in section 2.6. Many PFAS-impacted federal contaminated sites are located in areas where there is reliance on local resources (e.g., consumption of drinking water from private groundwater wells, hunting, gathering, fishing, small-scale and/or commercial farming, gardening, and recreational activities).

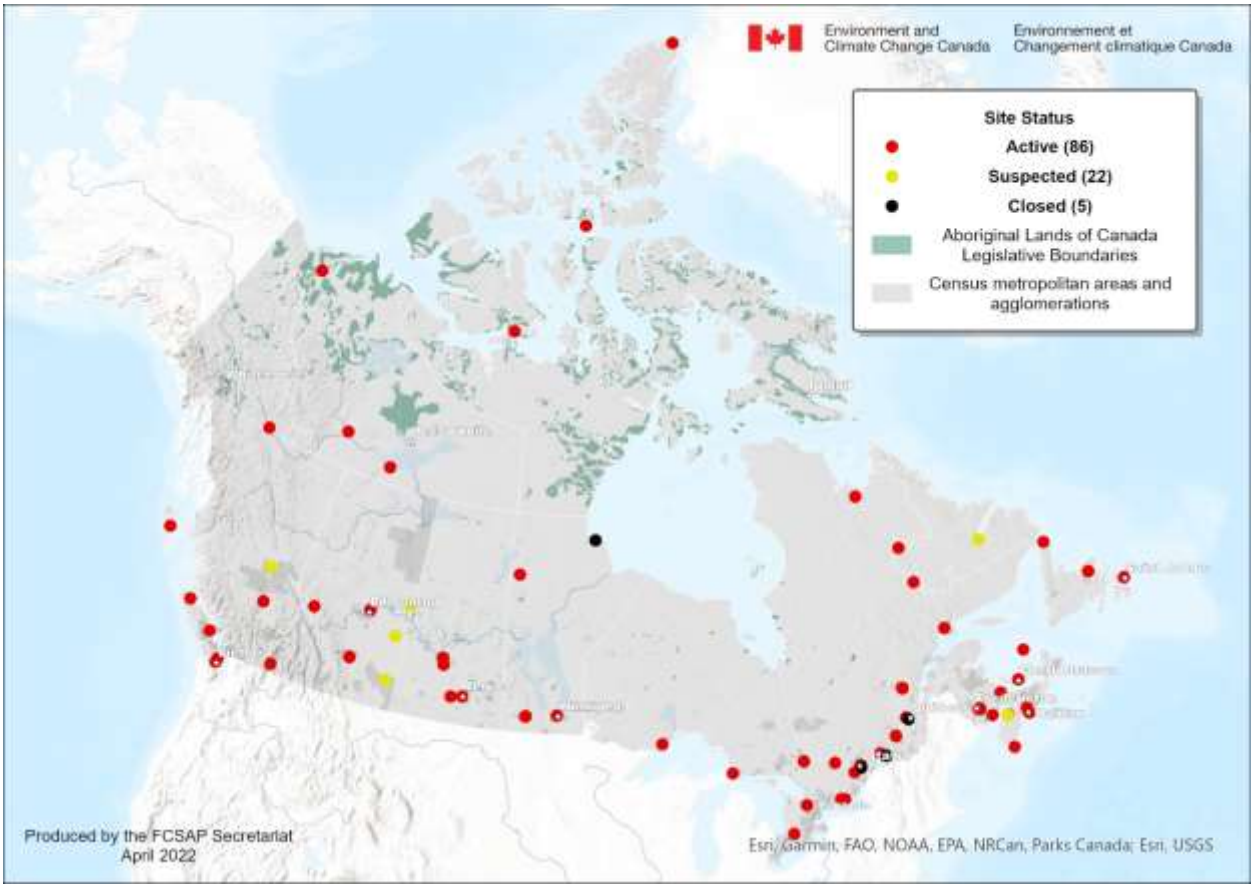


Figure 3. Federal contaminated sites with confirmed or suspected PFAS contamination, as of April 2022. Site status (i.e., Suspected, Active, and Closed) applies to the entire site and is not specific to PFAS contamination.

Non-federal PFAS-contaminated sites also exist in Canada. For example, AFFF used in the oil and gas industry and by municipal firefighting departments may have resulted in the release of PFAS to the environment. Contamination on non-federal lands is dealt with by the province/territory and/or the local health authority (refer to section 8.1.4).

As illustrated in Figure 2, PFAS detected in groundwater or surface water at a contaminated site can be considered mobile and are likely migrating with the groundwater or surface water flow. Other plausible transport pathways for off-site migration of PFAS may also include (but are not limited to) the migration of impacted surface soils, sediment, dust, stormwater/snow melt runoff (depending on local topography), and/or migration of firefighting foam from historical site use (e.g., overspray and wind transport).

Environmental guidelines and screening values for PFAS have been developed (section 8.1.3). These are set as benchmarks below which the concentrations of PFAS are not expected to pose a human health and/or environmental concern. Accordingly, PFAS concentrations found in the environment can be compared to PFAS guidelines and screening values to assess their significance. While numerous PFAS are known to be in AFFF, guidelines and screening values are currently available for only a few select PFAS. Furthermore, the PFAS guidelines and screening values are only available for a limited number of environmental media and exposure pathways. Thus, the assessment of PFAS at AFFF-contaminated sites may underestimate potential health and environmental concerns, as discussed in section 8.1.4.

Section 6.1 discusses plant uptake of PFAS and bioaccumulation in animals. Based on the findings of a 2018 literature review, fish and shellfish consumption were found to be the primary route of human exposure to PFOS and, to a lesser extent, PFOA (Intrinsik 2018). However, there is limited information regarding the uptake of PFAS from various environmental media by fish, shellfish, and mammals due to the variability and uncertainty inherent in the data, which is attributable to several different factors, including kinetics, ecology, region, tissues, and species differences. At this time, the available information does not support the use of generic PFAS uptake models (i.e., models used to predict PFAS uptake from environmental media into food sources) for assessing risks to human health at contaminated sites.

Health Canada commissioned a literature review of available information concerning the uptake of PFAS by plants and wildlife (Intrinsik, 2018). Based on the findings of this review and more recent work in this area, there is still insufficient data to support modelling PFAS uptake from soil or irrigation water into food sources (crops, livestock, and country foods). At contaminated sites where the consumption of country foods or agricultural operations are occurring, Health Canada's current recommendation is to conduct sampling of the edible portions of the plant or animal for PFAS analysis in order to accurately characterize exposure and assess potential risks.

2.4 Drinking water

PFAS may be present in both private drinking water wells and public drinking water supplies. No published data were found on the levels of PFAS in private wells in Canada. Because PFAS are not regularly monitored at water treatment plants in Canada, there is only limited data available for municipally supplied drinking water. In 2022, the validated and standardized analytical methods available for the quantitation of PFAS in drinking water measure a combined total of 29 compounds; although many other PFAS may be present, they cannot be measured. However, new methods that will measure a greater number of compounds are under development in many countries. In 2009–2010, Health Canada conducted a national survey of emerging contaminants in drinking water that included PFHxA, PFOA, PFNA, PFBS, PFHxS, and PFOS (Health Canada 2013b). Source and treated water from groundwater and surface water sources (rivers and lakes) were monitored across Canada in summer and winter at 35 locations in 2009 and 30 locations in 2010. Overall, PFOA was the most frequently detected of the 6 PFAS. In 2009, PFOA was detected (method detection limit [MDL] of 0.02 ng/L) in 68% (summer; average 0.067 ng/L) and 59% (winter; average 0.057 ng/L) of source water samples and 64% (summer; average 0.071 ng/L) and 55% (winter; average 0.056 ng/L) of treated water samples. In 2010, detection rates for PFOA were lower: 18% to 33% in source water (average 0.066 ng/L) and 15% to 27% in treated water (average 0.055 ng/L) (Health Canada 2013b). The maximum PFOA values detected were 0.22 ng/L in source water samples and 0.18 ng/L in treated water samples. PFHxA (MDL 0.05 ng/L) was detected in 40% of winter 2009 samples (average 16 ng/L) and 25% of winter 2010 samples (average 17 ng/L). Summer detections were less frequent at 15% (average 0.10 ng/L) and 3% (average 14 ng/L) in 2009 and 2010, respectively. The other 4 PFAS, including PFOS, were rarely detected despite low method detection limits of 0.03 ng/L to 0.15 ng/L (Health Canada 2013b).

At 7 sites in Quebec, source and treated water samples were collected monthly between April 2007 and March 2008. PFOA was detected in 75% of treated water samples (MDL of 0.3 ng/L

to 0.6 ng/L), with a median value of 2.5 ng/L and a maximum value of 98.0 ng/L. PFOS was detected in 52% of treated samples (MDL of 0.3 ng/L to 0.6 ng/L), with a median value of 1.0 ng/L (maximum value of 3.0 ng/L). PFNA and PFUDA were also detected in some samples (Berryman et al. 2012).

Between 2016 and 2021, samples were collected from 41 drinking water treatment systems in Quebec and tested for 18 PFAS (PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUndA, PFBS, PFHxS, PFHpS, PFOS, PFDS, FHUEA, FOUEA, 4:2 FTS, 6:2 FTS, 8:2 FTS). Both surface and groundwater systems were sampled, with the latter being added in 2018 (MELCC 2022). Detection limits ranged from 0.5 ng/L to 5 ng/L for raw water samples and from 0.3 ng/L to 5 ng/L for treated water samples. Among the 18 PFAS analyzed, 6 (PFPeA, PFHxA, PFHpA, PFOA, PFNA, and PFOS) were detected in 10% or more of the samples taken. The 2016 data showed a reduction in the maximum concentrations of PFOA and PFOS (6 ng/L and 3 ng/L, respectively) when compared with the maximum surface water concentrations from the same sites sampled in 2007–2008 (66 ng/L for PFOA and 8.8 ng/L for PFOS). In the St. Lawrence River and other rivers, 5 substances (PFHxA, PFHpA, PFOA, PFNA, and PFOS) were detected in at least 30% of the samples. PFOA and PFHxA were detected at the highest frequency (72% and 59%, respectively); both had a maximum concentration of 6 ng /L. In Lac Memphrémagog, PFOA (2 ng/L) and PFHxA (3 ng/L) were detected in raw water; both were detected in treated drinking water at 1 ng/L each. In groundwater sources, PFPeA (max.: 48 ng/L) and PFHxA (max.: 30 ng/L) were found in 14% and 17% of samples, respectively, while PFOA (max.: 4 ng/L) and PFOS (max.: 3 ng/L) were found in 6% and 4% of samples (MELCC 2022).

A study of tap water samples from Niagara-on-the-Lake, Ontario, found an arithmetic mean (5 samples) of 2.1 ng/L for PFOA and 3.3 ng/L for PFOS and detected PFBA, PFHxA, PFHpA, PFNA, PFDA, PFUnDA, PFHxS, PFEtS, PFOSA, and PFPeA (Mak et al. 2009). In 2016 to 2019, the Ontario Ministry of the Environment, Conservation and Parks measured the occurrence and concentrations of 14 PFAS (PFBS, PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFHxS, PFOS, PFDS, and PFOSA) in 25 drinking water systems in Ontario (Kleywegt et al. 2020). Method detection limits (MDL) ranged from 0.5 ng/L to 1 ng/L, and results less than the MDL were substituted with a value of half of the MDL. PFUnDA, PFDoDA, PFDS, and PFOSA were not detected in either the source water or treated drinking water samples. The most frequently detected compounds in Ontario drinking water were PFOA (73%; median 1.1 ng/L), PFBA (67%; median 2.4 ng/L), PFHxA (54%; median 1.3 ng/L), PFPeA (51%; median 1.0 ng/L), and PFOS (50%; 0.63 ng/L). In 2017 and 2018, additional screening level analyses of PFAS on 635 drinking water samples from 13 systems in Ontario did not detect individual PFAS compounds in any samples using a screening level detection limit of 10 ng/L (Kleywegt et al. 2020).

Similar median concentrations of PFOA, PFBA, PFHxA, PFPeA, and PFOS were reported in samples of drinking water sourced from 19 sites around Lake Ontario and the St. Lawrence River (n=8) and other lakes and small rivers in Canada (n=11). Concentrations of PFAS ranged from 1.0 ng/L (PFPeA) to 3.5 ng/L (PFOS). These values were similar to those found in tap water samples collected between February 2015 and June 2015 in Canadian cities. Other PFAS

that were frequently detected included PFBA (95%) and PFHxS and PFOS (both 89%), while PFPeA, PFHpA, PFOA, PFNA, PFDA, and PFBS were detected in at least 84% of the samples. Compounds detected less frequently in Canadian waters included FOSA (53%), 6:2 FTSA (37%), and 5:3 FTCA (11%) as well as PFUnDA, PFDoDA, and 7:3 FTCA, which were each detected in less than 10% of samples. A qualitative screening approach indicated that FBSA, FHxSA, PFECHS, and PFPeS were occasionally present in tap water (concentrations ranged from below the limit of detection to 1.2 ng/L), whereas PFEtS, PFPrS, and PFPeS were below the limit of detection for all Canadian samples. The limits of detection for tap water ranged from 0.01 ng/L to 0.08 ng/L (Kaboré et al. 2018).

2.5 Indoor air and dust

PFAS compounds have been measured in indoor air and dust in residential and non-residential environments (e.g., childcare facilities, fire stations) in Canada and other countries (e.g., US, Ireland, Belgium, Italy, Spain, Norway, Finland, and China) (de la Torre et al. 2019; Haug et al. 2011; Harrad et al. 2019; Winkens et al. 2018; Wu et al. 2020; Yao et al. 2018; Zheng et al. 2020). These studies were mostly conducted on a regional scale and reported approximately 70 PFAS in total. Sources of PFAS in indoor environments include rugs and carpets, treated floor waxes and stone/wood, food packaging, cosmetics, building materials, furnishings, paper products, clothing, insecticides, and electronics (Morales-McDevitt et al. 2021; Liu et al. 2015; Savvaides et al. 2021).

In Canada, 4 studies examined the airborne PFAS concentrations in 271 residential homes in 3 cities (Ottawa, Vancouver, Edmonton) from 2002 to 2008 (Beesoon et al. 2012; Makey et al. 2017; Shoeib et al. 2005, 2011). Overall, the data suggest that FTOHs (8:2, 6:2, and 10:2 FTOH), followed by the FOSAs (MeFOSA, EtFOSA), and FOSEs (MeFOSE, EtFOSE) appear to be the most prominent in the air samples collected from Canadian homes.

For PFAS in dust, 6 studies measured PFAS concentrations in household dust in 308 Canadian homes in 3 cities (Ottawa, Toronto, Vancouver) from 2002 to 2015 (De Silva et al. 2012; Eriksson and Kärrman 2015; Karaskova et al. 2016; Kubwabo et al. 2005; Shoeib et al. 2005, 2011). When comparing exposure through inhalation and ingestion of dust, inhalation was identified as the primary exposure pathway for neutral and ionic PFAS for adults, whereas for toddlers, intake via dust ingestion is more relevant due to the higher frequency of hand-to-mouth activities (Shoeib et al. 2005, 2011). The most abundant PFAS in indoor dust were diPAPs, PFOS, PFOA, PFNA, PFHxA, PFHpA, PFDS, PFHxS, PFDoDA, MeFOSE, EtFOSE, MeFOSA, EtFOSA, 6:2 FTOH, 8:2 FTOH, and 10:2 FTOH. For diPAPs, the dominating homologues were 6:2 diPAP, 6:2/8:2 diPAP, 8:2 diPAP, 8:2/12:2 diPAP, and 10:2 diPAP (De Silva et al. 2012; Eriksson and Kärrman 2015).

2.6 Waste/end of product life

PFAS are present in a wide variety of consumer and industrial products. The expected fate of these products is that they will be disposed of in Municipal Solid Waste (MSW) landfills or destined for MSW incineration.

2.6.1 Landfills

The disposal of products and materials that contain PFAS, including PFAS-contaminated soils and biosolids, into landfills can become an indirect pathway of release to the environment. PFAS may leach out of these products and materials and accumulate in landfill leachate and eventually be released to the environment, even if that leachate is sent to a wastewater treatment system. Other solid waste facilities, such as composting facilities, scrapyards, and recycling facilities, may also be a source of release to the environment. The responsibilities of waste management in Canada are discussed in section 8.1.5. Concentrations of PFAS in landfill leachate are discussed in section 4.2.3.

Most of the monitored landfills discharge untreated leachate to wastewater treatment plants (WWTPs). Approximately 87% of the leachate generated by large landfills in Canada (permitted to receive more than 40 000 tonnes of municipal solid waste per year) is directed to municipal WWTPs and 7.1% is treated on site prior to release. The remainder of leachate generated (approximately 5.5%), typically from small, unengineered landfills that have limited environmental controls, is released directly into the environment via groundwater or surface water without treatment.

MSW landfills are a known source of groundwater contamination, with leachate-impacted plumes that may extend greater than 1 km (Christensen et al. 2001). Many types of contaminants of emerging concern, including PFAS, have been found in the leachate of operating and closed municipal landfills and are described in section 4.2.3.

With respect to releases to air from landfills, monitoring data show that PFAS are dry deposited in areas downwind of landfills, which indicates that fugitive and point-source emissions could be sources. Flaring of landfill gas (LFG) is believed to incompletely destroy PFAS. Tian et al. (2018) directly measured PFAS content in landfill gas in China and found that concentrations ranged from 650 pg/m^3 to 850 pg/m^3 of LFG.

2.6.2 Incineration

PFAS may not fully degrade from incineration at temperatures below 1000°C, which may result in the formation of other volatile fluorinated compounds. Data suggest that temperatures of 1000°C and above, such as those found in MSW incinerators, are sufficient to destroy (i.e., mineralize) the most resistant of fluorinated compounds; however, further data is needed regarding the optimal residence times for sufficient and/or complete destruction of PFAS, including the breakdown of the highly stable $–CF_2–$ moieties, while avoiding the formation of other compounds (Yamada et al. 2005).

Due to the wide variety of products that contain these substances, it is reasonable to assume that the fraction of PFAS that is incinerated is equal to the total fraction of waste incinerated in Canada. A 2012 study by Cheminfo Services Inc. indicated that the percentage of MSW being disposed of in landfills in Canada (for 2008) was 96%, while 4% was disposed of through incineration. Since this figure is likely representative of current data, it can be assumed that 4% of PFAS are incinerated, while the remaining 96% are sent to landfills where they are potentially released to the environment (Cheminfo Services Inc. 2012).

2.6.3 Compost

PFAS persist when composted, may accumulate in the soil, and may be taken up by certain crops (see section 6.1) as well as the natural food chain. Compost made from PFAS-containing single-use paper products or food waste are expected to be contaminated with PFAS.

A study by Lazcano et al. (2020) found 17 PFAS, including PFOA and PFOS, to be present in 13 commercially available biosolid-based products, 6 organic composts (manure, mushroom, peat, and untreated wood), and 1 food and yard waste compost. Biosolid-based products had concentrations of PFAS ranging from 9 to 199 micrograms per kilogram (µg/kg, ppb), while composts made from various combinations of food scraps, yard trimmings, and other organic products had PFAS concentrations between 0.1 µg/kg and 18.5 µg/kg.

2.6.4 Wastewater treatment systems and biosolids

Municipal wastewater treatment systems act as pathways of PFAS to aquatic environments through the discharge of treated effluent, and to the terrestrial environment when biosolids are applied to land as soil amendments. Both pathways can subsequently impact groundwater, e.g., through riverbank filtration and soil water infiltration, respectively. ECCC's National Wastewater Monitoring Program gathers data on levels of PFAS entering municipal WWTPs, evaluates the fate of PFAS through the liquid and solids trains of typical treatment process types used in Canada, and determines levels of PFAS being discharged in WWTP effluents and solids residuals. These are described in section 4.2.4. On-site wastewater treatment (i.e., septic systems) releases liquid effluent via a subsurface drain field, while biosolids from septic holding tanks can also be land-applied; both pathways havethe potential to impact groundwater.

Many PFAS have been measured in WWTP influent and effluent (Guerra et al. 2014; Lenka et al. 2021), septic system effluent (Subedi et al. 2015), and WWTP biosolids (EFSA 2020; Lakshminarasimman et al. 2021). PFAAs can also be formed during wastewater treatment, likely as a result of the transformation of unmeasured precursors entering WWTPs (Guerra et al. 2014). The amount of PFAAs formed is dependent on process temperature and treatment type, with higher rates of formation in biological WWTPs operating at higher hydraulic retention times and temperatures (Guerra et al. 2014). In addition, concentrations of some PFAAs are higher in final stabilized biosolids than in raw sludge at some WWTPs, likely due to the transformation of unmeasured precursors during biosolids treatment (Lakshminarasimman et al. 2021). Concentrations of both PFOS and PFOA may increase during biological treatment processes due to the incomplete transformation of their precursors (Sinclair and Kannan 2006; Guerra et al. 2014; Lenka et al. 2021). Transformation of PFAS is described in section 3.2.3.

PFAS can be taken up by plants grown in agricultural fields, with accumulation dependent on soil concentrations, chain length of the PFAS, functional group, plant species and variety, and soil and applied biosolids characteristics (Ghisi et al. 2019) (see section 6.1). EFSA (2020) reported that PFBS, PFHpA, and PFBA have been shown to be available to plants via the root system with reported uptake into pea shoots and/or celery grown in soil amended with biosolids; however, as noted in section 2.2, concentrations of PFAS in retail foods tend to be below the LOD.

2.7 Substitution trends

Key substitutions observed with respect to fluorosurfactants have included the move to C6-based fluorotelomer substances from variable chain length LC-PFCA precursors, and the use of PFBS-based products as PFOS replacements (ACC 2022; 3M 2002). Polyfluorinated ether acid surfactants, such as ADONA and GenX, have also been substituted for the use of PFOA as a fluoropolymer processing aid (ITRC 2020b).

A retrospective analysis of substances notified for import to or manufacture in Canada under the NSNR highlights when substitutions have occurred over the years and illustrate how industry is acting to substitute hazardous substances (also known as informed substitution). New Substances Notifications may provide insight into new substances being introduced as potential substitutes. The Government of Canada may use other methods (e.g., CEPA section 71 surveys) to obtain new use information that may indicate substitutions and prioritize substance(s) for assessment.

Following the prohibitions put in place on 4 new fluorotelomer-based substances (PFCA precursors) in 2004, no further perfluoroalkyl substances with carbon chain lengths equal to or greater than C8 were notified under the NSNR (Figure 4). This could indicate that industry had already transitioned to replace those substances by the time the *Perfluorinated Carboxylic Acids (PFCAs) and Precursors: An Action Plan for Assessment and Management* and the PCTSR amendments were published in 2006 and 2016, respectively. Substitution for these substances was observed through an increase in notifications of short-chain PFAS.

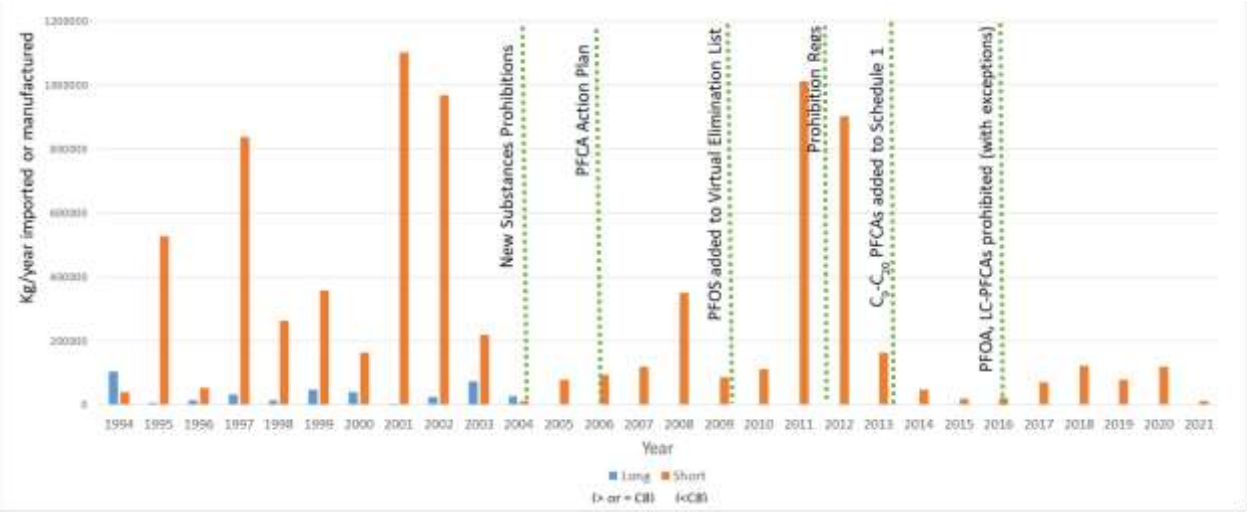


Figure 4. Quantities (kilograms per year) of chemical and polymeric PFAS notified under the NSNR per year, separated by long and short carbon chain lengths

When a new substance is notified under the NSNR, the importer or manufacturer must indicate the expected quantity of substance to be imported into or manufactured in Canada. These values are provided for the year of notification and, when known, the maximum amount in a 12-month period in the next 3 years. Apart from the quantities notified for blowing agents and refrigerants, which tend to be high in certain years, the quantities of new chemical and

polymeric PFAS notified under the NSNR are generally equal and relatively constant at roughly 10 000 kg/year to 30 000 kg/year for new PFAS being imported into or manufactured in Canada.

3 Key characteristics and environmental behaviour

KEY POINTS ON ENVIRONMENTAL BEHAVIOUR

- The physical and chemical properties of PFAS influence their fate and behaviour in the environment.
- Ionic PFAS (i.e., predominantly ionized at environmental pH) such as PFCAs and PFSAs are highly water-soluble and non-volatile, and thus partition predominantly to water where they can mobilize.
- Neutral PFAS such as FTOHs may be volatile and thus are more likely to be found in the atmosphere.
- FTOHs, as well as other polyfluoroalkyl substances and some side-chain fluorinated polymers, can undergo transformation to form more stable PFAS that are extremely persistent in the environment under ambient conditions.
- Some shorter-chain PFAS have proven to be even more mobile on a local scale than longer chain PFAS.
- Some PFAS are also capable of undergoing long-range transport in the atmosphere (i.e., for neutral, volatile PFAS) or in global ocean currents (i.e., for ionic PFAS), as can be seen by their widespread distribution around the world, including to remote regions.
- Experience with PFAS-contaminated sites has shown that remediation and management of these sites are very challenging and complex, and the removal of PFAS from the environment is not possible.

The purpose of this section is to summarize the key physical/chemical and fate properties of PFAS. The concept of PFAS precursor substances (PFAS that are capable of transforming into simpler environmentally stable PFAS, e.g., PFAAs), is also discussed. The general properties of these PFAS contribute to their environmental partitioning, persistence, mobility, and long-range environmental transport characteristics.

Fluorine has high electronegativity, low polarizability, and a small atomic radius. The combined effect produces a strong carbon-fluorine bond (about 108–120 kcal/mol), making it extremely stable. Fluorocarbon chemistry is resistant to heat and biological and chemical attack. With low surface energy and weak intermolecular interactions, it is both hydrophobic and lipophobic. It is these characteristics that provide desirable performance in many applications where surface protection, chemical resistance, thermal stability, and non-stick properties are sought.

Complex PFAS molecules, such as side-chain perfluoroalkyl polymers or sulfonamidoethanol compounds, contain the persistent PFAS moiety, although other portions of the molecule may undergo transformation and liberate a stable PFAS acid. Complex PFAS that can yield simpler persistent PFAS are referred to as precursor substances. In the case of fluoropolymers, it has been argued that the various stages of their life cycle must be taken into account when considering potential impacts to the environment and human health, including PFAS processing

aids used in their production, the presence of monomers/oligomers in products, and end-of-life issues such as fate in landfills and during incineration (Lohmann et al. 2020).

Although the precursor substances may exhibit a range of physical/chemical properties dependent in part on the non-fluorinated parts of the molecule, the simpler PFAS have physical/chemical properties that result in fate characteristics that are well understood. These properties will be highlighted in section 3.1.

3.1 Select physical and chemical properties

Water solubility: Various estimates for the pKa (i.e., acid dissociation constant) of PFOA have been generated (e.g., Brace 1962; Goss et al. 2008; Steinle-Darling and Reinhard 2008; Vierke et al. 2013), though the actual value is believed to be within the range of 1 to 2. Consequently, PFOA is predominantly found in the environment in the form of its conjugate base, the perfluorooctanoate anion. The water solubility of this conjugate base is 3.5 g/L at 20°C (EC, HC 2012). Similarly, the PFOS conjugate base anion, perfluorooctane sulfonate, is the most common form at pH values in the environment and human body. The water solubility for the potassium salt of PFOS is reported as being 519 mg/L to 680 mg/L (EC 2006). Liu and Lee (2005, 2007) reported water solubilities of 974, 18.8, 0.224 and 0.011 mg/L at 22°C for 4:2, 6:2, 8:2, and 10:2 FTOH, respectively. A review by Ding and Peijnenburg (2013) reported experimentally determined water solubilities for select PFAS ranging from 0.011 mg/L to 5.66×10^4 mg/L.

With a hydrophobic and lipophobic fluorocarbon tail and a polarized head, these acids exhibit surfactant behaviour and can aggregate in micelles above the critical micelle concentration.

Log*Kow*: Because PFAS acids behave as surfactants, the octanol/water partition coefficient (Log*Kow*) values are difficult to determine experimentally since the molecules aggregate at the octanol/water interface. Many reported Log*Kow* values are calculated for the neutral form of the molecules. As the neutral form is not present under normal environmental conditions, these values are of limited use in describing their environmental fate or bioaccumulation potential.

Log*Koc*: For PFAS acids, the values for the organic carbon-water adsorption/desorption coefficient are in part dependent upon the length of the fluorocarbon chain. Shorter-chain PFAS acids tend to have lower Log*Koc* values, indicating a greater affinity for water, while longer-chain PFAS acids may partition preferentially to soil and sediments. For these reasons, shorter-chain PFAS have greater mobility via groundwater.

Vapour pressure and Henry's law constant: The vapour pressure of the PFOS potassium salt is
3.31×10^{-4} Pa at 20°C and its Henry's law constant is 3.45×10^{-4} Pa m^3/mol (EC 2006), indicating a low likelihood to partition to and be transported by air. For the acid form of PFOA, the calculated vapour pressure and Henry's law constant are 2.2 Pa and 2.4 Pa m^3/mol, respectively, indicating a low likelihood of atmospheric transport (EC, HC 2012).

While the acids themselves are not susceptible to atmospheric transport, volatile precursor substances contribute to environmental transport. For example, although PFOS has low

volatility, several PFOS precursors are considered volatile, such as N-EtFOSE alcohol, which has a vapour pressure of 0.5 Pa and Henry's law constant of 1930 Pa m^3/mol. When present in products or used in industrial processes, volatile PFAS precursors can volatize into the atmosphere and travel long distances before transforming into non-volatile forms such as PFAAs. These volatile precursors contribute to the widespread environmental occurrence of PFAS, including in remote areas such as the Arctic (Muir et al. 2019).

Fluorotelomer alcohols are precursors to perfluorocarboxylic acids (PFCAs, which include PFOA). Vapour pressures of C_6-C_{12} FTOHs range from 144 Pa to 992 Pa at 25^{o}C (Stock et al. 2004), with the Henry's law constant for 8:2 FTOH estimated at 3506 Pa m^3/mol (Xie et al. 2013). These volatile precursors are globally distributed and also subject to transformation to PFCAs through reaction with hydroxyl radicals (Ellis et al. 2004), contributing to the wide dispersion of the resulting acids.

3.2 Environmental fate and behaviour

The environmental fate and behaviour of PFAS describes what happens to these substances when they are released into the environment. The behaviour of these substances in the environment can be influenced by their physical and chemical properties, which can vary between different PFAS. This section examines the fate and distribution of PFAS in various media, their persistence, and transport of these substances within and between media, including long-range environmental transport. Focus is given to PFAS that are well studied in terms of their environmental fate and behaviour. Some emerging PFAS (e.g., PFPAs, PFPiAs, PAPs) are much less understood in terms of their environmental fate (Guo et al. 2020); therefore, these PFAS are not discussed in detail in this section.

3.2.1 Environmental fate

As a result of the fluorinated alkyl tail and polar head group of ionic PFAS (i.e., predominantly ionized at environmental pH, such as PFAAs), the partitioning properties and electrostatic interactions of ionic PFAS can dictate their partitioning and distribution in the environment. Because of their hydrophilic head, PFAAs can exhibit high water solubility, which can allow the chemical to interact and disperse in water. This, combined with a negligible vapour pressure, explains why PFAAs primarily partition to surface waters, soil water, and groundwater (Prevedouros et al. 2006). PFAAs also tend to accumulate at the air-water interface as a result of their surfactant-like properties (i.e., their hydrophilic head group dissolves in water, while their hydrophobic tail orients itself to the air; Costanza et al. 2019), leading to retention in the unsaturated zone. Moreover, transport to the deep ocean and sediment burial are considered to be environmental sinks for PFAAs, given that they have a very long residence time in the environment (Prevedouros et al. 2006).

The organic carbon content in soil and sediment and alkyl chain length are strongly correlated to the sorption of many PFAS, which demonstrates the importance of hydrophobic interactions (Higgins and Luthy 2006; Liu and Lee 2005). In general, sorption to organic carbon increases with fluoroalkyl chain length in the ionic, non-volatile PFAS. Zhao et al. (2016) examined the distribution of PFAS in a river and found that short-chain PFAAs were predominantly found in water, whereas the long-chain PFAAs were present in suspended particulate matter and

sediment. A study of sediment cores by Ahrens et al. (2009) also determined that short-chain PFCAs were only found in pore water, whereas longer-chain PFCAs (C ≥ 11) were exclusively found in sediment. Moreover, partitioning and sorption is dependent on the properties of the functional groups present (ITRC 2020a). At a pH of above 3, most PFAAs exist in the anionic state in the environment; PFAAs in the environment therefore tend to repel negatively charged natural soils and sorb to positively charged minerals. For example, Higgins and Luthy (2006) determined that sorption of perfluoroalkyl substances (e.g., PFCAs, PFSAs, FASAs) to sediment increased at higher Ca^{2+} concentrations. However, differences have been noted in the sorption of PFAAs dependingon their functional groups, such as PFPAs which tend to be more sorptive than PFCAs at equal chain lengths in soil (ECHA 2022b; Lee and Mabury 2017). Sorption of cationic and zwitterionic PFAS to soil and sediment have been far less investigated in comparison with anionic PFAS species; however, recent studies have shown that cationic and zwitterionic PFAS sorb more strongly to soil and sediment than do anionic PFAS because of their electrostatic interactions (Barzen-Hanson et al. 2017; Nickerson et al. 2021; Xiao et al. 2019). It is important to note that trends in sorption potential (i.e., chain length and functional group) evidenced by different PFAS do not indicate that there is no sorption occurring with some PFAS but rather that sorption may occur to a lesser extent compared with more strongly sorbing PFAS.

Ionic PFAS are not commonly found in air because of their high solubility in water, low vapour pressure, and low Henry's law constant. In their anionic, less volatile form, PFAAs can adsorb to airborne particulate matter (ITRC 2021a). Moreover, other neutral PFAS (e.g., fluorotelomer-based substances) may have a greater volatility due to the functional groups that they possess (e.g., alcohols) and may therefore be more likely to be found in the atmosphere.

3.2.2 Persistence

Broadly speaking, PFAS are extremely persistent in the environment (i.e., long half-lives[2]) as fluorocarbon moieties (fundamentally $–CF_2-$) are very stable with resistance to biodegradation, hydrolysis, photolysis, and thermolysis. The vast majority of these so-called "forever chemicals" are non-degradable or, in cases where these transformation mechanisms may act upon other parts of more complex PFAS molecules, the stable PFAS transformation products are environmentally persistent (Cousins et al. 2020a). This extreme persistence of PFAS is due to their carbon-fluorine bonds, which, as previously described, are the strongest carbon-halogen bonds in nature. The carbon-fluorine bond contributes to the low polarizability and high bond energies of PFAS, which increase as the degree of fluorination increases.

Most of the current persistence data have focused on a select number of well-studied PFAS. As such, the information presented in this section is focused on PFOS and PFOA; however, it is believed that the vast majority of PFAS are highly persistent (Cousins et al. 2020a, 2020b), and

[2] According to the *Persistence and Bioaccumulation Regulations of CEPA*, half-life refers to the period that the concentration of a substance takes to be reduced by half, by transformation, in a medium.

substances of the same PFAS subgroup can be considered to be equally persistent (ECHA 2022b).

For PFOS, half-lives in water were determined to be >41 years via hydrolysis, estimated by varying pH from 1.5 to 11.0 and at a temperature of 50°C to facilitate hydrolysis (Stockholm Convention on Persistent Organic Pollutants 2006). No biodegradation has been found in studies of PFOS in activated sewage sludge, sediment cultures, and soil cultures. Moreover, PFOA is not expected to significantly photodegrade under environmental conditions, undergo significant biotic or abiotic degradation, or hydrolyze (EC, HC 2012). PFOA was also determined to have a half-life of about 235 years in water via hydrolysis (3M 2001, as cited in the Stockholm Convention on Persistent Organic Pollutants 2016). Although there are a limited number of studies from the literature, it is expected that PFECAs and PFESAs (alternatives to long-chain PFAAs) are likely to be highly persistent in the environment (Wang et al. 2015a). As will be discussed in further detail in section 3.2.3, some PFAS are capable of releasing PFAAs into the environment upon transformation; however, this process may be slow for some precursors under abiotic conditions. Washington and Jenkins (2015) tested the abiotic hydrolysis of a commercial acrylate fluorotelomer-based polymer, which yielded half-lives ranging from 55 to 89 years. The current data suggest that many PFAS will remain in the environment for long periods, with the result being that they can reach significantly higher concentrations in comparison with short-lived chemicals released in the same quantities (Cousins et al. 2019).

3.2.3 Transformation

Polyfluoroalkyl substances (e.g., fluorotelomers, polyfluoroalkyl ethers, perfluoroalkane sulfonamides) and some side-chain fluorinated polymers (e.g., fluorinated urethane polymers, fluorinated acrylate/methacrylate polymers, fluorinated oxetane polymers) can be considered to be “precursors” and undergo abiotic or biotic transformation to form more stable perfluoroalkyl transformation products that do not degrade under ambient environmental conditions (Buck et al. 2011). This can occur as a result of the nonfluorinated bond(s) (e.g., carbon-hydrogen, carbon-oxygen) in the structure of these polyfluoroalkyl substances and side-chain fluorinated polymers, which can create a “weak” point in the chemical structure that can be broken to release a perfluorinated alkyl moiety (ITRC 2021a). Studies have shown that fluorotelomer-based substances can undergo atmospheric oxidation (Ellis et al. 2004; Wallington et al. 2006) and aerobic transformation (D’Agostino and Mabury 2017) to form PFCAs. Vo et al. (2020) have also detected the precursors FOSA, FOSAA, FTOHs, and fluorotelomer sulfonic acids (FTSAs), which can transform to PFOS and PFOA via biological or chemical treatment in WWTPs. The atmospheric oxidation of HFCs and HFOs can also form trifluoroacetic acid (Young and Mabury 2010). In additionMoreover, metabolic transformation of PFAS precursors can also be a source of PFAAs (Ahrens and Bundschuh 2014). It has been shown that metabolic transformation of FTOHs to PFCAs can occur in rats and rainbow trout (EC, HC 2012).

A study reported that the main PFAS components in Scotchgard fabric protector products made before and after the year 2002 were identified as side-chain perfluorooctane sulfonamide-urethane polymer and side-chain perfluorobutane sulfonamide-urethane polymer, respectively (Chu and Letcher 2014). Furthermore, the same study reported that using a model microsomal *in vitro* assay (Wistar-Han rats liver microsomes), the rapidly formed metabolites were FOSA

and perfluorobutane sulfonamide (PBSA), respectively. In another study using a liver microsomal *in vitro* assay performed on polar bear (from Iceland), Wistar-Han rats, and ringed seal and beluga whale (Canadian Arctic), N-ethyl-perfluorooctanesulfonamide (N-EtFOSA) was found to be dealkylated rapidly to FOSA by polar bears and rats, more slowly for ringed seals, and very slowly for beluga whales (Letcher et al. 2014).

3.2.4 Mobility

In general, PFAS are capable of being transported from point sources to other locations as a result of their physical-chemical properties. Volatile PFAS (which generally have a neutral charge at environmental pH, such as FTOHs) are also capable of undergoing airborne transport from release sources (e.g., stack emissions) and are capable of being dispersed by the wind. Eventually, some PFAS can be removed by atmospheric deposition and accumulate in soil, groundwater, and surface water. This can occur by both wet deposition (i.e., precipitation) and dry deposition (i.e., removal of particles from the atmosphere due to gravity). Shimizu et al. (2021) concluded that wet deposition is able to remove PFAS from the atmosphere more effectively than dry deposition.

Ionic, short-chain PFAAs are considered to possess greater mobility in the aquatic environment and soils due to their increased water solubility and lower sorption potential to solids (ECHA 2017; Ghisi et al. 2019). Although some major manufacturers have phased out the production of long-chain PFAAs and have turned to homologues with shorter chains, research has demonstrated that short-chain PFAAs are capable of being even more mobile in the aquatic environment (Kwiatkowski et al. 2020). Advection, which is the transport of a chemical within a fluid, can be considered a primary driver of PFAS transport, such as in an expanding groundwater plume or downstream in a river (ITRC 2020c). Moreover, Lohmann et al. (2013) determined that vertical eddy diffusion is also capable of moving PFAAs from the ocean surface water to the deep ocean.

Ionic, non-volatile PFAS tend to associate with the organic carbon fraction of soil and air-water interfaces but can also leach through the vadose zone (i.e., unsaturated zone) to the aquifer and form groundwater plumes, particularly in areas with point sources such as landfills (Abunada et al. 2020). This downward migration can be caused by precipitation, irrigation, runoff, and stormwater (Sharifan et al. 2021). Xiao et al. (2015) found increasing levels of PFOS and PFOA with increasing depth in subsurface soils, indicating that there is potential for the substances to contaminate the groundwater aquifer.

3.2.5 Long-range environmental transport

Some PFAS are also capable of undergoing long-range environmental transport, as evidenced by their widespread distribution around the globe, even to remote regions. It is believed that this can occur via both atmospheric transport and global ocean currents (Zhao et al. 2012). In general, long-range atmospheric transport tends to occur more quickly in comparison with transport through water, which could take decades (Young and Mabury 2010).

In the case of releases of PFAS to air (e.g., stack emissions, volatilization from products) and the potential for air to disperse PFAS over long distances in all wind directions, airborne

transport becomes a relevant migration pathway. More specifically, neutral volatile precursors (e.g., FTOHs) have been found in remote regions due to their high volatility (Wania 2007). These neutral volatile precursors are often the most prevalent PFAS present in the gas phase (Wang et al. 2014a). The long-range transport and transformation of PFAS and PFAS precursors has been seen as a potential cause for the presence of PFAAs in remote regions, as precursors can be subject to transformation processes and be deposited via precipitation. For example, a study by Stock et al. (2007) found evidence to support the transformation of volatile precursors in the Canadian Arctic. Another study by Young and Donaldson (2007) found that 8:2 FTOH can transform to PFOA within the atmosphere and deposited in distant environments, such as the polar regions. Other FTOHs, short-chain FOSAs, and FOSEs are also potential sources of PFCAs and PFSAs via atmospheric transformation (ATSDR 2021). Although not in polar regions, remote/rural sampling sites in other Canadian locations (Golden, BC; Egbert, ON) that are distant from emission sources have identified FTOHs and PFCAs in surface water (Loewen et al. 2008) and ambient air (Gawor et al. 2014).

Ionic PFAS (e.g., PFAAs) are mainly distributed in surface waters and are believed to be predominantly transported globally by marine ocean currents due to their higher water solubility (Yamashita et al. 2008; Zhao et al. 2012). It is also believed that PFAAs can be transported from the ocean to the atmosphere via sea spray aerosols, which can occur with breaking waves and rough sea conditions (Prevedouros et al. 2006). Johansson et al. (2019) estimated the annual global emissions of PFOA and PFOS to the atmosphere via sea spray aerosols to be 122 tonnes/year and 183 tonnes/year, respectively. It has been suggested that sea spray aerosols are capable of circulating significant amounts of PFAAs between the ocean and atmosphere and can be considered a possible contributor to the long-range transport of PFAAs (Johansson et al. 2019; Prevedouros et al. 2006; Sha et al. 2022).

This global cycling of PFAAs in the world's hydrosphere, combined with their high persistence, will lead to levels of PFAAs in atmospheric deposition that are poorly reversible. Measurements of 4 PFAS (PFOA, PFOS, PFHxS, and PFNA) in various global environmental media (rainwater, soils, and surface waters) showed the ubiquitous exceedance of several guideline values (see section 4.1). Consequently, the authors stressed the importance of rapidly restricting uses and emissions of PFAS due to the "poor reversibility of exposure and their associated effects" (Cousins et al. 2022).

3.2.6 Potential PFAS removal and treatment technologies

PFAS are widely used because they are resistant to heat and chemical extremes, but these same characteristics make most conventional treatment technologies ineffective for PFAS removal or destruction both at contaminated sites (see section 2.3) and for drinking water treatment. Experience with PFAS-contaminated sites has shown that the remediation and management of these sites are complex and present unique challenges. This often leads to cleanup and monitoring costs that are higher than those associated with sites contaminated with other substances. The field of PFAS treatment and remediation is rapidly evolving and advancing, with new information becoming available as experience is gained through conducting activities at contaminated sites. Detailed information regarding PFAS remediation at contaminated sites is available from the ITRC (2020d).

PFAS are generally resistant to physical, biological, and chemical processes and are typically unaffected by conventional treatments used for landfill leachate and wastewater (see section 2.6). This has been demonstrated for PFOA, PFNA, PFDA, PFUnDA, PFHxS, and PFOS (Sinclair and Kannan 2006; Xiao et al. 2013).

Separation technologies are most commonly used for the treatment of environmental media contaminated with PFAS, although destructive technologies are under active research.

The effectiveness of drinking water treatment for PFAS removal depends on several factors, including source water chemistry as well as the concentration and physical-chemical properties of the PFAS. Conventional treatment is not effective for PFAS removal. The most effective treatment technologies for the removal of PFAS (including PFOS and PFOA) are, alone or combined, granular activated carbon, membrane filtration (reverse osmosis and nanofiltration), and anion exchange (Appleman et al. 2013, 2014; Dickenson and Higgins 2016; Lin et al. 2021), although there are technical challenges associated with short-chain PFAS breakthrough (Li et al. 2020a). To avoid the release of PFAS into the environment, spent filtration and ion exchange media require specialized disposal (e.g., high temperature regeneration/destruction). Similarly, membrane technologies require treatment and disposal of the concentrate residual stream (US EPA 2020).

Results from studies on PFOS and PFOA show that sonochemical degradation can be an effective and rapid process to treat these substances in landfill leachate (EC 2014). PFOS and PFOA have a tendency to partition into sludges and have been found to be resistant to treatment of the sludge (Gómez-Canela et al. 2012; Sun et al. 2012).

All of these treatments are limited in their ability to be widely used, such that PFAS remediation is currently limited to specific locations where deploying one or more of these technologies is economically and logistically feasible. As a result, removing PFAS from the broader environment is not possible.

Since PFAS removal and treatment technologies are not specific to individual PFAS, the measurement of total PFAS would allow for more comprehensive remediation and treatment planning by providing more information on the total “PFAS load” that requires treatment/removal to ensure that the strategies used are appropriate. The use of analytical Total Oxidizable Precursors (TOP) assays is beneficial as a line of evidence in this application.

4 Environmental occurrence

KEY POINTS ON ENVIRONMENTAL OCCURRENCE

- Globally, PFAS are routinely detected in virtually all environmental compartments and in the tissues of numerous species.
- The highest concentrations of PFAS are usually found in proximity to points of release; however, PFAS are ubiquitous in precipitation and global soils, including in remote areas.

- Because environmental monitoring studies have focused on limited subsets of PFAS, total PFAS concentrations and the extent of cumulative exposure are uncertain and likely underestimated.
- In Canada, PFAS are routinely detected in various environmental samples collected from coast to coast to coast, including ambient air, aquatic ecosystems, landfill leachate, wastewater, and biosolids as well as aquatic and terrestrial wildlife. In some instances, certain fluoropolymers have even been detected.
- The Government of Canada conducts a variety of monitoring programs and research studies to understand trends in PFAS occurrence in Canadian ecosystems and wildlife.

4.1 Overview of environmental occurrence

As might be expected on the basis of the mobility and long-range transport potential of PFAS, numerous studies and reviews have documented the presence of PFAS globally within a wide variety of ecosystems and biota, including in remote areas far from locations where PFAS are initially discharged to the environment (e.g., Ankley et al. 2021; Cousins et al. 2022; Gewurtz et al. 2013; Houde et al. 2008; Lau et al. 2007; Muir et al. 2019; Muir and Miaz 2021). The highest PFAS concentrations have generally been found in proximity to points of release of AFFF and industrial activities (e.g., Hu et al. 2016; Lanza et al. 2016) as well as in landfill leachates (e.g., Hamid et al. 2018) and wastewater treatment plant effluents (e.g., Arvaniti and Stasinakis 2015). However, measurable concentrations have also been reported in ecosystems at varying degrees of removal from these locations, including but not limited to agricultural land and crops (e.g., Ghisi et al. 2019), the Arctic and Antarctic (e.g., Muir et al. 2019; MacInnis et al. 2017; Pickard et al. 2018; Wong et al. 2021), the Great Lakes (e.g., Houde et al. 2008), and oceans and coastal waters (e.g., Muir and Miaz 2021).

PFAS are also routinely found in the blood and tissues of a wide variety of organisms, both those in close proximity to points of PFAS release (e.g., near sites where AFFF have been used in firefighting activities) and in remote locations. For example, an early study by Giesy and Kannan (2001) examined select fluorinated organic compound (FOC) concentrations in tissues of aquatic mammals, birds, fish, and amphibians collected during the 1990s as part of monitoring studies in the United States, Canada, and internationally. They found that while few samples contained PFOSA, PFHxS, or PFOA above the limit of quantitation (LOQ), PFOS was detectable in most samples, including those collected from remote marine regions (e.g., the Arctic Ocean). Houde et al. (2011) also reviewed post-2005 monitoring information on perfluorinated compounds in aquatic biota. PFOS was determined to be the most predominant substance, likely due to a combination of its high biomagnification potential, persistence, and the continued international use of PFOS precursors. However, the ubiquity of PFCAs was also noted across tissue samples. Recognition of the ubiquity of PFOS, PFOA, and long-chain PFCAs in global environments and biota has been a key driver in regulatory action both in Canada (EC 2006, 2012; EC, HC 2012) and internationally, which includes the listing of PFOS, PFOA, and related substances as Persistent Organic Pollutants under the Stockholm Convention.

PFOS and PFOA have been identified in many different foods, particularly protein-rich foods, in areas of both known contamination and no point sources of PFAS contamination (Intrinsik 2018). The Ontario Ministry of the Environment, Conservation and Parks (MECP) recently carried out studies examining short-chain (PFHxA, PFPeA, PFBA, PFHpA, and PFBS) and long-chain (PFOS, PFHxS, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFOSA, and PFDS) uptake into tomatoes, lettuce, and beets following irrigation with PFAS-contaminated surface water. The result of this study demonstrated that irrigation water impacted by AFFF-contaminated sites has the potential to impact crops irrigated with contaminated water, particularly for the short-chain PFAS (McDonough et al. 2021). This study also demonstrated elevated concentrations of short-chain PFAS in the tomato flower, which may have implications for pollinators (McDonough et al. 2021).

Recently, the European Chemicals Agency (ECHA) completed an extensive review of the European and global environmental occurrence of PFAS (ECHA 2022c). The occurrence and concentration of individual PFAS were highly variable depending on location; however, PFAS were found in surface waters, groundwater, soil, contaminated sites, wastewater influent and effluent, and sewage sludge in virtually all locations that were examined. PFAS were also found to be present in nearly all organisms tested worldwide.

A number of studies and reviews have noted declines in environmental concentrations of regulated PFAS (e.g., De Silva et al. 2021; Muir and Miaz 2021), supporting the effectiveness of these regulatory actions. However, this trend is not universal, and some studies have reported different (or a lack of) temporal trends for a single study species and/or the same geographic region depending on sampling location (e.g., see section 4.2.2). For example, a recent review by Cousins et al. (2022) found that concentrations of select PFAAs in global rainwater samples routinely exceeded US EPA lifetime drinking water health advisories for PFOS and PFOA; the Danish Environmental Protection Agency drinking water limit value for the sum of PFOS, PFOA, PFNA, and PFHxS; and the European Union freshwater environmental quality standard (EQS) for PFOS, including in remote and sparsely populated regions. Some urban rainwater levels reported in this study for PFOA and PFOS also exceeded current Canadian drinking water guidelines. Though data for soils from remote regions remain sparse, the authors concluded that one outcome of these findings is the global contamination of soils due to the environmental ubiquity and poor reversibility of PFAAs in atmospheric deposition. Recent studies have also noted increases in the concentrations of short-chain PFAS (e.g., see section 4.2), presumably due to the use of these substances as replacements for regulated long-chain PFAS. An additional concern regarding this trend is that environmental monitoring has typically focused on limited suites (from a few to approximately 30) of the estimated greater than 4700 PFAS (e.g., Buck et al. 2021; De Silva et al. 2021; OECD 2018b), and the detection of a broader spectrum of PFAS is dependent on the development of new analytical methods. This is a critical limitation as manufacturing has shifted to other perfluorinated substances (e.g., see section 2.7). The limited scope of monitoring was illustrated in a recent review by Xiao (2017), in which it was determined that aquatic studies published between 2009 and 2017 identified 455 new PFAS in natural waters, fish, sediments, wastewater, activated sludge, soils, AFFF, and commercial fluorinated polymer surfactants. The narrow scope of most existing monitoring data has also led

to concerns regarding the potential for higher than anticipated concentrations of currently unquantified, common transformation products from multiple precursors.

While historically the scope of PFAS examined in many studies has largely been limited, studies have increasingly noted the broad occurrence of and co-exposure to a range of PFAS. Broad and/or non-target analyses have detected a variety of PFAS in various substrates, including for example, Northern European and Arctic sea waters (Joerss et al. 2020), Arctic lake and air samples (Stock et al. 2007), surface waters in the Netherlands (Hensema et al. 2021), biosolids (Letcher et al. 2020) and organic waste in France (Munoz et al. 2022), urban air particulate matter in China (Yu et al. 2018), and indoor dust samples collected from homes in the United States (Young et al. 2021). Examples of broad detection of co-occurring PFAS in organism tissues include in marine mammals (Spaan et al. 2020), St. Lawrence beluga whales (Barrett et al. 2021), sea birds (Letcher et al. 2015; Robuck et al. 2020; Su et al. 2017), tree bark, and fish species from various regions (e.g., Baygi et al. 2021; Liu and Gin 2018; Pignotti et al. 2017). This evidence of broad PFAS co-exposure among such varied regions, environmental media, and organisms suggests that widespread co-occurrence is increasingly the norm and that studies that do not account for a broader (and possibly unanticipated) suite of PFAS may not adequately describe cumulative exposure. To this end, a number of techniques to detect total PFAS in environmental samples are being investigated, including total organic fluorine (TOF), extractable organic fluorine (EOF), and total oxidizable precursors (TOP) methods (e.g., Nikiforov 2021). It is hoped that, in the future, these or other newly developed methods may be used to provide a more complete understanding of PFAS diversity and concentrations in the environment and organisms.

4.2 Environmental monitoring in Canada

In addition to monitoring international trends and developments regarding the environmental occurrence of PFAS, the Government of Canada conducts a variety of monitoring programs to understand trends in PFAS occurrence in Canadian ecosystems and wildlife. A summary of results generated to date is provided in this section.

4.2.1 Ambient air

The Government of Canada has monitored PFAS (including C4-14, C16, C18 PFCAs, and C4, C6, C8, C10 PFSAs and their precursors) in air at the Canadian High Arctic Station of Alert, Nunavut, since 2006 with high volume active air samplers (AMAP 2014, 2017; Wong et al. 2018, 2021). PFOA and PFOS concentrations in air at Alert increased from 2006 to 2013. After 2013, the concentrations of PFOA and PFOS have steadily declined (Wong et al. 2021). PFHxS appeared to decline from 2013 onwards but this was probably driven by the few high measurements in 2013 and low measurements in 2017. PFNA showed non-changing trends, while PFDA and PFUnDA showed increasing trends. It should be noted that the evaluation of trends for PFAAs other than PFOA and PFOS at Alert has been hampered by low detection frequencies (DF) and inconsistent blank levels (Wong et al. 2021). The AMAP (2017) report also included several new PFAS compounds, including perfluoroethylcyclohexane sulfonic acid (PFECHS, an analog of PFOS), perfluorobutane sulfonamide (PBSA, a precursor of PFBS), and 6:2-chloro-polyfluorinated ether sulfonic acid (6:2-Cl-PFAES or F-53B, a chlorinated polyfluorinated ether sulfonic acid).

Research projects have also been conducted on the atmospheric deposition of PFAS in remote areas through the analysis of PFAAs (including C4-14 PFCAs, C4, C6, C8, C10 PFSAs, PFECHS, FOSA) in Arctic snow, glaciers (MacInnis et al. 2019a), and ice cores (MacInnis et al. 2017; Pickard et al. 2018). These studies have confirmed the ubiquitous presence of PFAAs in remote regions. These abiotic samples are pertinent as they demonstrate higher concentrations of short-chain PFAAs that are not prevalent in biota. Analyses in sectioned and dated ice cores were used to calculate annual fluxes of PFAAs via atmospheric deposition. Furthermore, PFCA congener analysis was consistent with long-range environmental transport of fluorotelomer precursors followed by atmospheric deposition.

In the Great Lakes Basin, PFAS (including C4 to C12 PFCAs and C4, C6, and C8 PFSAs) have been monitored in precipitation since 2006 at Point Petre on the coast of Lake Ontario, Evansville on Lake Huron, and Sibley on Lake Superior (Gewurtz et al. 2019; Government of Canada 2021). PFOS and PFOA concentrations generally decreased in Great Lakes precipitation. However, concentrations of shorter-chained PFAAs, which are not regulated in Canada, did not decrease, while those of PFHxA and PFBA recently increased (since approximately 2010 to 2016 depending on the location), which could be due to their use as replacements since the longer-chained PFAAs are being phased out by industry (Gewurtz et al. 2019). PFAS have been monitored in air at Point Petre since October 2018 and at Evansville since July 2019.

The Government of Canada monitors PFAS (C4-C14, C16, C18 PFCAs and C4, C6, C8, C10 PFSAs and their precursors) in passive air samples under the Global Atmospheric Passive Sampling (GAPS) network (initiated in 2004) at 13 Canadian sites (Rauert et al. 2018). Between the years 2009 and 2015, FTOHs and fluorinated sulfonamides and sulfonamidoethanols (FOSAs and FOSEs) did not change significantly at these sites. However, PFSA concentrations including PFBS, PFHxS, and PFOS increased significantly in 2015. Total PFCA concentrations including PFHxA, PFHpA, PFOA, PFNA, and PFDA also showed an increase in 2015 but such changes need to be confirmed. The results from passive air samplers (Rauert et al. 2018) are consistent with those from high volume air samplers described above (AMAP 2014, 2017; Wong et al. 2018, 2021).

PFAS emissions from the waste sector (i.e., WWTPs and landfills) to air have also been investigated (Ahrens et al. 2011; Shoeib et al. 2016). Ahrens et al. (2011) collected PFAS air samples on and around one WWTP and two solid waste landfills in Ontario in 2009. The samples were analyzed for 5 groups of PFAS (FTOHs, FOSAs, FOSEs, PFSAs, and PFCAs). Compared with the reference sites, the total PFAS concentrations in air were 3 to 15 times higher within the WWTP and 5 to30 times higher at the landfill sites. The emissions of FTOHs (6:2 FTOH was dominant at the WWTP, and 8:2 FTOH was dominant at landfill sites) were about 2 orders of magnitude higher than the other PFAS classes evaluated in this study. Among the PFSAs and PFCAs, PFOS and PFBA represented the highest emissions to the atmosphere from the WWTP, and PFBA emissions were highest at the landfill sites.

4.2.2 Aquatic ecosystem and wildlife

The Government of Canada carries out freshwater monitoring at sites across Canada. From 2013 to 2020, 29 sites were sampled for PFAS to determine concentrations and trends in ambient surface waters. This work did not target specific releases from industrial sources. Sampling sites were located in every province except Alberta and Prince Edward Island; PFAS were detected in the surface water of every province tested. Overall, 13 PFAS were measured in 566 Canadian freshwater samples, with concentrations ranging from below the laboratory detection limit (LOD range: 0.4 ng/L to 1.6 ng/L) to a maximum of 138 ng/L (for PFBS). While PFOS and PFOA concentrations were declining over this time period, other compounds such as PFBA and PFPeA increased (Lalonde and Garron 2022).

PFAS (including C8-C12 PFCAs and C7, C8 PFSAs) are measured in whole body homogenates of fish from water bodies across Canada (Burniston et al. 2011; Chu et al. 2016; Gewurtz et al. 2012; Government of Canada 2019; McGoldrick and Murphy 2016; US EPA, Government of Canada 2019). This monitoring provides information on the presence and accumulation of PFAS in the aquatic environment. Concentrations of PFOS in Lake Ontario lake trout increased from the early 1990s to early 2000s, declining subsequently, although trends were not as clear in Lake Huron, and concentrations remain above federal guidelines for wildlife consumption at Great Lakes sites (McDaniel et al. 2021; ECCC, US EPA 2021). In contrast, increasing concentrations of PFCAs were seen within the past decade in Lake Huron lake trout, whereas concentrations declined in Lake Ontario (McDaniel et al. 2021). Monitoring to inform sport fish consumption guidance is conducted by the Province of Ontario (ECCC, US EPA 2021).

Surveillance studies of PFAS (including C4 to 14, C16, C18 PFCAs and C6, C8, C10, PFSAs) in Arctic and Subarctic locations are performed as part of the Northern Contaminants Program (NCP) core Environment Monitoring and Research (EMR) projects (AMAP 2016, 2017, 2018; Braune and Letcher 2013; CIRNAC 2018; Letcher et al. 2014, 2018; Lucia et al. 2015; Muir et al. 2019; Routti et al. 2019a; Sonne et al. 2021). Under these projects, Arctic seawater has been analyzed each year since 2011 and constitutes the longest continuous data set for this medium; PFOS and PFCAs have declined in seawater collected in more recent years (CIRNAC 2018). Ringed seals and Arctic char have been analyzed every year since the 1990s and constitute the longest continuous temporal data set for these media. Declining trends for total (C7 to C14) PFCA were observed in ringed seals from 4 locations in the Canadian Arctic for the period 2005 to 2010 (Muir et al. 2019). However, more recent trends indicate an increase in these PFCAs in ringed seals from two of the locations, Hudson Bay and Lancaster Sound (Muir et al. 2019). C7 to C14 PFCAs in landlocked Arctic char from Lake Hazen, Char Lake, and Amituk Lake appear to be declining from their peak during the period 2006 to2009 (Muir et al. 2019). PFAAs were analyzed in the food web of Lake Melville (including in ringed seals), where local residents are concerned about contaminant levels in the country foods they harvest (CIRNAC 2018). PFAA concentrations in Lake Melville ringed seal pups increased annually from 2013 to 2016 (CIRNAC 2018). Concentrations of PFAA in Arctic char have generally declined since the period 2008 to 2009 but the trends vary among the high Arctic lakes evaluated and among specific chemicals (CIRNAC 2018; Muir et al. 2019). PFAS were measured in the blood of adult thick-

billed murres, a marine Arctic seabird that preys on fish, in southern Hudson Bay. This research has provided additional information on the presence and possible effects of PFAS on this Arctic seabird in the marine environment but have yet to be validated by peer review. PFAS were assessed in polar bears from different populations in Hudson Bay and correlated with liver metabolites. Temporal trends were also assessed in polar bears along with their diet in the Hudson Bay region (Letcher et al. 2018; Morris et al. 2019; Muir et al. 2019; Pedersen et al. 2016). There were no obvious increasing or decreasing trends in total PFCA and PFOS concentrations in the liver tissue of two subpopulations of polar bears from the southern and western Hudson Bay (Nunavut) over the 2007 to 2016 period (INAC 2017; CIRNAC 2018; Muir et al. 2019).

Outside of the NCP, Government of Canada researchers have led research projects on PFAS in Arctic and Subarctic environments. Analyses of short-chain and long-chain PFCAs and PFSAs in High Arctic ice fields (MacInnis et al. 2017; Pickard et al. 2018, 2020), snow melt, and glacier melt (Cabrerizo et al. 2018; MacInnis et al. 2019a) are relevant to the aquatic environment due to accelerated melting mediated by climate change. This was supported by the PFAA depth profile in a dated sediment core from Lake Hazen, Nunavut, and its correlation with glacial discharge (MacInnis et al. 2019b). PFAAs have also been measured in Arctic water (Cabrerizo et al. 2018; Lescord et al. 2015; MacInnis et al. 2019a) and lake sediment (Lescord et al. 2015).

The Government of Canada monitors, among other chemicals, PFAS in fish and wildlife across Canada as part of research and monitoring programs under the CMP. These include analysis of C4 to C16 PFCAs, C4 to C10 PFSAs, and novel PFAS (perfluoroalkyl phosphinic acids) in fish and birds from the Great Lakes and St. Lawrence River (De Silva et al. 2016; Houde et al. 2013) and in beluga whales from the St. Lawrence Estuary (Barrett et al. 2021). Time trends were also evaluated in beluga whales from the St. Lawrence Estuary, where a general decline in regulated legacy PFAA and PFOSA was observed after the mid-2000s (Barrett et al. 2021). However, unregulated short-chain PFAS alternatives, single-hydrogenated perfluorocarboxylic acids (H-PFCAs; detected for the first time in this study), and odd-chain fluorotelomer-based carboxylic acids (FTCA) were found to increase over time (Barrett et al. 2021). Eggs from aquatic (gull species) and terrestrial wildlife (European Starlings) have been monitored for PFAS in the Atlantic provinces, St. Lawrence River, Great Lakes, prairies, Pacific coast, and the Subarctic (Elliott et al. 2021; Gewurtz et al. 2016, 2018; Letcher et al. 2015; Miller et al. 2015, 2020; Su et al. 2017). Eggs of these species have been collected annually since 2008 and analyzed for PFAS that include C4 to C14, C16, and C18 PFCAs and C4, C6, C8, and C10 PFSAs. There was evidence of decreasing trends for concentrations of PFOS (comprising >90% of total PFSA) and total long-chain PFCAs in eggs collected from 14 of 39 sites/colonies monitored from 2008 to 2021. For the unregulated short-chain PFAS, which were found at relatively lower concentrations, there was no evidence of a temporal change in concentrations at these sites/colonies, with the exception of a few sites where either an increase (2 sites) or decrease (3 sites) in total PFBS and PFHxS concentrations were found during this period. PFAS were measured in the eggs and blood of nestling peregrine falcons, a terrestrial predator of other avian species, in southern Ontario and the north shore of Lake Superior (Sun et al. 2020, 2021). A total of 22 PFAA and 4 FASA were determined; the PFSA were PFBS, PFHxS, PFEtCHxS, PFOS, and PFDS, and the PFCAs (C4 to C14, C16, and C18) were PFBA, PFPeA, PFHxA,

PFHpA, PFOA, PFNA, PFDA, PFUdA, PFDoA, PFTrDA, PFTeDA, PFHxDA, and PFODA. PFSA (including PFHxS, PFOS, and PFDS) were detected in most eggs and plasma samples. In addition, 11 PFCAs (C5 to C14, C16) were detected in most egg samples, and 8 PFCAs (C8 to C14, C16) were detected in most plasma samples. PFPiAs, PFCAs, and PFSAs were surveyed in fish, dolphins, and birds from various freshwater and marine locations in North America (De Silva et al. 2016). This was the first report of PFPiAs in fish, dolphin, and bird plasma. Total PFPiA levels were 1 to 2 orders of magnitude lower than those of PFCAs and PFSAs in the same samples. PFAS concentrations were measured in turtles, invertebrates, and water samples in rural and urban environments and downstream of an airport in southern Ontario (de Solla et al. 2012). The PFAS evaluated included C4 to C15 PFCAs, C4, C6, C8, and C10 PFSAs, several PFAA precursors (e.g., PFOSA), and PFECHS (a cyclic PFAS used in aircraft hydraulic fluid). This study found elevated levels of PFAS downstream of the airport compared with the other locations evaluated (de Solla et al. 2012). PFAS were also measured in invertebrates and water collected upstream and downstream of 3 airports, 3 WWTPs, and along the Grand River in southern Ontario in 2018.

In addition, PFOA and PFOS have been identified as contaminants of concern for 3 species of at-risk whales: the Southern Resident Killer Whale, the St. Lawrence Estuary Beluga, and the North Atlantic Right Whale. As part of the Initiative to Protect and Recover Endangered Whale Populations, the Government of Canada has committed to increasing monitoring and research to improve understanding of the sources and possible impacts of contaminants on whales and their prey. This initiative includes air and fresh water monitoring within whale habitat as well as monitoring of potential land-based contaminant sources.

4.2.3 Landfill leachate

Landfill leachate was collected at 13 selected large (permitted to receive 40 000 tonnes of municipal solid waste annually) MSW landfills across Canada between 2008 and 2014 under the CMP Environmental Monitoring and Surveillance program. PFAS (C4 to C12 PFCAs, C4, C6, and C8 PFSAs, PFOSA) were analyzed in the leachate samples collected between 2009 and 2011 at 12 different landfills (Gewurtz et al. 2013; Government of Canada 2013). The total concentration of PFAS measured in leachate ranged from 320 ng/L to 9 400 ng/L before any treatment (median of 3 227 ng/L) and from 800 ng/L to 14 201 ng/L (median of 4 498 ng/L) after on-site leachate treatment. The total concentration of PFAS measured in leachate generally increased after on-site leachate treatment (discussed further in section 2.6.4).

The Government of Canada recently completed a research project that investigated the presence of various contaminants of emerging concern, including 17 PFAS (C4 to C14 PFCAs, C4, C6, C8 and C10 PFSAs, PFECHS, FOSA) within groundwater impacted by leachate from historic landfills (those closed for >25 years; few have leachate collection systems) (Propp et al. 2021). A survey was performed that collected 48 samples of leachate-impacted groundwater from 20 historic landfills (with closing dates from the 1920s to early 1990s) in Ontario, Canada. Several of these landfills, closed in the 1960s or later, had total PFAS concentrations similar to those reported for modern landfills, with a maximum of 12 700 ng/L. Subsequently, a set of field-based investigations was conducted (ending 2022) at two of these historic landfill sites where a surface water aquatic ecosystem (one a pond and one a stream) was receiving discharge from

groundwater plumes contaminated with landfill leachate. The investigations assessed exposure to various contaminants, including PFAS. These projects were supported through an agreement with the Province of Ontario's Ministry of Environment, Conservation and Parks.

Ad hoc analysis of PFAS sampled and analyzed by the Government of Canada included 29 PFAS analytes that were measured in 6 leachate samples in 2019 to 2020 (2 consecutive days at 3 sites) at operational landfills. Many of the 29 analytes were detected often. Only 8 analytes (4:2 FTS, N-EtFOSA, N-MeFOSA, PFDoS, PFDS, PFNS, PFTeDA, and PFTrDA) were seldom detected.

The Government of Canada is also currently sampling leachate from 10 operational MSW landfills in Canada to determine the presence and concentration of specific substances, including certain PFAS, in landfill leachate. The sampling is being conducted over a 5-year period (2019 to 2024) under the Initiative to Protect and Recover Endangered Whale Populations.

PFAS emissions to air from the waste sector are described in section 4.2.1.

4.2.4 Wastewater and biosolids

The Government of Canada gathers data on levels of PFAS entering municipal WWTPs, evaluates the fate of PFAS through the liquid and solids trains of typical treatment process types used in Canada, and determines levels of PFAS being discharged in WWTP effluents and solids residuals (Gewurtz et al. 2013, 2020; Government of Canada 2013, 2021a; Guerra et al. 2014; Lakshminarasimman et al. 2021). The Government of Canada has developed partnerships with municipalities throughout Canada in order to evaluate typical Canadian WWTP types (including primary, secondary, advanced, and lagoon treatment) and geographic regions (mountain, prairie, Great Lakes/St. Lawrence, coastal). As discussed in section 2.6.4, PFAAs are formed during wastewater treatment, which is likely a result of transformation of unmeasured precursors (Guerra et al. 2014).

Guerra et al. (2014) examined the fate and behaviour of 13 PFAS (including C4 to 12 PFCAs, C4, C6, and C8 PFSAs, PFOSA) in influent, effluent, and solids samples collected from 15 Canadian WWTPs. Of the PFAA measured, PFOA was the predominant PFAA in waste water, with concentrations ranging from 2.2 ng/L to 150 ng/L in influent and 1.9 ng/L to 140 ng/L in effluent. PFOS was the predominant compound in primary sludge, waste biological sludge, and treated biosolids, with concentrations ranging from 6.4 ng/g to 2 900 ng/g dry weight, 9.7 ng/g to 8 200 ng/g dry weight, and 2.1 ng/g to 17 000 ng/g dry weight, respectively.

Lakshminarasimman et al. (2021) evaluated the formation and removal of 13 PFAS (including C4 to 12 PFCAs, C4, C6, and C8 PFSAs, PFOSA) in 9 different sludge treatment systems. Of the 13 target PFAS, only 4 (PFOA, PFDA, PFDoDA, and PFOS) were detected appreciably (>1%) in both raw sludge and biosolids samples. The concentrations of PFOA and PFOS ranged from below the laboratory reporting limit to 4.8 ng/g and 27 ng/g dry weight in raw sludge and ranged from below the laboratory reporting limit to 23 ng/g and 25 ng/g dry weight in biosolids, respectively.

Recently, a Government of Canada research project reported on the distribution of selected PFAS (including ionizable PFAS such as PFOS and PFOA and their precursors) in aquatic sediment and agricultural soils where WWTP-sourced biosolids application occurred, and in samples from sites in the Great Lakes basin (Chu and Letcher 2017). Thirteen soil samples were collected (2015) from a WWTP-biosolids applied and two non-biosolids applied farm field sites in southern Ontario. Novel side-chain fluoroalkyl co-polymers, which are important commercial PFAS products, were also evaluated in this study. The side-chain fluoroalkyl co-polymers were detected in 100% of the soil samples from biosolid-augmented agricultural sites and at concentrations much greater than in the aquatic sediment samples. The concentrations of side-chain fluoroalkyl co-polymers in soil and sediment samples were also much greater than the total concentration of other PFAS that were measured (including PFOS and PFOA). For the same project, side-chain fluoroalkyl co-polymers and established PFAS were detected in biosolids samples from 20 Canadian WWTPs, and the novel fluorinated polymers were at much higher concentrations than those of other commonly monitored PFAS (including PFOS and PFOA) (Letcher et al. 2020). Studies have shown that PFAS are taken up from soil by plants and transferred to animals and humans through the consumption of crops (Zhu and Kannan 2019); however, as has been discussed in greater detail in section 2.3, the overall process of PFAS uptake and accumulation in plants and crops has not been fully determined, and concentrations of PFAS in retail foods tend to be below the LOD.

5 Human biomonitoring

KEY POINTS ON HUMAN BIOMONITORING

- Although more than 4700 PFAS have been identified by the OECD, very few PFAS (typically 6 to 8 commonly known PFCAs and PFSAs) have been commonly monitored in human biomonitoring (HBM) surveys.
- Canadian HBM data have demonstrated that, although levels are declining for certain PFAS (e.g., PFOA, PFOS, and PFHxS), these PFAS are present in almost 100% of the Canadian population (in blood) despite risk management measures being in place in Canada for several years. Other PFAS (PFDA and PFUnDA) are commonly detected in over 50% of the population. At any given time, Canadians demonstrate exposure to multiple PFAS.
- Currently, Canada is the only country that has a nationally representative PFAS data set for children, and results demonstrate that children as young as 3 can be exposed to multiple PFAS.
- Certain population groups in Canada are likely to be exposed to higher levels of certain PFAS than the general population. For example, Anishinabe children (3 to 5, 6 to 11) and youth (12 to 19) have elevated levels of PFNA, up to 21-fold higher, compared with similar age groups (for similar time periods) in the Canadian Health Measures Survey (CHMS). Adults (male and female) and pregnant women in Nunavik also had PFNA levels that were 7- and 6.3-fold higher than comparable populations in CHMS (for similar time periods).
- Exposure to certain PFAS is increasing in certain populations of Canada; specifically, concentrations of PFNA in the serum of pregnant women in Nunavik have increased in the 5 years between 2011 to 2012 and 2016 to 2017.
- In the most recent CHMS survey of the general population (3 to 79 years) in Canada, as well as in specific subpopulations (e.g., adults and pregnant women in Nunavik,

adults in Dene communities in the Dehcho region of the Northwest Territories [NWT]), more than 25% of the sampled group are above an international HBM guidance value developed by EFSA for combined exposure to PFOA, PFNA, PFHxS, and PFOS.
- Firefighters appear to have elevated levels of PFHxS, PFOS, PFDA, and PFOA when compared to the general population, and most firefighter biomonitoring studies found mean serum levels of PFOA or PFOS above HBM-I values.

5.1 Introduction to human biomonitoring and PFAS

Human biomonitoring (HBM) is the measure of a chemical, its metabolites, or reaction products in biological matrices (e.g., blood, urine). It provides a biologically relevant, integrated measure of systemic exposure to environmental chemicals that may occur across multiple routes (e.g., oral, dermal, and inhalation) and sources (e.g., natural and anthropogenic, environmental media, diet, and frequent or daily use products) (Haines and Murray 2012; Sexton et al. 2004; Zidek et al. 2017). However, HBM data also have limitations. HBM data from population-level biomonitoring surveillance programs alone cannot provide information on the source of exposure and have uncertainty in identifying the period of exposure, especially for substances with longer half-lives. That being said, the use of HBM data can support a variety of public health initiatives. HBM data can be used to establish reference concentrations of chemicals representing the upper margins of background exposures in Canadians, which allows the identification of individuals or subpopulations with an increased level of exposure compared with the background exposure, comparisons of populations within Canada (e.g., individuals living in Northern Canada and the Canadian Health Measures Survey [CHMS] general population), and comparisons with other countries (Haines et al. 2017). Additionally, if data from multiple sample collection periods are available, HBM data support the identification of levels of or trends for chemicals in populations using factors such as sex, age, and time (HC 2023a). While HBM data are increasingly used in the characterization of exposure and risks from a number of chemical substances (HC 2016a, 2016b), this data may also be readily screened in a risk context through direct comparisons with health-based biomonitoring guidance values such as biomonitoring equivalents and the German HBM values (Faure et al. 2020; St-Amand et al. 2014). HBM data are also invaluable in assessing the effectiveness of risk management actions (Canada 2020b; ECCC 2020) and identifying future research needs, such as potential links between exposure to certain chemicals and specific health effects (Eykelbosh et al. 2018; HC 2020).

More than 4700 PFAS have been identified on the Comprehensive Global Database of PFAS (OECD 2018a); however, very few PFAS (e.g., 6 to 8 commonly known PFCAs and PFSAs) have traditionally been commonly monitored in HBM surveys. Available HBM studies have demonstrated that certain PFAS, particularly PFOA, PFNA, PFHxS, and PFOS, are ubiquitous, while others (e.g., PFDA, PFUnDA) are commonly found in the blood (plasma or serum) of the general population of countries where the surveys have taken place, e.g., Canada, US, France, Sweden (Bjermo et al. 2013; CDC 2022; Fillol et al. 2021; HC 2019a). Table B-1 of Appendix B provides a summary of the most frequently detected PFAS in blood in Canada and internationally, including studies that are national, regional, or small in scale; some studies are birth-cohorts (i.e., examining a group of people born at a similar time). In addition, PFAS have also been reported in cord blood and human milk in various parts of the world, e.g., Canada, US, France, Spain, Korea, Japan, China (Arbuckle et al. 2013; Cai et al. 2020; Cariou et al.

2015; Fisher et al. 2016; Fujii et al. 2012; Kang et al. 2016; Kubwabo et al. 2013; LaKind et al. 2022; Lorenzo et al. 2016; Monroy et al. 2008; Rawn et al. 2022b; Zheng et al. 2021).

Due to the persistence, high bioavailability in the environment, and widespread use (current and historical) of PFAS, people can be exposed to multiple PFAS at any given time from various sources (Bil et al. 2021; HBM4EU 2019). The relative contributions of different PFAS vary between people (EFSA 2020). Because of the likelihood of exposure to multiple PFAS, the importance of considering these substances as a class of compounds or of examining a group of PFAS together (e.g., commonly found PFAS, including PFOA, PFNA, PFHxS, and PFOS) has received much attention in recent publications such as Bil et al. (2021), EFSA (2020), and HBM4EU (2019).

5.2 Factors to consider when using HBM data to assess PFAS exposures

To evaluate whether and how HBM data can be used to consider exposure to a substance, the adequacy of the biomarker, quality of the data, and appropriateness of the data set should be examined (Zidek et al. 2017). Chemical-specific information that is important to consider for the use of HBM data include: appropriateness of the biomarker(s), appropriateness of the biological matrix, and knowledge of biological half-lives. Study-specific information related to the use of HBM data include detection limits, geographic location of sampled population, timing of sample collection, age of study, subpopulation(s) monitored, and sample size. The following sections provide more details on chemical-specific factors. Study-specific information is described in later sections where PFAS-specific biomonitoring results are discussed (sections 5.4, 5.5, and 5.6).

5.2.1 Biomarkers

Many PFAS may degrade to PFAAs (including PFCAs and PFSAs) under environmentally relevant conditions; these PFAAs are considered to be stable end products (Bil et al. 2021). Serum or plasma concentrations of PFCAs or PFSAs (e.g., PFOA or PFOS) have been considered appropriate biomarkers for PFAS, representing either direct exposure to these PFCAs or PFSAs or exposure to precursor compounds that are then degraded or metabolized to these terminal acids. PFAS that are commonly monitored in biomonitoring studies include PFOA, PFNA, PFDA, PFUnDA, PFHxS, and PFOS.

Uncertainty may arise, however, given that the number and concentrations of co-occurring, unidentified precursors in serum of the general population is unknown (McDonough et al. 2022). No precursor substances were examined in the CHMS; however, certain substances have been included in some international biomonitoring studies and in small-scale studies (Table B-1 of Appendix B). Precursors are not typically measured in HBM studies due to analytical issues as well as the lack of knowledge on production, use, and subsequent human exposure. Some intermediate metabolites of PFCA or PFSA precursors may have higher toxicity than the final PFCA or PFSA degradation products (Rand et al. 2014; Rice et al. 2020). Recent studies have indicated that some of the intermediate short-chain PFAS metabolites, such as 5:3 fluorotelomer carboxylic acid (FTCA), may biopersist and bioaccumulate (Kabadi et al. 2018, 2020). Further analytical methods to simultaneously analyze as many PFAS as possible would be a useful indicator of PFAS exposures (HBM4EU 2021).

5.2.2 Biological matrix

In most biomonitoring studies, PFAS concentrations have been measured in either blood plasma (e.g., Canadian Health Measures Survey [CHMS] and Maternal-Infant Research on Environmental Chemicals study [MIREC]) or serum (e.g., the US National Health and Nutrition Examination Survey [NHANES]). Individuals occupationally exposed to PFOA and PFOS and individuals living near a PFOA manufacturing facility have been observed to have much higher plasma or serum concentrations in comparison with the general population, suggesting that plasma or serum concentration is an appropriate matrix to measure biomarkers of exposure (ATSDR 2021). PFAS are also measured in whole blood in some biomonitoring studies (ATSDR 2021; EFSA 2020). Whole blood has the additional advantage of representing the entire circulating fluid (EFSA 2020). Some studies have shown that whole blood is the most appropriate matrix for PFHxA (EFSA 2020; Poothong et al. 2017). ATSDR (2021) further reported that only PFHxA, and not PFHxS, enters the cellular components of blood.

The ratio of most PFAS in serum to plasma is assumed to be approximately 1:1. Poothong et al. (2017) identified the median serum-to-plasma ratios of certain PFAS (PFOA, PFNA, PFUnDA, PFHxS, PFOS, and 6:2 diPAP) as ranging from 0.9 to 1.3; however, other PFAS demonstrated wider serum-to-plasma ratios, such as PFTrDA (2.9) and PFBS (0.8). Similarly, median serum (or plasma) to whole blood ratios of PFOA, PFNA, PFUnDA, PFHxS, and PFOS were approximately 2 (EFSA 2020; Poothong et al. 2017). However, the ratios were variable for PFDA, PFDoDA, PFTrDA, PFBS, PFHpS, and PFDS, probably as a result of differences in distribution in the blood compartments. Additionally, these substances are generally found in low concentrations in the body, resulting in analytical uncertainties (EFSA 2020).

PFAS are also measured in human milk, but the levels in human milk are substantially lower than in serum, with concentrations ranging from one to several orders of magnitude lower (ATSDR 2021; EFSA 2020).

PFAS can also be measured via other non-invasive methods, such as in umbilical cord blood, hair, and nails. However, it is still unclear how to interpret these results (ATSDR 2021; EFSA 2020).

PFAS with shorter biological half-lives (e.g., PFBA, PFHxA) are more efficiently eliminated in urine than long-chain PFAS with longer half-lives (ATSDR 2021; Calafat et al. 2019). However, Calafat et al. (2019) demonstrated that when paired serum-urine data for 12 PFAS from 2273 participants in the US NHANES were analyzed for serum and urine concentrations, PFAS was rarely detected in urine compared with serum. Thus, the authors concluded that the findings of this study do not support biomonitoring of urine as a preferred biomarker for PFAS (including short-chain PFAS) for the general population. Similar observations were reported by multiple authors that examined paired urine-serum samples from other regions, e.g., South Korea, China (Kato et al. 2018, as cited in EFSA 2020; Zhang et al. 2015).

5.2.3 Biological half-lives of PFAS

PFAS with half-lives of years-to-decades (e.g., PFOA, PFNA, PFHxS, and PFOS, on the basis of declines in serum PFAS over time) are well suited for population-level biomonitoring surveys,

such as the CHMS, as the levels measured are indicative of long-term steady-state serum or plasma concentrations. In contrast to these PFAS, certain SC-PFAS are more rapidly excreted, with serum or plasma half-lives of several days to several weeks. For example, mean half-lives are on the scale of days (e.g., 72 to 87 hours on the basis of serum decline) for PFBA and weeks (e.g., 32 days on the basis of serum decline) for PFHxA (ITRC 2020b). This is not the case for all SC-PFAS (e.g., the biological elimination half-life of PFHpA is estimated to be 1.2 to 1.5 years) (Zhang et al. 2013). Some of these SC-PFAS are less commonly detected in population-level biomonitoring surveys compared to those with longer half-lives, but have been found in smaller biomonitoring studies (often with lower limits of detection) (CA OEHHA 2020; Poothong et al. 2017).

5.3 Existing HBM guidance values

A health-based HBM guidance value is an important tool in interpreting HBM data or as a screening value to assist in the evaluation of general or specific population biomonitoring data. HBM guidance values for general population exposure for individual PFAS have been published in several reports and journal articles, including Borg et al. (2013), ECHA (2015), EFSA (2018), and the German Human Biomonitoring Commission (HBM Commission) (Hölzer et al. 2021; Schümann et al. 2021; Umwelt Bundesamt 2015). Key chronic HBM guidance values identified in the literature, derived by international organizations, are summarized in Table 1 below. HBM guidance values derived by different organizations vary depending on the selected critical effect level, selected uncertainty factors, and the derivation method.

In a 2020 assessment, the EFSA Panel on Contaminants in the Food Chain derived a Tolerable Weekly Intake (TWI) using a $BMDL_{10}$ of 17.5 µg/L for the sum of 4 frequently detected PFAS (PFOA, PFNA, PFHxS, and PFOS) in serum. As certain PFAS are known to be persistent in the body, the EFSA (2020) derived a TWI rather than a Tolerable Daily Intake (TDI). The critical study selected by the EFSA for derivation of their TWI is based on the sum of 4 prevalent PFAS, which suggests that this approach acknowledges potential co-exposures of the general population to PFAS at any given time.

The benchmark dose level ($BMDL_{10}$) used by the EFSA for the derivation of their TWI was based on decreased immune responses (i.e., reduction in antibody titres against diphtheria) observed in 1-year-old children. The EFSA then estimated a serum level in mothers that would result in levels in human milk leading to serum levels in infants that would be associated with decreased immune response. Using physiologically-based pharmacokinetic (PBPK) modelling and assuming 12 months of breastfeeding, the $BMDL_{10}$ of 17.5 µg/L in infants was converted into a serum concentration of 6.9 µg/L in mothers at 35 years of age, which corresponded to an oral PFAS intake of 0.63 ng/kg bw/day (TWI of 4.4 ng/kg bw/week) by mothers (EFSA 2020). Thus, these serum concentrations (i.e., 17.5 µg/L and 6.9 µg/L for infants and women of reproductive age, respectively) were used as the basis for the EFSA TWI values and are referred to as “reference serum levels” in this document.

There are uncertainties associated with the EFSA guidance values (EFSA, 2020), such as the use of PFOA and PFOS PBPK modelling to derive the intake of the PFAS mixture by mothers that would result in serum levels in the 1-year-old infant at the effect level, or the assumption of

equal potencies for effects of the 4 PFAS on immune outcomes; however, this is one of the only approaches that examine a mixture of PFAS.

Bil et al. (2021) have proposed a relative potency factor approach in mixture risk assessment of PFAS. Using dose-response modelling for liver effects (i.e., absolute liver weight, relative liver weight, and liver hypertrophy) in rats exposed via oral route, they derived the relative potencies of 22 PFAS compared against the potency of the index compound PFOA. The derived relative potency factors can be applied to measured PFAS quantities, resulting in the sum of PFOA equivalents in a mixture. This approach requires an additional step, such as PBPK modelling, to convert relative potencies to blood (serum/plasma) levels. Mixture effects of PFAS and uncertainties of approaches are further discussed in section 7.5.

The Commission for Human Biomonitoring (HBM Commission) of the Federal Environment Agency (UBA) of Germany has established human biomonitoring values (HBM-I and HBM-II) for PFOA and PFOS in serum or plasma (Hölzer et al. 2021; Schümann et al. 2021). According to the German HBM Commission, "the HBM-I value represents the concentration of a substance in a body matrix at and below which, according to the HBM Commission's current assessment, adverse health effects are not expected and therefore, no exposure reduction measures are necessary" (Hölzer et al. 2021). The HBM-II is defined as the "the concentration in human biological material which, when exceeded, may lead to health impairment which is considered as relevant to exposed individuals" (Schümann et al. 2021). The HBM-I and HBM-II values for PFOA and PFOS are primarily based on human studies considering the following effects: developmental toxicity, reduced birth weights, reduced fertility, immune system/reduced antibody formation, increased cholesterol concentration, and Type II diabetes/gestational diabetes (Hölzer et al. 2021; Schümann et al. 2021).

ECHA (2015) identified several different internal derived-no-effect-level ($DNEL_{internal}$) values for PFOA using animal data and human data and for different endpoints. According to the EU's Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Annex 1 Section 1.0.1, a DNEL is defined as "a level of exposure to the substance above which humans should not be exposed" (ECHA 2012). The lowest $DNEL_{internal}$ values were based on reduced birth weight in a human study and increased total cholesterol and low-density lipoprotein (LDL) in human serum. These values are presented in Table 1.

While both German HBM values and ECHA (2015) internal DNELs are available for the interpretation of PFOA HBM data in the general population, the German HBM-I and HBM-II values are considered to be more robust. This is because they are based on a weight of evidence approach that examines key health effects (e.g., pregnancy and fertility, birth weight, lipid metabolism, immunological effects) observed in a large number of epidemiological and animal studies, including the two critical epidemiological studies (i.e., Fei et al. 2009; Steenland et al. 2009) that form the basis of the ECHA $DNEL_{internal}$ values.

Guidance values have also been derived for workers. ECHA (2015) derived a $DNEL_{internal}$ value for PFOA for workers, which is described below in Table 1.

The German Research Foundation, also known as Deutsche Forschungsgemeinschaft (DFG), also derived health-based guidance values for workers, which they designate as BAT (Biologischer Arbeitsstoff-Toleranz-Wert) values, for PFOA and PFOS (DFG 2017, 2019, 2021). The BAT values for PFOA and PFOS were based on critical effect levels from animal studies since the DFG considered that internal concentrations associated with health effects could not be determined based on existing epidemiological studies (DFG 2017, 2019). The derived BAT values for PFOA and PFOS were 5 000 µg/L and 15 000 µg/L in serum, respectively. The difference between the PFOA German BAT value and the ECHA PFOA $DNEL_{internal}$ for workers (ECHA, 2015) was due to the derivation methods used. The ECHA $DNEL_{internal}$ was based on a critical effect level from a human study and included an uncertainty factor for intra-individual variation, whereas the German BAT value for PFOA was related to a critical effect level identified from an animal toxicity study and an uncertainty factor was not included; therefore, this reference value is not used further in this section.

Table 1. Available chronic health-based biomonitoring guidance values for PFOA, PFNA, PFHxS, and PFOS

Organization (year)	PFAS	Critical endpoint	Critical dose level (in serum/plasma)	HBM guidance value (µg/L)
EFSA (2020)	Sum of PFOA, PFNA, PFHxS, and PFOS	Decreased antibody titres for diphtheria of 1-year-old infants (Abraham et al. 2020 as cited in EFSA 2020)	$BMDL_{10}$ = 17.5 µg/L (serum concentration infants) used by EFSA to derive TWI	Reference serum level = 17.5 (children)[a]
EFSA (2020)	Sum of PFOA, PFNA, PFHxS, and PFOS	Decreased antibody titres for diphtheria of 1-year-old infants (Abraham et al. 2020 as cited in EFSA 2020)	$BMDL_{10}$ = 17.5 µg/L (serum concentration infants) used by EFSA to derive reference serum level in women of reproductive age	Reference serum level = 6.9 (women of reproductive age)[a,b]
German HBM values (Umwelt Bundesamt 2015; Hölzer et al. 2021; Schümann et al. 2021)	PFOS	Based on weight of evidence from epidemiology data and animal data	1–15 µg/L plasma	HBM-I = 5
German HBM values (Umwelt Bundesamt 2015; Hölzer et al. 2021;	PFOS	Based on weight of evidence from epidemiology data and animal data	1–30 µg/L plasma	HBM-II = 10 (women of childbearing age)

Schümann et al. 2021)				
German HBM values (Umwelt Bundesamt 2015; Hölzer et al. 2021; Schümann et al. 2021)	PFOS	Based on weight of evidence from epidemiology data and animal data	1–30 µg/L plasma	HBM-II = 20 (all other population groups)
German HBM values (Umwelt Bundesamt 2015; Hölzer et al. 2021; Schümann et al. 2021)	PFOA	Based on weight of evidence from epidemiology data and animal data	1–10 µg/L plasma (for HBM-I)	HBM-I = 2
German HBM values (Umwelt Bundesamt 2015; Hölzer et al. 2021; Schümann et al. 2021)	PFOA	Based on weight of evidence from epidemiology data and animal data	3–10 µg/L plasma (for HBM-II)	HBM-II = 5 (women of childbearing age)
German HBM values (Umwelt Bundesamt 2015; Hölzer et al. 2021; Schümann et al. 2021)	PFOA	Based on weight of evidence from epidemiology data and animal data	3–10 µg/L plasma	HBM-II = 10 (all other population groups)
ECHA 2015	PFOA-related substances	Reduced birth weight in a human study (Fei et al. 2009 as cited in ECHA 2015)	3.9 µg/L (serum concentration)	$DNEL_{internal}$ = 0.7 (general population)[c]
ECHA 2015	PFOA-related substances	Reduced birth weight in a human study (Fei et al. 2009 as cited in ECHA 2015)	3.9 µg/L (serum concentration)	$DNEL_{internal}$ = 1.3 (workers)[d]
ECHA 2015	PFOA-related substances	Increased total cholesterol and LDL in human serum (Steenland et al. 2009 as cited in ECHA 2015)	13.1 µg/L (serum concentration)	$DNEL_{internal}$ = 2.2 (general population)[c]

ECHA 2015	PFOA-related substances	Increased total cholesterol and LDL in human serum (Steenland et al. 2009 as cited in ECHA 2015)	13.1 µg/L (serum concentration)	$DNEL_{internal}$ = 4.4 (workers)[d]

LOAEL = lowest observed adverse effects level; NOAEL = no observed adverse effects level; BMD = benchmark dose; BMDL = 95% lower confidence limit on the BMD; $DNELs_{internal}$ = derived no effects levels (internal); HBM-I; II = human biomonitoring value-1, 2

[a] "No additional uncertainty factors (UF) need to be applied, because $BMDL_{10}$ is based on infants which are expected to be a sensitive population groups, as is true for many immunotoxic chemicals" (EFSA 2020).

[b] Using a PBPK model, and assuming 12 months of breast feeding, EFSA estimated that the $BMDL_{10}$ in infants corresponds to an intake by the mother of 0.63 ng/kg bw per day for the sum of the 4 PFAS. Such intake would result in a serum level in the mother of 6.9 µg/L at 35 years of age (EFSA 2020).

[c] Uncertainty factor (UF) = 6 for intra-individual variation

[d] Uncertainty factor (UF) = 3 for intra-individual variation

5.4 Summary of human biomonitoring data on PFAS in Canada

5.4.1 PFAS measured in the Canadian Health Measures Survey (CHMS)

In Canada, 9 PFAS have been measured as part of the CHMS. Carried out since 2007, the CHMS is a cross-sectional national survey in which many environmental chemicals or their metabolites are measured in the blood or urine of Canadians. It is an ongoing survey conducted in 2-year cycles and is representative of the general Canadian population. The population surveyed in cycles 1 and 2 of the CHMS included persons living in the 10 provinces and 3 territories of Canada. Subsequent cycles of CHMS did not include the territories. The target population of CHMS excludes persons living on reserves and in other Indigenous settlements in the provinces, full-time members of the Canadian Forces, institutionalized populations, and residents of certain remote regions. All together, these exclusions represent less than 4% of the Canadian population. In addition to the nationally representative data for PFAS available through the CHMS, published Canadian PFAS biomonitoring data are available for certain populations not included in the CHMS, e.g., persons living on reserves, in certain communities (e.g., Innu and Anishinabe communities, communities in Nunavik) and in the territories (e.g., Dene communities in the Dehcho region of the Northwest Territories and Gwich'in community in the Yukon) (AFN 2013; Aker et al. 2021; Caron-Beaudoin et al. 2019, 2020; Garcia-Barrios et al. 2021). These data are discussed in the next section.

CHMS biomonitoring data on PFAS are available for 4 cycles from 2007 to 2019 (HC 2010, 2013, 2019a, 2021b). Cycle 1 (2007 to 2009) included PFOA, PFHxS, and PFOS. CHMS cycles 2 (2009 to 2011), 5 (2016 to 2017), and 6 (2018 to 2019) measured 9 PFAS, specifically PFBA, PFHxA, PFOA, PFNA, PFDA, PFUnDA, PFBS, PFHxS, and PFOS (Appendix B, Table B-2). A summary of the PFAS plasma concentrations from cycles 1, 2, 5, and 6 is presented in Table B-3 of Appendix B.

Results from the CHMS cycles demonstrate a statistically significant decreasing trend ($p<0.001$) in PFOA, PFNA, PFDA, PFHxS, and PFOS concentrations in the Canadian population aged 12 or 20 to 79 years (HC 2023a). Between 2007 and 2019, plasma concentrations of PFOA and PFOS declined significantly, with a 52% decline for PFOA and a 67% decline for PFOS, on the

basis of geometric mean values found in the data from the CHMS for people aged 20 to 79 years. Despite these declines, PFOA and PFOS continue to be detectable in almost all of the population. The most recent cycle of the CHMS (cycle 6) reported that both PFOA and PFOS were detected in the plasma of over 99% of the population aged 3 to 79 years on the basis of an LOD of 0.066 µg/L for PFOA and 0.43 µg/L for PFOS (Table B-3 of Appendix B). Consistent with results found in other regional and national biomonitoring surveys, results for the Canadian general population aged 3 to 79 years from CHMS cycle 6 have shown that, compared to other monitored PFAS, PFOS is found in the highest concentrations (geometric mean [GM] = 2.5 µg/L) in the plasma, followed by PFOA (GM = 1.2 µg/L) (Table B-3 of Appendix B). This illustrates that despite risk management measures being in place in Canada for several years (e.g., PFOS has been regulated since 2008; PFOA and LC PFCAs were added to PCTSR in 2016), these PFAS are still ubiquitous in the Canadian population.

Comparison of the levels of PFHxS across the 4 cycles of the CHMS has shown that geometric mean plasma concentrations declined significantly (i.e., by 64%) in the Canadian population between 2007 and 2019 in Canadians aged 20 to 79 years (HC 2021c). PFHxS was still detected in over 99% of the population aged 3 to 79 years in cycle 6, with geometric mean plasma concentrations reported to be 0.76 µg/L (LOD = 0.063 µg/L).

Other trends observed over the course of the 4 cycles of CHMS include higher concentrations of PFOA, PFHxS, and PFOS in the plasma of males compared to females and generally higher concentrations of all PFAS in adults compared to children in the Canadian population (HC 2021c).

PFNA, PFDA, and PFUnDA were monitored in CHMS cycles 2, 5, and 6. In cycle 6, PFNA was detected in over 98% (LOD of 0.13 µg/L) of the population (3 to 79 years). The geometric mean plasma concentration of PFNA was 0.44 µg/L, the fourth-highest plasma concentration of measured PFAS among CHMS participants after PFOS, PFOA, and PFHxS (Table B-3 of Appendix B). Although PFDA was found in lower concentrations (GM of 0.12 µg/L), the substance is still very prevalent, with a detection frequency of over 65% (LOD of 0.092 µg/L) in 3 to 79 year olds. PFUnDA was less prevalent than PFOA, PFNA, PFDA, PFHxS, and PFOS (36.3% detection frequency with an LOD of 0.12 µg/L) in cycle 6, and consequently, a geometric mean was not calculated (i.e., >40% of samples are below LOD). Between 2009 and 2019, plasma concentrations of PFNA and PFDA declined by 47% and 36%, respectively, on the basis of geometric mean values in the Canadian population aged 12 to 79 years. However, unlike PFOA, PFHxS, and PFOS, plasma concentrations of PFNA and PFDA were similar between sexes (HC 2021c).

Throughout cycles 2, 5, and 6 of the CHMS, detection frequencies of PFBA, PFHxA and PFBS were generally low (e.g., in cycle 6, PFBA was at 5.4%, PFHxA at 1.0%, and PFBS at 0.3%). In the CHMS, when over 40% of samples are below the LOD, geometric means are not calculated, which was the case for PFBA, PFHxA, and PFBS (Table B-3 of Appendix B). PFBA, PFHxA, and PFBS have shorter biological half-lives, which may be associated with lower detection frequencies for these PFAS; however, other studies with lower detection limits have demonstrated that a higher proportion of samples were found to be above the detection limit.

For example, PFBS was measured in both plasma and serum of adults in a small-scale study in Oslo, Norway, resulting in percentages above the method detection limit (MDL) of 100% and 51%, respectively, on the basis of an MDL of 0.018 (plasma) and 0.009 (serum) µg/L (Poothong et al. 2017). The plasma and serum detection limits from these studies are both lower than 0.066 µg/L (the LOD of PFBS in cycle 6 of the CHMS).

5.4.2 PFAS measured in First Nations (on-reserve) populations, Inuit communities, and other Indigenous or northern communities

Data are available on PFAS concentrations measured in plasma or serum of First Nations (on-reserve) people, Inuit communities, and other Indigenous or northern communities in Canada (AFN 2013; Aker et al. 2021; Caron-Beaudoin et al. 2019, 2020; Garcia-Barrios et al. 2021). When results from these studies are compared to CHMS plasma concentration values for similar age and sex subpopulations during similar time periods (e.g., cycle 5), notable observations may be made for certain long-chain PFCAs and PFSAs.

Caron-Beaudoin et al. (2020) examined 9 PFAS (PFBA, PFHxA, PFOA, PFNA, PFDA, PFUnDA, PFBS, PFHxS, and PFOS) in serum of pregnant Inuit women (16 to 40 years) from communities in Nunavik participating in the Nutaratsaliit Qanuingisiarningit Niqituinnanut (NQN) Pregnancy Wellness with Country Food Project (2016 to 2017). When compared with plasma concentrations in women of childbearing age (18 to 40 years) from cycle 5 of the CHMS (2016 to 2017), Caron-Beaudoin et al. (2020) noted that serum concentrations of certain PFAS (specifically PFNA, PFDA, PFUnDA, and PFOS) were higher in the pregnant Inuit women from communities in Nunavik (Figure 5 and Table B-4 of Appendix B). Indeed, PFNA, PFDA, and PFOS in the NQN participants were 6.3, 3.3, and 1.8 times higher, respectively, than in the CHMS participants. In addition, PFUnDA was detected in 100% of samples in pregnant Inuit women from Nunavik (LOD = 0.1 µg/L), whereas PFUnDA had a detection frequency of less than 40% in cycle 5 of the CHMS (LOD = 0.12 µg/L). Additionally, maternal serum concentrations of PFNA, PFDA, and PFUnDA in pregnant Inuit women in Nunavik increased by 19%, 13%, and 21%, respectively, between 2011 to 2012 and 2016 to 2017, while the levels of PFNA and PFDA in the general population (CHMS) decreased over a similar time period of 2009 to 2019 (Caron-Beaudoin et al. 2020; see Table B-4 of Appendix B). A trend could not be assessed for PFUnDA in the CHMS due to the low number of samples with detection (detection frequency was 36.3%, less than 40%; Health Canada 2021b, 2021c). Caron-Beaudoin et al. (2020) noted that LC-PFCAs concentrations, particularly for PFNA, of pregnant Inuit women from Nunavik in 2016 to 2017 were among the highest compared to other recently reported PFNA concentrations in the circumpolar region (AMAP 2021). It may be noted that the comparison of PFAS concentrations in serum or plasma of pregnant women with non-pregnant women of childbearing age may have uncertainty associated with differences in plasma volumes (Aguree and Gernand, 2019).

In the study population examined by Caron-Beaudoin et al. (2020), maternal serum levels of PFOA, PFHxS, and PFOS showed statistically significant downward trends ($p<0.0001$) between 2007 (PFOA and PFHxS) or 2004 (PFOS) and 2017, similar to those observed for the general population in the CHMS. PFOA and PFHxS were significantly lower in the NQN than in cycle 5 of the CHMS. Figure 5 below presents the geometric mean serum or plasma concentrations of

PFOA, PFNA, PFDA, PFUnDA, PFHxS, and PFOS from both pregnant Inuit women (aged 16 to 40 years) in the NQN study and women of childbearing age (18 to 40 years) from cycle 5 of the CHMS.

Aker et al. (2021) reported results from the Qanuilirpitaa? 2017 Health Survey for PFAS in plasma from adults (18+ years, sampled in 2017) from the 14 Inuit communities in Nunavik. These results were also compared with CHMS values (18 to 79 years) from cycle 5 and are presented in Figure 5. These data demonstrate higher levels of PFNA (7-fold), PFDA (3-fold), and PFOS (1.5-fold) in the adults sampled in Nunavik as well as the variability in levels of certain PFAS among subpopulations in Canada. The figure below only describes data for the 6 PFAS included in both surveys or studies and does not capture all PFAS to which individuals may be exposed.

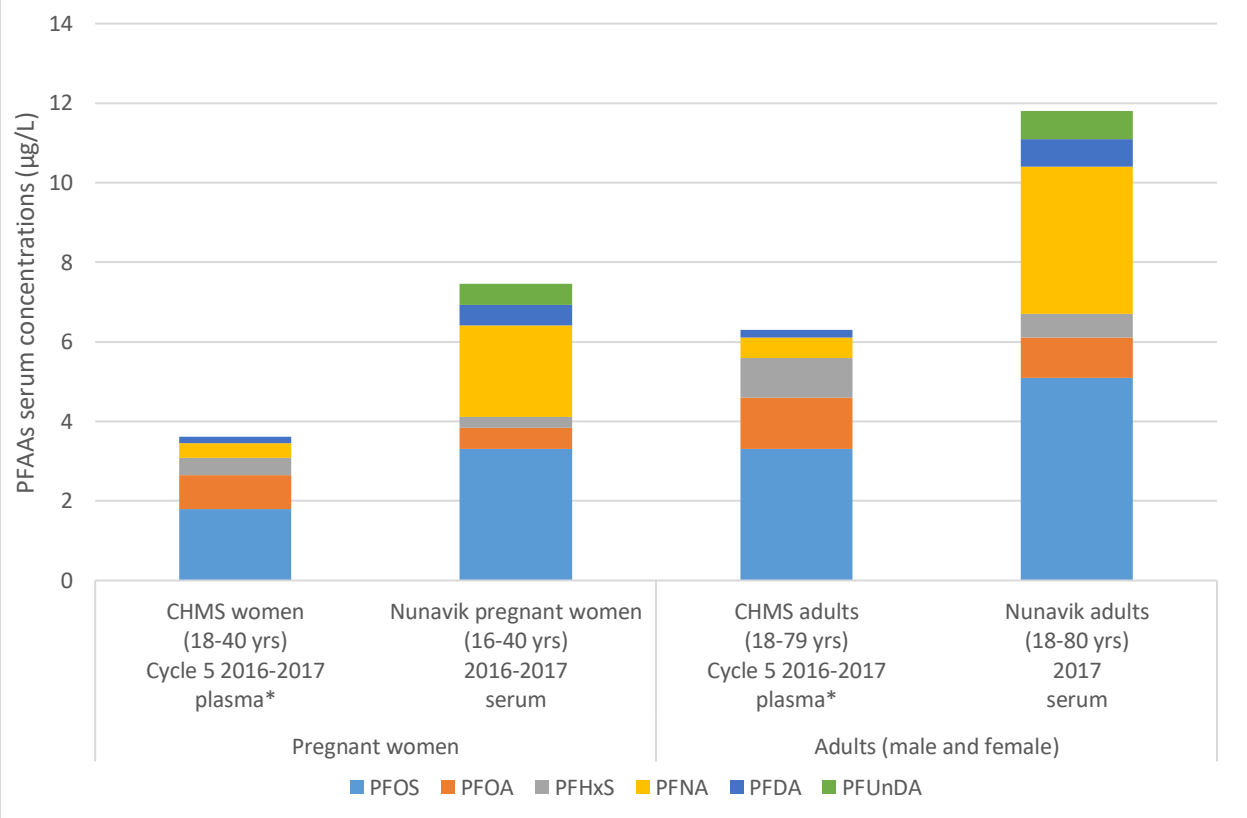


*Figure 5. Comparison of geometric mean plasma or serum concentrations of 6 PFAS (PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFOS) in women (18–40 years) in CHMS cycle 5 (2016–2017) with pregnant Inuit women (16–40 years) from Nunavik (2016–2017), and comparison of geometric mean plasma or serum concentrations of these 6 PFAS in adults (18–79 years) in CHMS cycle 5 (2016–2017) with adults (18–80 years) from Nunavik (2017). *CHMS does not report GM if >40% of samples are below the LOD, resulting in no reported concentration for PFUnDA in CHMS populations (Aker et al. 2021; Caron-Beaudoin et al. 2020; HC 2019a).*

Other northern communities have also demonstrated elevated levels of PFNA compared to levels detected in the CHMS (based on comparisons of similar age groups and time periods). Garcia-Barrios et al. (2021) reported PFAS in serum or plasma of people residing in several northern communities, specifically Old Crow (Yukon) and 6 nations in the Dehcho region of the Northwest Territories. Average PFNA concentrations in adults were found to be 1.8 times higher

in a Gwich'in community and 2.8 times higher in the Dehcho region when compared to plasma concentrations of PFNA in adults in the CHMS. These results are summarized in Table B-5.

Results from the First National Biomonitoring Initiative (FNBI) carried out in 2011 indicated that concentrations of PFOA, PFHxS, and PFOS were higher in adults (20 to 79 years) in CHMS cycle 2 (2009 to 2011) when compared to plasma concentrations found in the First Nation on-reserve population (aged 20 years and older) (AFN 2013; HC 2023a).

There are also studies available that have analyzed PFAS in Indigenous youth and children. O'Brien et al. (2012) collected blood samples from young Inuit children (mean age 2.1 years) attending childcare centres in Nunavik from 2006 to 2008 to document benefits of a nutrition program and detected PFOA, PFHxS, and PFOS in 100%, 50%, and 100% of samples, respectively (LODs of 0.3 µg/L). In a later study conducted in 2015 and examining Indigenous youth aged 3 to 19 years old from 4 First Nation communities in Quebec, serum PFNA concentrations in Anishinabe participants were 7 to 21 times higher than plasma concentrations of PFNA for the same age groups (3 to 5, 6 to 11 and 12 to 19 years) in CHMS cycle 5 (2016 to 2017) (Caron-Beaudoin et al. 2019; Dubeau et al. 2022; Lemire et al. 2019). These results are presented in Figure 6 and are also summarized in Table B-5 of Appendix B.

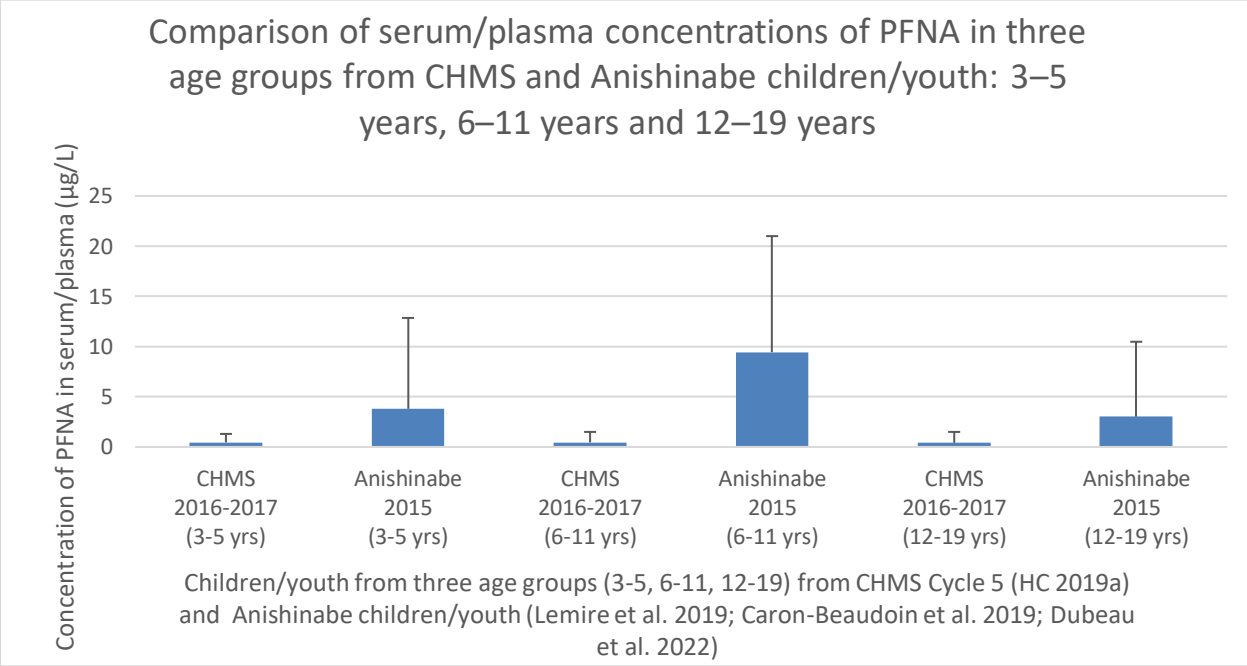


Figure 6. Geometric mean (whiskers are the 95th percentile) concentrations of PFNA in plasma or serum of children from the following age groups: 3–5 years, 6–11 years, and 12–19 years each from CHMS cycle 5 (2016–2017) (HC 2019a) and Anishinabe children/youth (2015) (Caron-Beaudoin et al. 2019; Dubeau et al. 2022; Lemire et al. 2019)

5.4.3 PFAS measured in cord blood and human milk

PFOA, PFHxS, and PFOS have been measured in the plasma and cord blood plasma of approximately 2000 pregnant women from 10 cities across Canada between 2008 to 2011 as part of the MIREC study (Fisher et al. 2016). Maternal plasma results were somewhat similar to

CHMS cycle 1 (2007 to 2009) results for women (aged 20 to 39 years); PFOA, PFHxS, and PFOS were also found in cord plasma. The presence of PFAS in cord blood suggests that children may be exposed to PFAS in utero.

Few Canadian studies have examined PFAS in human milk. However, a study by Kubwabo et al. (2013) focused on improving analytical detection methods for measuring a broad range of PFAS in human milk. In this study, 5 PFCAs, 2 PFSAs, and 8 diPAPs (polyfluoroalkyl phosphate diesters) were analyzed in 13 human milk samples collected between 2003 and 2004 from a study population in Kingston, Ontario. Of the PFCAs and PFSAs analyzed, only PFOA was detected in 85% of the samples (LOD = 0.24 µg/L). Only 4 diPAPs were quantifiable in 3 to 8 of the 13 samples. Kubwabo et al. (2013) concluded that diPAPs are present in human milk. Additionally, these authors note that low detection levels or variability in detection of PFAS in human milk may be due to several factors, including the lack of standardization of methods used for determination of PFAS in milk, the complexity of the matrix, and PFAS being strongly bound to the protein fraction in human blood. In addition, 13 PFAS were analyzed in human milk samples from 553 to 664 women in Canada participating in the MIREC study. PFOA and PFOS (linear and branched isomers) were highly detected in these samples (87.7% to 99.5%) and were the dominant contributors to the overall sum of PFAS concentrations. PFNA and PFHxS were less frequently detected (61% and 63%, respectively), while PFHxA and PFBS were infrequently detected (0.7% and 0.9%, respectively). The remaining 7 compounds were not detected, i.e.,PFHpA, PFDA, PFUnDA, PFDoDA, PFTeDA, PFHpS, and PFDS (Rawn et al. 2022b).

5.5 Summary of international human biomonitoring data on PFAS

5.5.1 PFAS measured in serum, plasma, or whole blood

There are many studies varying in scope and purpose that examine human biomonitoring of PFAS in various populations around the world. Certain studies are national, others are regional or small in scale, while others examine birth cohorts (studies examining children or infants born around the same time). Some caveats associated with comparing these results include variation between sampling years and matrices (e.g., plasma or serum), and methodological differences. In addition, national surveys such as the CHMS and NHANES are weighted to provide population-level detection frequencies, whereas smaller studies simply report the percentage of samples above the LOD or LOQ. Results from several PFAS biomonitoring studies representing a range of geographical regions (e.g., US, France, Sweden, South Korea, Germany, Norway, Denmark [Greenland, the Faroe Islands], and Japan) demonstrate that, at a given time, multiple PFAS occur consistently in many regions (Table B-1, Appendix B). PFOA, PFNA, PFHxS, and PFOS were the most commonly detected PFAS, with percentage of samples detected or population-level detection frequencies generally ranging from 90% to 100%; PFDA and PFUnDA were the next most commonly detected PFAS in these studies. PFBA, PFHxA, PFHpA, PFDoDA, PFTrDA, PFHpS, PFDS, and PFOSA generally have low detection frequencies in national surveys; however, they were each reported to be detected in over 50% of samples in at least two studies.

Certain short-chain PFCAs and PFSAs have been reported to have shorter half-lives than LC-PFAS; however, it is noted that these PFAS are detected in some smaller-scale studies, which in some cases may be attributed to issues such as greater sensitivity of the analytical method. Other factors that may contribute to the variation in detection frequencies across studies are the cohort characteristics (e.g., dietary preferences or use of traditional remedies; CA OEHHA 2020).

Several international studies have analyzed exposure to PFAS in children, infants, and fetuses (e.g., Dassuncao et al. 2018; Li et al. 2020; Mamsen et al. 2019; Rappazzo et al. 2017). Rappazzo et al. (2017) conducted a systemic review of the literature available on PFAS exposure and child health outcomes. The studies were predominately conducted in the United States, Taiwan, UK, and Scandinavian countries (i.e., Denmark, Norway). Study designs were primarily cohort or cross-sectional, and measurements of PFAS were primarily in serum. In Denmark and Sweden, Mamsen et al. (2019) measured the concentrations of 6 PFAS (PFOA, PFNA, PFDA, PFUnDA, PFHxS, PFOS) in maternal serum and human embryonic and fetal organs from first, second, and third trimester pregnancies. Mamsen et al. (2019) found that, in general, PFAS concentrations in embryo/fetal tissue were lower than maternal serum but similar to placenta concentrations, suggesting that human fetuses were intrinsically exposed to a mixture of PFAS throughout gestation and PFAS deposit to embryo and fetal tissues. Li et al. (2020b) detected 16 of 32 PFAS in 50% to 100% of maternal serum and cord serum samples of participants from the Maoming Birth cohort study (China) between 2015 and 2018, not only demonstrating transplacental transfer of PFAS but also identifying differences in transfer in preterm and full-term deliveries (Li et al. 2020b).

5.5.2 PFAS measured in human milk

Several international studies have examined PFAS in human milk with analysis of samples collected from US, France, Japan, China, Sweden, Spain, Korea, and South Africa (Cariou et al. 2015; Fujii et al. 2012; Kang et al. 2016; Lorenzo et al. 2016; Macheka et al. 2022; Tao et al. 2008; Zheng et al. 2021; Zheng et al. 2022). In 2019, Zheng et al. (2021) recruited 50 women residing in Seattle, US. The analysis included 39 PFAS, 12 (PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFHxS, PFHpS, PFOS, and PFNS) of which were found to have detection frequencies ranging from 58% to 100%. PFOA and PFOS were found in 86% and 100% of samples and were the predominant PFAS (median concentrations of 0.014 µg/L and 0.03 µg/L, respectively). Zheng et al. (2021) noted that when compared with levels in human milk from a previous study based in the United States (Tao et al. 2008), levels of PFOA and PFOS in human milk appear to have declined since 1996. Zheng et al. (2021) also compared their results with currently available data on SC-PFAS in human milk and demonstrated that the detection frequency (normalized to the highest detection limit reported for each individual PFAS across the studies included in the analysis) of short-chain (C4 to C7) PFAS has increased since the early 2000s, doubling every 4.1 years for all of the C4 to C7 PFAS included in the analysis.

Detection frequencies and concentration ranges of the PFAS tested varied widely across the studies. It is possible that differences in analytical sensitivity (e.g., detection or quantification limits) may be a factor in the variability of these results.

Overall, data from various studies suggest that infants may be exposed to at least a dozen PFAS through the consumption of human milk.

5.6 Occupational HBM data - Firefighters

Firefighter exposure to PFAS is of particular interest as PFAS have been used in certain types of firefighting foams (e.g., AFFF) as well as in firefighters' protective clothing and may be released from burning products treated with or containing PFAS (Graber et al. 2021; ITRC 2020e; Peaslee et al. 2020).

There are no available Canadian studies examining biomonitoring levels of PFAS in firefighters. However, 10 studies examining serum levels of various PFAS in firefighters were identified in the available literature. Eight of the studies were carried out in the United States (Barton et al. 2020; Dobraca et al. 2015; Graber et al. 2021; Jin et al. 2011; Khalil et al. 2020; Leary et al. 2020; Shaw et al. 2013; Trowbridge et al. 2020), one study examined firefighters in Australia (Rotander et al. 2015), and one study sampled firefighters in Finland (Laitinen et al. 2014). All studies took place between 2005 and 2019.

Various numbers of specific PFAS, with perfluorinated carbon chain lengths ranging from 3 (e.g., PFBA) to 13 (e.g., PFTeDA), were examined in the studies; however, PFOA, PFNA, PFHxS, and PFOS were examined in all 10 studies. Certain short-chain PFCAs and PFSAs (PFBA, PFPeA, and PFHpS) were not detected in any of the firefighter serum samples (Barton et al. 2020; Dobraca et al. 2015; Khalil et al. 2020; Rotander et al. 2015; Shaw et al. 2013). Although PFBS was detected in only one of the studies, it was detected in 73% of samples in that study (Trowbridge et al 2020). PFHxA and PFHpA were detected more frequently across studies, with the percentage of samples above detection limits ranging from 50% to 92% (Dobraca et al. 2015; Rotander et al. 2015; Shaw et al. 2013; Trowbridge et al. 2020).

Serum levels of PFAS from the firefighter studies were compared with concentrations in the general population. The ratios resulting from this comparison for 6 of the most commonly detected PFAS in firefighters and the general population are shown in Figure 7. In the eight studies that examined firefighters in the United States, the firefighter serum concentrations were compared with serum concentrations from NHANES (representing the general population of the United States). In the two studies that were not carried out in the United States (i.e., in Australia and Finland), the firefighter serum concentrations were compared to relevant PFAS plasma concentrations from the CHMS (i.e., the Canadian general population). These comparisons were done for similar years of serum/plasma sampling, similar age groups (e.g., age 20 to 60), and similar sexes. Although a statistically rigourous comparison could not be done to compare the firefighter data and the general population data, geometric mean concentration values from each of the studies were compared to the upper confidence interval (CI) of the geometric mean from the general population. For each of the 6 PFAS, the ratios (GM firefighter serum values/upper Cl of the GM of the general population) were calculated for each study and PFAS-specific average ratios were calculated. The average ratios for each PFAS are presented in Figure 7. PFOA, PFNA, PFDA, PFHxS, and PFOS all had average ratios of >1, suggesting that, on average across the 10 studies, firefighter serum geometric mean values were dissimilar from (specifically higher than) the geometric mean values of these PFAS in the general population

(based on a similar time of sampling, similar age group, and similar sex). PFHxS had the largest ratio, suggesting a larger difference in the firefighter serum concentrations compared to the general population for this specific PFAS.

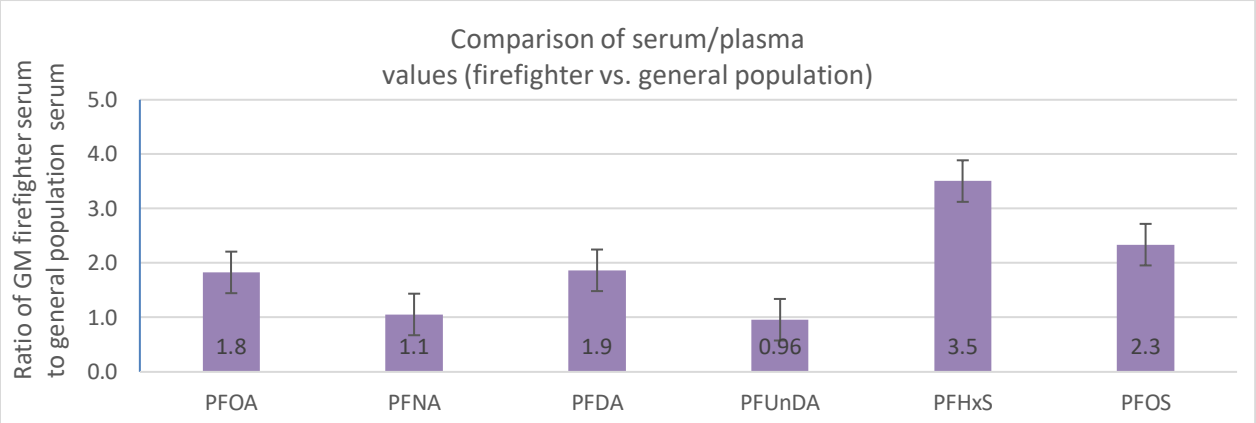


Figure 7. Average of ratios of geometric mean (or lower CI of GM) firefighter serum levels to upper CI of geometric mean serum (or plasma) levels in the general population averaged across 10 studies (each ratio is derived from similar time period, sex, and age group comparison between study population and general population biomonitoring values). Information on the GM (CI) of firefighter serum values, GM (CI) for reference populations, and ratios for each of the 6 PFAS are found in Table D-1

5.7 Interpretation of HBM data

5.7.1 Canadian general population and Indigenous communities

In this section, biomonitoring values from various populations groups in Canada were compared to the EFSA reference value for the sum of 4 PFAS (PFOA, PFNA, PFHxS, and PFOS) and the HBM-I and HBM-II values for PFOA and PFOS identified in Table 1.

Canadians are likely co-exposed to multiple PFAS due to the widespread use of these substances in products and the presence of PFAS in the environment. Additionally, people can be co-exposed to several PFAS due to the long biological half-lives of certain PFAS in humans and their historical uses. The concentration of co-occurring, unidentified PFAS in serum or plasma in the general population is not known. According to the CHMS data on PFAS (HC 2021b) the highest plasma concentrations reported in the Canadian population were for PFOS, PFOA, PFHxS, and PFNA (Table B-3 of Appendix B). As described above, EFSA (2020) identified reference serum levels of 6.9 µg/L and 17.5 µg/L for women of reproductive age and infants, respectively (see Table 1) for the sum of exposure to 4 PFAS (i.e., PFOA, PFNA, PFHxS, and PFOS). In Figure 8, the EFSA reference serum level for women of reproductive age was compared with box plots identifying the 25th to 75th percentile values for the sum of 4 PFAS (PFOA, PFNA, PFHxS, and PFOS) in 6 population groups, i.e., cycle 6 of the CHMS (all population, ages 3 to 79), cycle 6 of the CHMS (women of childbearing age, ages 18 to 40), pregnant women in Nunavik, adults in Dene communities in the Dehcho region of NWT, adults in a Gwich'in community in the Yukon, and adults in Nunavik (Aker et al. 2021; Caron-Beaudoin et al. 2020; Garcia-Barrios et al. 2021; personal communication, emails from the Population

Studies Division, Health Canada (HC), to the Existing Substances Risk Assessment Bureau, HC, May 4, 2022 and May 5, 2022; unreferenced). See Table C-1 in Appendix C for details.

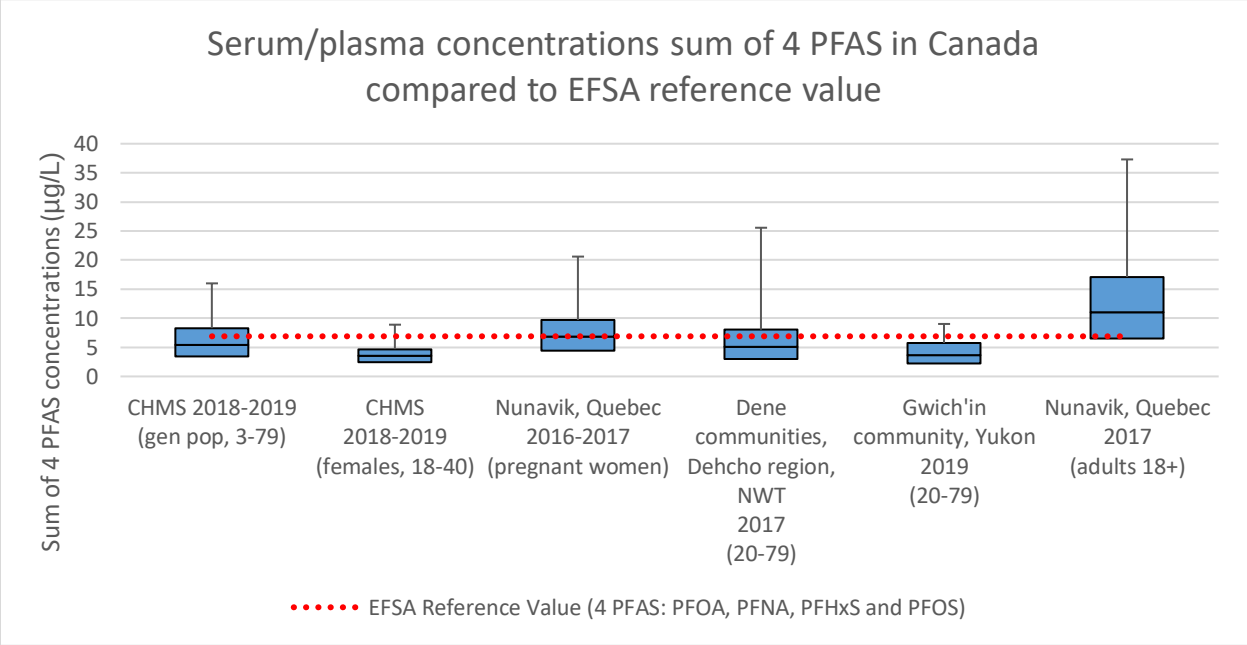


Figure 8. Comparison of the EFSA reference value of 6.9 µg/L with box plots identifying the 25thto 75th percentiles including geometric means (lines) and 95th percentile (whiskers) of the sum of 4 PFAS concentrations (in µg/L) in 6 population groups: CHMS cycle 6 total population (3 to 79 years; HC 2021b), CHMS cycle 6 females (8 to 14; personal communication, HC Population Studies Division, 2022; unreferenced), Nunavik pregnant women (16 to 40 years; Caron-Beaudoin et al. 2020), adults living in the Dehcho region of the Northwest Territories (20 to 79 years), adults living in a Gwich'in community, Yukon (20 to 79 years; Garcia-Barrios et al. 2021), and Inuit adults (18+ years) living in 14 communities in Nunavik (Aker et al. 2021).

The geometric mean of the sums of PFOA, PFNA, PFHxS, and PFOS in serum of pregnant Inuit women in Nunavik (6.8 µg/L in serum) was very close to the EFSA reference level (6.9 µg/L), indicating that approximately 50% of the sampled population was above the reference value. In adults in Nunavik, close to 75% of the sampled population was above the EFSA reference value. In the other population groups, a proportion of the sampled population (approximately 35% or less) was above the reference level.

The German HBM Commission's HBM-I and HBM-II values for PFOS and PFOA were also examined in relation to biomonitoring data for the Canadian population.

In Figures 9 and 10, HBM-I and HBM-II values for PFOS and PFOA were presented in relation to box plots outlining the 25th to 75th percentile concentrations for PFOA and PFOS in 6 population groups, specifically: CHMS cycle 6 (general population 3 to 79 years), pregnant women in Nunavik, on-reserve populations of Indigenous adults across Canada (20+ years), First Nations people (20 to 79 years) living in Dene communities in the Dehcho region of the Northwest Territories, First Nations people (20 to 79 years) living in a Gwich'in community in the Yukon, and Inuit adults living in 14 communities in Nunavik (AFN, 2013; Aker et al. 2021; Caron-Beaudoin et al. 2020; Garcia-Barrios et al. 2021; personal communication, emails from

Population Studies Division HC to Existing Substances Risk Assessment Bureau, HC, May 2022; unreferenced). As noted earlier, CHMS data represents PFOA and PFOS exposure in the general population of Canada; Figures 9 and 10 include smaller-scale studies examining specific populations of people that were not represented in the CHMS.

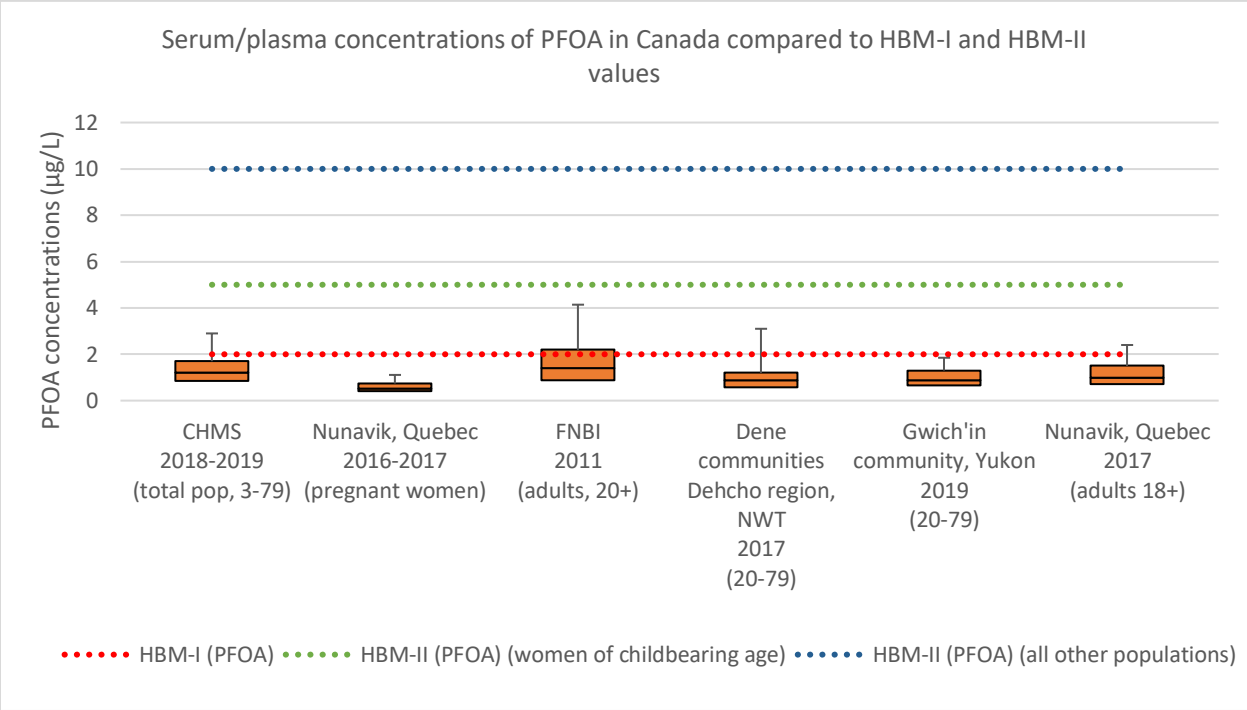


Figure 9. Box plots identifying the 25th to 75th percentiles (including geometric means [lines] and 95th percentile [whiskers]) of the PFOA concentrations (in µg/L) in 6 population groups: CHMS cycle 6 total population (3 to 79 years; HC 2021b; personal communication, emails Population Studies Division, HC, to Existing Substances Risk Assessment Bureau, HC, May 2022; unreferenced), Nunavik pregnant women (16 to 40 years; Caron-Beaudoin et al. 2020), Indigenous on-reserve populations across Canada (20+ years; FNBI; AFN 2013), adults living in the Dehcho region of the Northwest Territories (20 to 79 years), adults living in a Gwich'in community in the Yukon (20 to 79 years; Garcia-Barrios et al. 2021), and Inuit adults (18+ years) living in 14 communities in Nunavik (Aker et al. 2021), presented in relation to PFOA HBM-I, HBM-II (women of childbearing age), and HBM-II (other population groups) values (Holzer et al. 2021; Schümann et al. 2021) (data in Appendix C-Table C-2).

According to Figure 9, the geometric means of PFOA concentrations in all 6 groups (AFN 2013; Aker et al. 2021; Caron-Beaudoin et al. 2020; Garcia-Barrios et al. 2021; HC 2021b) were below the HBM-I and HBM-II values. The 95th percentiles of PFOA concentrations for all populations assessed, except for pregnant women in Nunavik and the Gwich'in community in the Yukon, exceeded the HBM-I value but were lower than the HBM-II (women of childbearing age) value.

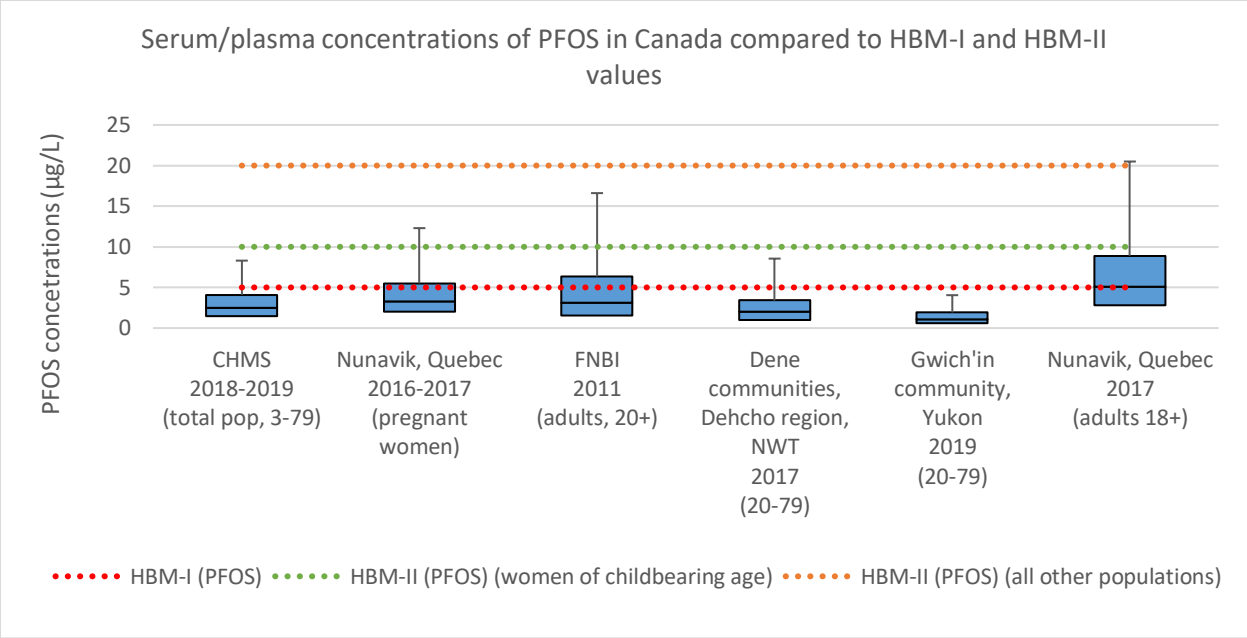


Figure 10. Box plots identifying the 25th to 75th percentiles (including geometric means [lines] and 95th percentile [whiskers]) of PFOS concentrations (in µg/L) in 6 population groups: CHMS cycle 6 total population (3 to 79 years; HC 2021b, personal communication, emails Population Studies Division, HC, to Existing Substances Risk Assessment Bureau, HC, May 2022; unreferenced), pregnant Nunavik women (16 to 40 years; Caron-Beaudoin et al. 2020), Indigenous on-reserve populations across Canada (20+ years; AFN 2013), adults living in the Dehcho region, Northwest Territories (20 to 79 years), adults living in a Gwich'in community, Yukon (20 to 79 years; Garcia-Barrios et al. 2021), and Inuit adults (18+ years) living in 14 communities in Nunavik (Aker et al. 2021) in relation to PFOS HBM-I, HBM-II (women of childbearing age), and HBM-II (other population groups) values (Holzer et al. 2021; Schümann et al. 2021) (data in Appendix C-Table C-2).

Although the geometric mean of PFOS concentrations in all the population groups was below the HBM-I value, certain portions of each of these populations were above the HBM-I value. Figure 10 shows that the 75th percentile values are above the HBM-I values for 3 groups, specifically pregnant women in Nunavik, Indigenous adults living on reserve (sampled in 2011), and adults living in Nunavik. Furthermore, a subset of these 3 population groups were above the HBM-II value (women of childbearing age). In addition, the 95th percentile for adults in Nunavik was above the HBM-II value (population groups other than women of childbearing age; 20 µg/L).

The 95th percentiles of PFOS concentrations in the CHMS and in the plasma of First Nations people living in Dene communities in the Dehcho region of the Northwest Territories fell between HBM-I and HBM-II values.

According to the German HBM Commission, if measured concentrations are found to exceed the HBM-I level, the causes of the increase should be investigated, and sources of exposure should be reduced or eliminated to the extent possible (Holzer et al. 2021), whereas exceedance of the HBM-II values requires immediate attention as indicated by the German HBM Commission (Schümann et al. 2021; Umwelt Bundesamt 2015).

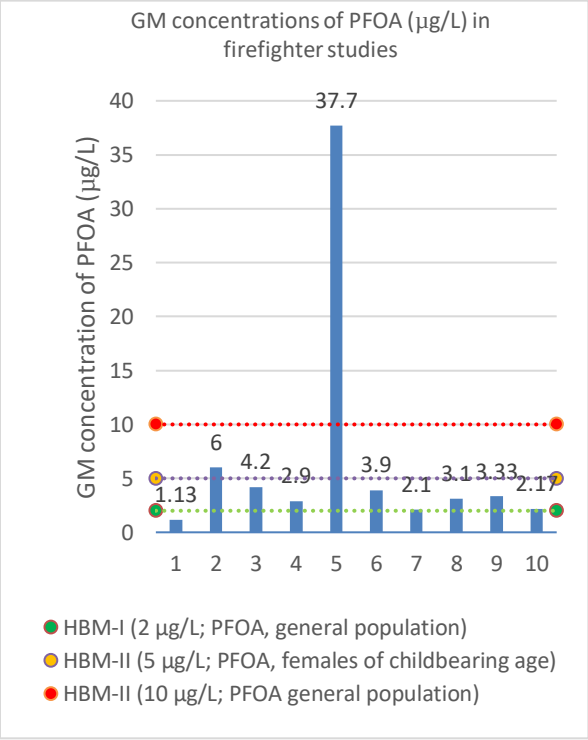
In summary, although geometric means of the concentrations of PFOS and PFOA in the general Canadian population and in the Indigenous populations living in northern communities and

south of the 60th parallel are generally below the HBM-I guidance values and although these substances have risk management in place, the geometric mean of PFOS concentrations in adults in Nunavik is above the HBM-I value (5.1 µg/L vs. 5 µg/L, respectively). The 95th percentile concentration levels for PFOA and PFOS in most populations also exceed the HBM-I value. In pregnant women in Nunavik, the 95th percentile of PFOS in serum exceeds the HBM-II value for childbearing women. The geometric mean of the sums of 4 PFAS in pregnant Inuit women in Nunavik was slightly below the EFSA (2020) serum reference level, indicating that a proportion of the population is above this reference level. The 95th percentile of the sum of the 4 PFAS exceeded the EFSA (2020) serum reference level.

5.7.2 Firefighters

As noted in section 5.7, there are no available Canadian studies examining biomonitoring levels of PFAS in firefighters. Geometric mean (or median) concentrations of PFOA and PFOS found in 10 international studies examining firefighters (see section 1.19; Barton et al. 2020; Dobraca et al. 2015; Graber et al. 2021; Jin et al. 2011; Khalil et al. 2020; Laitinen et al. 2014; Leary et al. 2020; Rotander et al. 2015; Shaw et al. 2013; Trowbridge et al. 2020) were considered in relation to the HBM-II values for PFOA and PFOS (Figure 11).

The HBM-II value is not derived with the intention of interpreting occupational biomonitoring data; however, it was considered to be the most appropriate reference level of those available for comparison with firefighters' exposure to PFOA and PFOS. HBM-II is a concentration in a human biological material, above which there is an increased risk for adverse health effects and an acute need for exposure reduction measures and the provision of biomedical advice.



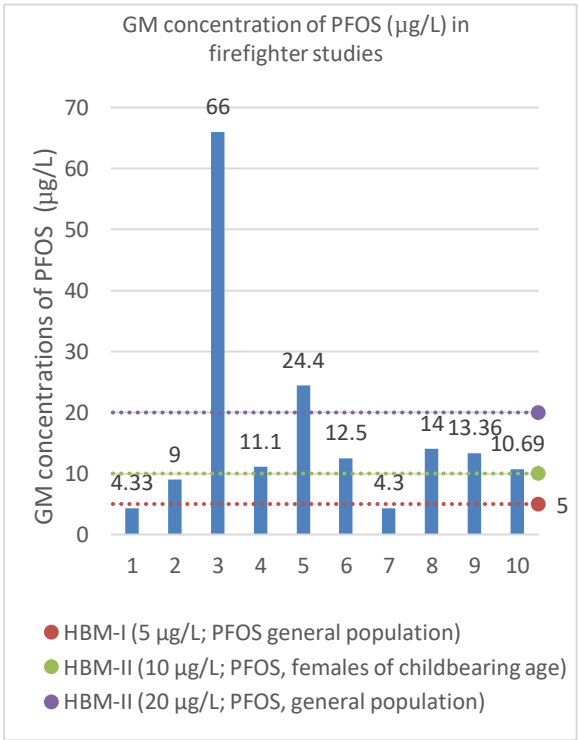


Figure 11. Geometric mean (or median) concentrations of PFOA and PFOS in serum of firefighters (sampling year ranging from 2005 to 2019) from 10 studies (data in Appendix C-Table C-3) compared to HBM-I and HBM-II values for PFOA and PFOS.
Study 1 = Trowbridge et al. 2020; Study 2 = Shaw et al. 2013; Study 3 = Rotander et al. 2015; Study 4 = Laitinen et al. 2014; Study 5 = Jin et al. 2011; Study 6 = Dobraca et al. 2015; Study 7 = Graber et al. 2021; Study 8 = Barton et al. 2020; Study 9 = Khalil et al. 2020); Study 10 = Leary et al. 2020.

Three studies demonstrated geometric mean results above PFOA or PFOS HBM-II values for other population groups (other than women of childbearing age): one study for PFOA (Study 5; Jin et al. 2011) and two studies for PFOS (Jin et al. 2011; Rotander et al. 2015). Jin et al. (2011) collected samples from 2005 to 2006 as part of a project implemented after the drinking water near a DuPont facility in West Virginia was contaminated, which made this population group considered likely to have higher background levels of PFAS. In 2013, Rotander et al. (2015) sampled firefighters working at AFFF training facilities in Australia. Of note, Study 1 (Trowbridge et al. 2020) examined only female firefighters, highlighting the importance of taking into consideration the HBM-II value for women of childbearing age for PFOA and PFOS.

As many studies report geometric mean values above the HBM-I values for PFOA and PFOS, this analysis suggests that exposure to PFOA and PFOS in firefighters is higher than in the general population and is above reference values. Because the biomonitoring data for firefighters are not specifically Canadian, they may have limitations (e.g., some studies took place several years prior to restrictions being imposed on certain PFAS). However, firefighters in North America (and perhaps Europe and Australia) may have similar PFAS exposures as a result of working with AFFF and personal protective equipment containing PFAS, and these considerations may mean that firefighter exposure to PFAS is not unique to each country. Therefore, even with limitations, these studies may have relevance for Canada.

6 Ecotoxicity

KEY POINTS ON ECOTOXICITY

- Some well-studied PFAS have been shown to bioaccumulate in wildlife and plants. Air-breathing organisms (e.g., mammals, birds) have been reported to have a high potential for biomagnification, which may increase the likelihood of adverse toxicological effects being observed.
- Certain PFAS have been demonstrated to cause apical (e.g., growth, reproduction, development) and mechanistic (e.g., immunotoxicity, neurotoxicity) endpoint effects in biota.
- On the basis of the available data, the magnitude of ecotoxicity (including bioaccumulation) in organisms appears to vary with the structural features of PFAS (e.g., chain length, functional groups); however, this does not indicate a lack of hazard for some PFAS (e.g., short-chains).
- There are significant data gaps in the literature available for certain species (e.g., amphibians, reptiles, birds, mammalian wildlife), subgroups of PFAS (e.g., polyfluoroalkyl substances, fluoropolymers, perfluoropolyethers, side-chain fluorinated polymers), and types of effects studied (e.g., multigenerational effects, cumulative effects), which makes it difficult to identify and understand trends in ecotoxicity.

- Although the vast majority of ecotoxicology studies have focused on the effects seen with exposure to a single PFAS, organisms are typically exposed simultaneously to multiple PFAS in the environment, which has the potential to increase impacts on them.
- Uncertainties in ecological hazard can be reduced through further study and possibly through the use of new approach methodologies (NAM).

The following section provides an overview of the available literature on PFAS bioaccumulation and biomagnification, as well as ecotoxicity in invertebrates (including aquatic and terrestrial), vertebrates (including fish, birds, mammals, and amphibians/reptiles), and plants (including aquatic and terrestrial). Where available, discussions on mode/mechanism of action and multigenerational effects in species are included in the ecological effects section. This section is not intended to be a comprehensive review of the current literature and does not include a critical review of each study. Most studies in the literature focus on PFAAs (more specifically, PFOS and PFOA) and studies in aquatic organisms (i.e., fish, aquatic invertebrates). Fewer studies are available on the other groups of PFAS (e.g., polyfluoroalkyl substances, fluoropolymers, perfluoropolyethers, side-chain fluorinated polymers) and on terrestrial species (i.e., terrestrial invertebrates, amphibians, reptiles, birds, mammalian wildlife). A more in-depth review of the toxicological effects of PFAS is provided in Ankley et al. (2021), who have compiled ecotoxicity data for PFAS in different species from the available literature. Where applicable, other studies are included to supplement and/or support the information.

6.1 Bioaccumulation

The use of logK_{ow} to predict bioaccumulation potential is based on the assumption that the main mechanisms governing partitioning are the hydrophobic and lipophilic interactions (EC 2006). However, this assumption cannot be easily applied to many PFAS (e.g., PFAAs) due to their surfactant-like properties. As PFAS generally have the combined properties of oleophobicity, hydrophobicity, and hydrophilicity over different portions of their chemical structure, logK_{ow} is not considered to be an appropriate metric of bioaccumulation potential. The combination of a hydrophobic fluorinated alkyl chain paired with a polar functional group in PFAA resembles the structure of a fatty acid, which facilitates both hydrophobic and ionic interactions with proteins (Bischel et al. 2010). It is important to note that rather than accumulating in lipids, some of these substances preferentially bind to proteins and are therefore found in protein-rich tissues such as liver and blood.

In Canada, the regulatory criteria for bioaccumulation potential, as set out in the *Persistence and Bioaccumulation Regulations* of CEPA (Canada 2000), are met when the bioaccumulation factor (BAF) or bioconcentration factor (BCF) is ≥ 5000 or logK_{ow} is ≥ 5. However, as these threshold criteria were based on historical experience with neutral, non-metabolized organic substances and many PFAS tend to preferentially bind to proteins, the regulatory paradigm based on low logK_{ow} value cannot be applied for this class of substances (EC, HC 2012). The application of BAF and BCF data is only one component of the overall weight of evidence in determining the potential of a substance to bioaccumulate in organisms. Even if regulatory criteria are not met, a substance can still be deemed as having bioaccumulation potential.

A literature search for studies on PFAS bioaccumulation in aquatic species was performed by Burkhard (2021). In this paper, data from 22 taxonomic classes were compiled to determine median BAF and BCF values and to assess the availability of such data in the literature. A summary of the available BCFs and BAFs for fish is provided in Table 2. It should be noted, however, that empirical BCF and BAF data alone cannot be used to reliably determine bioaccumulation potential as results for typically tested model organisms (i.e., fish, daphnia, and algae) may underestimate bioaccumulation potential (ECCC 2023). Moreover, the available BCF and BAF data from the literature are also quite limited. In general, PFAAs are relatively data rich for aquatic species, whereas data are limited or nonexistent for other PFAS such as the fluorotelomers. In addition, PFAAs with very short (C<5) or very long (C>12) alkyl chain lengths also appear to be data scarce (Burkhard 2021).

Table 2. Select median bioconcentration factors and bioaccumulation factors in fish (adapted from Burkhard 2021)

PFAS group (subgroup)	Chemical name	Median whole body BCF (L/kg ww)	Median whole body BAF (L/kg ww)
PFAAs (PFCAs)	PFBA	15.1 (n=2)	144.5 (n=6)
PFAAs (PFCAs)	PFPeA	0.9 (n=1)	83.2 (n=7)
PFAAs (PFCAs)	PFHxA	9.5 (n=3)	17.8 (n=12)
PFAAs (PFCAs)	PFHpA	18.2 (n=1)	63.1 (n=10)
PFAAs (PFCAs)	PFOA	22.9 (n=15)	144.5 (n=48)
PFAAs (PFCAs)	PFNA	602.6 (n=6)	707.9 (n=42)
PFAAs (PFCAs)	PFDA	6166.0 (n=3)	3162.3 (n=43)
PFAAs (PFCAs)	PFUnDA	3715.4 (n=5)	2951.2 (n=21)
PFAAs (PFCAs)	PFDoDA	4365.2 (n=8)	151.4 (n=1)
PFAAs (PFCAs)	PFTrDA	21 877.6 (n=2)	NA
PFAAs (PFCAs)	PFTeDA	25 118.9 (n=4)	NA
PFAAs (PFCAs)	PFHxDA	4786.3 (n=2)	NA
PFAAs (PFCAs)	PFOcDA	371.5 (n=2)	NA
PFAAs (PFSAs)	PFBS	11.5 (n=7)	100.0 (n=5)
PFAAs (PFSAs)	PFHxS	117.5 (n=6)	199.5 (n=25)
PFAAs (PFSAs)	PFOS	1023.3 (n=21)	3548.1 (n=84)
PFAAs (PFECAs)	F-53B	707.9 (n=6)	21 379.6 (n=5)
Perfluoroalkyl sulfonamides (FASAs) and derivatives	FOSA	NA	5011.9 (n=12)
FT-based substances	4:2 FTSA	NA	13 803.8 (n=1)
FT-based substances	6:2 FTSA	34.7 (n=3)	NA
FT-based substances	8:2 FTSA	NA	72 443.6 (n=2)
Perfluoroalkyl phosphinic acids (PFPiAs)	C6/C6 PFPiA	131 825.7 (n=2)	NA
Perfluoroalkyl phosphinic acids (PFPiAs)	C6/C8 PFPiA	22 908 677.5 (n=2)	NA
Perfluoroalkyl phosphinic acids (PFPiAs)	C8/C8 PFPiA	199 526 231.5 (n=2)	NA
Perfluoroalkyl phosphinic acids (PFPiAs)	C6/C10 PFPiA	331 131 121.5 (n=2)	NA

Perfluoroalkyl phosphinic acids (PFPiAs)	C8/C10 PFPiA	616 595.0 (n=2)	NA
Perfluoroalkyl phosphinic acids (PFPiAs)	C6/C12 PFPiA	1 995 262.3 (n=2)	NA

Abbreviations: NA, not available; ww, wet weight.

The chain length and functional group(s) present in PFAS seem to determine the extent of bioaccumulation in animals. Studies have shown that sulfonates (i.e., PFSA) and PFAS with a longer perfluoroalkyl chain (i.e., C ≥ 9) tend to accumulate more in water-breathing organisms (e.g., fish, aquatic invertebrates) than do carboxylates (i.e., PFCAs) and substances with a shorter-chain length (Dai et al. 2013; Martin et al. 2003). Additionally, based on published field studies compiled in the *Supporting Document: Ecological State of the Science Report on Short-chain PFCAs, Short-chain PFSAs, and Long-chain PFSAs* (ECCC 2023), air-breathing organisms (e.g., terrestrial mammals, marine mammals, birds) are more likely to accumulate certain PFAS in comparison to water-breathing organisms. The BCF and BAF values for ionic PFAS (i.e., PFAA) in fish are relatively low, likely due to their polar and non-volatile nature. PFAAs tend to have a high water solubility, which can lead to a more rapid elimination of the substances in the water phase via gill exchange in fish. However, higher levels of PFAA bioaccumulation may occur in air-breathing organisms as their bioaccumulation potential is primarily driven by the low volatility of PFAA (i.e., respiration is not a viable loss mechanism) and the polarity of PFAA facilitates protein binding in the body. It should be noted that these trends do not imply that there is no potential for bioaccumulation with some PFAS and aquatic organisms but rather that it may occur to a lesser extent.

Biomagnification can also be observed in the food chain, often with the top predators having the highest levels of PFAS. This is especially of concern when concentrations reach levels that can cause adverse effects in organisms. In the Canadian Arctic, Kelly et al. (2009) found a high degree of PFAA biomagnification in upper trophic level wildlife (i.e., whales, polar bears, and seals). They also noticed no biomagnification occurring in aquatic organisms, which they attributed to the high solubility of PFAA. These findings align with Canada's past screening assessments of PFOS, PFOA, and long-chain PFCAs and their salts and precursors, which concluded that air-breathing mammals and avians have higher biomagnification factors (BMFs) and trophic magnification factors (TMFs)[3] in comparison with water-breathing organisms (EC 2006, 2012; EC, HC 2012). For example, in the case of PFOS, food webs involving air-breathing mammals were determined to have a TMF of about 20, while aquatic piscivorous food webs in Lake Ontario yielded TMFs ranging from 1.9 to 5.9 (De Silva et al. 2021). It should be noted, however, that there is a considerable degree of variability in the literature for BMFs and TMFs of any specific PFAS (Franklin 2016).

[3] The BMF is defined as the ratio of a chemical in an organism divided by the concentration of chemical in its food (i.e., prey or diet). The TMF is an extension of this concept, in which BMFs are adjusted according to stable isotopes of carbon and nitrogen (ITRC 2021a). TMFs are often believed to be a more objective metric in terms of biomagnfication between multiple organisms along a trophic chain. Moreover, BMF and TMF values greater than 1 are widely considered to be good indicators of biomagnification (Franklin 2016).

PFAS can also be absorbed by plants and crops from sources of releases such as compost (see section 2.6.3) and biosolids (see section 2.6.4). For this reason, consumption of plants is a possible contributor to the PFAS concentrations seen in animals and humans (Ghisi et al. 2019). Unlike the definition used in animal studies, plant uptake studies define BAF and BCF[4] as the PFAS concentration in plant divided by the concentration in soil (ITRC 2021a). Generally speaking, terrestrial plant uptake of PFAA seems to vary with chain length and functional group. In contrast to what is seen in animals, longer-chained PFAS generally have lower levels of accumulation in plants than do shorter-chained PFAS (Blaine et al. 2014; Krippner et al. 2015), which may be a function of their water solubility and root uptake (Lesmeister et al. 2021). PFSAs have also displayed lower levels of bioaccumulation than PFCAs have. The extent of PFAS uptake by plants or crops is highly dependent on several factors, including soil properties and characteristics (pH, organic matter, salinity, temperature), plant type, and physiology (Lesmeister et al. 2021; Wang et al. 2020). Differences in PFAS accumulation between species may be attributed to various factors such as protein content, root system surface area, and biomass accumulation (Ghisi et al. 2019). Plants tend to display a high level of accumulation in the vegetative compartments (e.g., leaves, stems) in comparison to reproductive and storage organs, which may be a result of their root uptake mechanism (Lesmeister et al. 2021). Moreover, Li et al. (2021a) found that leafy vegetables had the highest BAF values for PFBA and PFOA, followed by fruit vegetables and root vegetables.

Overall, the bioaccumulation potential of PFAS, as well as its persistence (section 3.2.2), indicate an increased potential for risk to the environment. PFAS can remain in the environment for long periods as a result of their persistence, which can contribute to global presence and increase the likelihood of organism exposure. Moreover, some PFAS have been demonstrated to have the potential to bioaccumulate and biomagnify in food webs to a degree that could allow them to reach levels that can cause adverse effects in organisms. Ultimately, bioaccumulation could result in an increased potential for toxicity in organisms.

6.2 Ecological effects

6.2.1 Invertebrates

1.1.1.1 Aquatic invertebrates

Several studies have examined PFAS toxicity in aquatic invertebrates. In general, toxicity in aquatic invertebrates is higher for PFAS with a longer fluoroalkyl chain, with crustaceans commonly being the most sensitive taxa (Ankley et al. 2021). It has also been determined that PFSAs are typically more hazardous than PFCAs. For example, Li (2009) found that PFOS had a higher acute toxicity than PFOA in all of the aquatic invertebrates tested. There are also more acute toxicity studies for aquatic invertebrates available in the literature than chronic toxicity studies (ITRC 2021b). Ankley et al. (2021) determined that the 50% effective concentration (EC50) and 50% lethal concentration (LC50) values from chronic exposures ranged from 0.03 mg/L to >100 mg/L and were generally in the same order of magnitude as values from acute

[4] A BAF or BCF of 1 indicates no net accumulation from soil to plant; however, this is not indicative of equilibrium.

exposures for the same species. The aqueous toxicity of PFOA was evaluated in chronic tests with *Hyalella azteca* (amphipod) by Bartlett et al. (2021), where it was found that environmental concentrations of PFOA in global surface waters were generally below those that caused toxicity in this study (LC50 = 51 mg/L).

Effects on growth, development, and reproduction have been reported with PFAS exposure in aquatic invertebrates (Boudreau et al. 2003; Fabbri et al. 2014; Seyoum et al. 2020). In general, developmental effects tend to be seen at lower concentrations than growth and reproductive endpoints (Ankley et al. 2021). Moreover, PFAS have been shown to cause oxidative stress and affect immune-related cell viability. Liu and Gin (2018) observed measurable reductions in the immune fitness of green mussel (*Perna viridis*) following exposure to PFAS, as shown through significant decreases in biomarker responses (i.e., neutral red retention, phagocytosis, and spontaneous cytotoxicity of hemocytes). In a study of adult Eastern oyster, *Crassostrea virginica*, exposed to a technical mixture of PFOS (linear and branched isomers) by Aquilina-Beck et al. (2020), no significant damage to lipid membranes or the glutathione phase II enzyme system was observed; however, significant cellular lysosomal damage was observed. Genotoxic effects have also been seen, where Liu et al. (2014) observed irreversible genetic damage caused by elevated concentrations of PFAAs in green mussel. Additionally, neurotoxic effects, such as altered brain morphology and reductions in locomotor velocity, have been observed in planaria (*Dugesia japonica*; Ankley et al. 2021). Foguth et al. (2020) found that PFOS is capable of significantly affecting the expression of genes that are important for neuronal development in planaria in a dose- and time-dependent manner. Furthermore, it was suggested that PFECHS has endocrine disruption potential in chronically exposed *Daphnia magna* at concentrations higher than levels reported in the aquatic environment (Houde et al. 2016). PFAAs have also been found to cause multigenerational effects among aquatic invertebrates, where reductions in growth and individual fitness were seen across generations by Marziali et al. (2019) and Jeong et al. (2016), respectively.

1.1.1.2 **Terrestrial invertebrates**

In comparison to the toxicological studies on aquatic invertebrates, fewer studies have been conducted with terrestrial invertebrates. Using a high-throughput system with nematodes (*Caenorhabditis elegans*), Ankley et al. (2021) noted that developmental toxicity generally increased with longer-chain PFAS. Various studies have also found behavioural, reproductive, and neurotoxic effects when nematodes were exposed to PFAAs (Chowdhury et al. 2021; Foguth et al. 2020; Sammi et al. 2019; Sana et al. 2021). In European honey bees (*Apis mellifera*), PFOS exposure caused brood development to cease entirely and led to adverse behavioural effects (i.e., colony activity, temperament, hive maintenance, defence; Sonter et al. 2021). Moreover, in earthworms (*Eisenia fetida*), Xu et al. (2013b) found that exposure to PFOS can induce DNA damage and oxidative stress. The toxicity of PFOS was also assessed in two invertebrates (*Collembolan Folsomia candida* and mites, *Oppia nitens*) in two soil types to assess the inclusion of these two study species in the risk assessment of PFOS in soil (Princz et al. 2018).

6.2.2 Vertebrates

1.1.1.3 Fish

Several studies have examined PFAS toxicity in fish species, with freshwater Cyprinidae—more specifically zebrafish (*Danio rerio*)—having the most data available (Ankley et al. 2021). More studies have also been completed on freshwater species than on marine fish. In general, PFAS have a relatively lower acute toxicity to fish compared to aquatic invertebrates (Ankley et al. 2021). Acute toxicity in fish species seems to vary with chain length and functional group. In most of the fish families studied, short-chain PFAAs as well as sulfonates have been shown to display lower LC50s than long-chain PFAAs and carboxylates. A similar trend was also seen in chronic toxicity studies.

A review by Lee et al. (2020) compiled the existing literature on the adverse effects of PFAA on fish and other aquatic organisms. Exposure to PFAAs has been found to cause effects on reproduction, growth/development, mobility, and survival. For example, studies have shown that PFAA exposure in zebrafish larvae can lead to decreased body length, decreased locomotor speed, decreased hatching rate, increased mortality, and disruption in larval morphology (e.g., uninflated swim bladder, less developed gut, curved spine) (Chen et al. 2014; Guo et al. 2018; Zhang et al. 2018a). Moreover, PFAAs can induce oxidative stress and alter the regulation of genes and nuclear receptors related to xenobiotic, lipid, and carbohydrate metabolism in fish (Lee et al. 2020). Effects on the endocrine and reproductive system have also been reported, such as by Zhang et al. (2016a), who found that chronic exposure of zebrafish to PFNA can lead to dysfunction in the hypothalamic-pituitary-gonadal-liver axis and sex hormone synthesis as well as a decrease in gonadosomatic index (a measure of sexual maturity) and fertility. In terms of neurotoxicity, Foguth et al. (2020) reported altered levels of norepinephrine, epinephrine, and acetylcholine following PFBS exposure to marine medaka (*Oryzias melastigma*). Additionally, multigenerational studies have noted that PFAA exposure can impact mortality, fecundity, gonad development, and swimming rate in fish offspring (Ji et al. 2008; Lee et al. 2017; Wang et al. 2011) as well as disrupt the thyroid endocrine system (Chen et al. 2018a).

1.1.1.4 Amphibians and reptiles

Only a limited number of toxicology studies for amphibians have been published, which focus on a few subgroups of PFAS. The amphibian studies identified by Ankley et al. (2021) examined only PFCAs, PFSAs, and fluorotelomers. Similar to what has been observed in fish, PFAS have relatively lower acute toxicity in amphibians compared to aquatic invertebrates following acute exposure. The toxicity of PFAS in amphibians also seems to vary with fluoroalkyl chain length and functional group. For instance, when examining the acute toxicity of PFAA in amphibian species, Tornabene et al. (2021) and Flynn et al. (2019) determined that PFOS was more hazardous than PFOA. Moreover, PFAS has been observed to have impacts on the growth and development of early amphibian life stages (Ankley et al. 2021). In northern leopard frog (*Rana pipiens*) larvae, Flynn et al. (2021) observed that exposure to PFOS and PFOA under environmentally relevant conditions led to developmental delays. Flynn et al. (2019) also found reductions in snout-vent length when American bullfrog (*Rana catesbeiana*) tadpoles were exposed to a mixture of PFOS and PFOA. Although the majority of amphibian studies have

focused on the earlier aquatic life stages, it has also been found that PFAS can induce sublethal effects on postmetamorphic amphibians (Abercrombie et al. 2021). More specifically, these authors found that exposure to PFOS, PFOA, PFHxS, or 6:2 fluorotelomer sulfonate can impact final snout-vent length and scaled mass index (a measure of relative body condition) in juvenile American toads (*Anaxyrus americanus*), eastern tiger salamanders (*Ambystoma tigrinum*), and northern leopard frogs (*Rana pipiens*); however, the observed effects were dependent on the species and chemical tested.

Even fewer studies have examined reptilian species, with recent investigations focusing on turtles. Some impacts seen in turtles include reduced emergence success of hatchlings when exposed to long-chain PFCAs (Wood et al. 2021), negative correlations between PFAA exposure and body mass (Bangma et al. 2019), and negative metabolic impacts from PFAS mixtures (Beale et al. 2022).

1.1.1.5 **Mammalian wildlife**

There are very few existing studies on PFAS toxicity in mammalian wildlife. Although Ankley et al. (2021) did not identify any laboratory toxicity studies on mammalian wildlife, there are some field studies that point to a significant association between PFAS exposure and the expression of biomarkers of effects. Pedersen et al. (2015) found that PFSA and PFCA concentrations in East Greenland polar bears (*Ursus maritimus*) could lead to alterations in their neurochemistry. In the bottlenose dolphin (*Tursiops truncatus*), plasma PFAA concentrations were observed to have a statistically significant association with hematologic, biochemical, and immunologic endpoints (Fair et al. 2013). As mentioned previously in section 6.1, air-breathing organisms are more likely to accumulate ionic PFAS in comparison to water-breathing organisms because of their low volatility and protein binding mechanism in tissue. As a result, it is expected that these substances would have a greater potential for exposure in air-breathing organisms (including birds, discussed in the following section) due to their significant bioaccumulation potential, which can lead to adverse effects (ECCC 2023).

Due to the lack of research on PFAS toxicity in mammalian wildlife, studies on laboratory mammals (e.g., rodents, rabbits, monkeys) may be used as surrogates for toxicity in mammalian wildlife as this has been the focus of many studies from the current literature. Exposure to PFAS has the potential to cause adverse effects on multiple systems and organs (e.g., liver, kidney, immune system, reproduction, endocrine system, and nervous system), according to studies of laboratory mammals (refer to section 7.2 for key health effect findings in laboratory animals). In addition, toxicity seems to vary with fluoroalkyl chain length in studies of laboratory mammals exposed to PFAA (Ankley et al. 2021). According to the findings of rat studies, the lowest observed adverse effects levels (LOAELs) for ecologically relevant endpoints were between 1.0 mg/kg bw/d (PFUnDA) and 200 mg/kg bw/d (PFHxA) for the PFCAs and between 1.6 mg/kg bw/d (PFOS) and 1000 mg/kg bw/d (PFBS) for the PFSA. It is expected that adverse effects similar to those seen in laboratory animals could be seen in mammalian wildlife. However, it should be noted that the effects demonstrated and the magnitude of effects displayed in mammals can vary between mammalian species. Furthermore, most toxicokinetic data on mammalian species focus on laboratory animals and are discussed in section 7.1.

Some effects (e.g., hepatotoxicity) of PFAS exposure in mammals are believed to be mediated in part through activation of the peroxisome proliferator-activated receptor alpha (PPARα), which plays a role in lipid and glucose metabolism. This mechanism is well studied in laboratory animals (i.e., rodents) and is discussed further in section 7.4. However, it should be noted that there are some effects that occur as a result of this mechanism in laboratory animals but are not relevant to humans. For instance, PPARα activator-induced hepatocarcinogenesis seen in rodent models is not applicable to humans due to biological differences (Corton et al. 2018). Some studies of mammalian wildlife have also reported this mechanism of action, including studies on cetaceans (Kurtz et al. 2019), polar bears (Routti et al. 2019b), and seals (Ishibashi et al. 2008). PPARα-independent transcript regulation in mammals following PFAS exposure is also possible (Rosen et al. 2017) and is discussed further in section 7.4.

1.1.1.6 **Birds**

The available literature on bird toxicity is quite limited. In a study of chronic PFOS exposure in northern bobwhite quail (*Colinus virginianus*), Dennis et al. (2021) established species- and tissue-specific chronic toxicity values, associated with a LOAEL threshold of 226, 50.4, and 92.4 ng/g wet weight in adult liver tissue, offspring liver tissue, and whole egg, respectively. In avian species, it has been found that fluoroalkyl chain length and functional groups are key factors that appear to determine the toxicity of PFAS (Ankley et al. 2021). Broadly speaking, compounds with 8 carbons as well as sulfonates were found to be more hazardous than short-chain PFAS and carboxylates. Both PFOS and PFOA were determined to be more hazardous than PFBS on the basis of LC50 values obtained from northern bobwhite (*C. virginianus*) and Japanese quail (*Coturnix japonica*) acute toxicity studies (Ankley et al. 2021). Moreover, Bursian et al. (2021) concluded that PFOS exhibits a higher subacute toxicity in Japanese quail compared to PFOA and that this effect may be additive.

Studies of the peregrine falcon (*Falco peregrinus*) in the Laurentian Great Lakes have also found that exposure to PFAA can lead to potential physiological impacts on nestlings and impaired immune function (Sun et al. 2020, 2021). The toxicity of PFUnDA was determined using genomic responses in exposed liver cells of embryonic chicken (O'Brien et al. 2013). Furthermore, hatching success and toxicogenomic responses were assessed in chicken embryos following exposure to PFHxS and PFHxA (Cassone et al. 2012a, 2012b). Other studies of avians have observed reductions in body weight, increases in liver weight, and impaired hatching success (Bursian et al. 2021; Custer et al. 2013; Dennis et al. 2021; Molina et al. 2006; Newsted et al. 2007).

6.2.3 Aquatic and terrestrial plants

Most studies that have examined the toxicity of PFAS in aquatic and terrestrial plants have been limited to PFOS and PFOA. According to data summarized by the ITRC (2021b), studies that examined PFOS toxicity in aquatic plants had no observed effect concentration (NOEC) values ranging from 7 mg/L to 30 mg/L for acute exposures and from 0.3 mg/L to 11.4 mg/L for chronic exposures. A review by Li et al. (2021a) examined the toxic effects of PFAS on various plants from a physiological, biochemical, and molecular standpoint. At the physiological level, PFAS can cause damage to cell morphology and impact the photosynthetic pigments. In algae (*Chlorella pyrenoidosa*), tested concentrations of PFOA and its substitute GenX were found to

inhibit growth and negatively affect photosynthetic activity (Li et al. 2021a). The transcriptional and cellular responses of the green alga *Chlamydomonas reinhardtii* to PFPAs were evaluated where potential impacts to the antioxidant defensive system were observed (Sanchez et al. 2015). Moreover, PFAS exposure can also induce the overgeneration of reactive oxygen species (ROS; reactive chemicals derived from molecular oxygen), perturb the expression of genes, regulate the proteins involved in photosynthesis, and disturb some major pathways in energy metabolism (Li et al. 2021b).

6.2.4 Mixtures and cumulative effects in the environment

Although the vast majority of ecotoxicology studies have focused on the effects seen with exposure to a single PFAS, organisms are typically exposed simultaneously to multiple PFAS in the environment, as can be seen from environmental occurrence and monitoring data. Wildlife can be exposed to other chemical, biological, and physical stressors in their ecosystem, which can contribute to the actual impact that PFAS exposure can have on organisms in the environment. Some field-based wildlife studies also group PFAS together, sometimes with other chemicals, and examine the effect observed in the organism (ECCC 2023). The *Supporting Document: Ecological State of the Science Report on Short-chain PFCAs, Short-chain PFSAs, and Long-chain PFSAs* (ECCC 2023) provides a compilation of published cumulative effect studies for select PFAS in various wildlife species. Although some studies have reported potential additive (Flynn et al. 2019; Hoover et al. 2019), antagonistic (Rodea-Palomares et al. 2012), and synergistic effects (Yang et al. 2019) of multiple PFAS in biota (Yang et al. 2019), as well as a combination of the three (Ding et al. 2013), there are still significant data gaps in the species, substances, and endpoints examined.

6.2.5 New approach methodologies for ecotoxicity

The evolving landscape of chemical production has rendered toxicological testing using traditional models (i.e., live animals) impractical, and advances in science coupled with ethical concerns have resulted in government agencies, including the United States (US EPA 2021b), European Union, and Canada (Bhuller et al. 2021), committing to reduce, refine, and potentially eliminate the use of mammalian models from certain regulatory testing requirements, where scientifically justified. New approach methodologies (NAMs) are broadly described by the international risk assessment community as any technology, method, approach, or a combination of these that can be used to reduce, refine, or replace animal testing and allow more rapid and effective screening of chemicals. These methods may include the use of computer models or assays with biological molecules, cells, tissues, or organs as well as exposure measurement approaches.

The evolution and advantages of NAM for ecological risk assessment of PFAS are reviewed in Ankley et al. (2021). Similar to NAM for human health risk assessment, a major focus has been on measures of bioactivity, the rationale being that this could lead to a mechanistic understanding of PFAS toxicity to aid in the identification of susceptible species and endpoints and to support cross-species extrapolation. A number of studies have aimed to identify the biological pathways affected by PFAS by evaluating changes in gene or protein expression in non-mammalian test systems (Ankley et al. 2021). However, a review of adverse effects of

PFAA on aquatic organisms determined that toxicity involves diverse metabolic processes, highlighting the challenge of elucidating linkages and interactions among metabolic pathways (Lee et al. 2020). Combining molecular information with computational models could be used to inform adverse outcome pathways (AOPs) to confidently identify PFAS-specific molecular initiating events and changes at higher levels of biological organization (i.e., key events) to elucidate how these changes translate into adverse effects and outcomes (i.e., apical endpoints; Ankley et al. 2010).

7 Human health hazard

KEY POINTS ON HUMAN HEALTH HAZARD

- Toxicological and epidemiological information is available for less than 50 PFAS with most research focused on PFOA and PFOS.
- Recent information on well-studied PFAS, particularly PFOA and PFOS, shows negative effects on human health at lower levels than previous studies.
- Some well-studied PFAS have been demonstrated to be readily absorbed into the body and are eliminated very slowly. Consequently, some PFAS can accumulate and persist in the body for years.
- Exposure to PFAS can affect multiple organs and systems. The main targets include the liver, immune system, kidney, reproduction, development, endocrine disruption (thyroid), nervous system, and metabolism (lipids, glucose homeostasis, body weight). Effects on most of these endpoints have been observed in both animal and human studies.
- Since humans are typically exposed to mixtures of PFAS, it is reasonable to assume that culmulative effects may occur. However, the specific hazards associated with these mixtures are largely unknown.
- New approach methodologies (NAMs) can help fill gaps in the data by generating information using time- and resource-efficient techniques, including high-throughput screening.

7.1 Toxicokinetics

Toxicokinetic data are available primarily for PFAAs. Available data on specific PFAAs indicate that these substances are readily absorbed following oral ingestion, and although data on inhalation and dermal exposure are extremely limited, available studies indicate that absorption occurs by these routes as well (ATSDR 2021). Once absorbed, the studied PFAAs bind to serum protein albumin and other proteins in the blood, which serve as the primary transport mechanism of these substances within the body (Forsthuber et al. 2020). Information on studied PFAAs indicates that they are distributed throughout the body and accumulate in the blood and well-perfused tissues such as the liver and kidneys (Kudo 2015). A number of PFAS (e.g., PFAAs and FOSA) have been shown to cross the placental barrier, resulting in in utero exposure to the developing fetus (Wang et al. 2019a). They can also be transferred to infants and children via human milk (VanNoy et al. 2018). Many PFAS, including PFAAs, are not metabolized in the body, likely because of their high stability and low reactivity of carbon-fluorine

bonds (ATSDR 2021). However, precursors such as FTOHs and PAPs can be biotransformed to several metabolites including PFAAs (Butt et al. 2014).

Some PFAS have been shown to be eliminated very slowly from the human body, likely due to their interaction with transporters involved in renal, hepatic, and intestinal reabsorption processes (EFSA 2020; Yang et al. 2010). As a result, these substances persist and accumulate in humans and can take a very long time to be cleared from the body. Biological half-lives have been identified for 37 PFAS in humans and/or animal models (Table 3). These values represent the time it takes for half of the original concentration of the substance to be cleared by the body through excretion (e.g., urine, feces). As these values were derived for different groupings of individuals using various methodological approaches and with different statistics, the half-lives are not necessarily directly comparable. However, there are clear species differences in the elimination rates of PFAS, with the longest half-lives often being observed in humans and the shortest in rodents. In humans, C8 to C11 PFCAs, C6 to C8 PFSAs, and 6:2 Cl-PFESA have the longest half-life values (years to decades). It is noted that there is some uncertainty in the human values since the washout studies typically used for determining half-lives in animal studies are not used to determine half-lives in humans (FSANZ 2016b). The determination of half-lives in humans is more complicated because other parameters, such as continuous exposure, need to be considered (Russell et al. 2015a). For some PFAS such as PFCAs (C4 to C12) and PFSAs (C4 to C8), the longer the chain length, the more slowly the PFAS is eliminated from the body (Kudo 2015). Studied PFAS are excreted primarily in the urine and feces and, to a lesser extent, in human milk and menstrual fluid (ATSDR 2021). The latter excretion routes may contribute to sex differences observed in some human monitoring studies (Mondal et al. 2014; Wong et al. 2014).

Table 3. Biological half-lives for PFAS in animals and humans (adapted from Sanexen 2021)

PFAS group	PFAS	Mouse	Rat	Monkey	Pig	Human	References
PFCAs	PFBA	hours[a]	hours–days	days	--	days	Chang et al. 2008; Russell et al. 2015b
PFCAs	PFPeA	--	hours	--	--	--	Choi et al. 2020
PFCAs	PFHxA	hours	minutes–hours	hours–days	days	weeks	Chengelis et al. 2009a, 2009b; Dzierlenga et al. 2020; Gannon et al. 2009; Himmelstein et al. 2008, Iwai 2011; Noker 2001; Numata et al. 2014; Ohmori et al. 2003; Russell et al. 2013; Russell et al. 2015b
PFCAs	PFHpA	--	hours	--	months	months–years	Numata et al. 2014; Russell et al. 2015b; Xu et al. 2020a; Zhang et al. 2013
PFCAs	PFOA[b]	weeks	hours–weeks	weeks-months	months	years–decades	Bartell et al. 2010; Benskin et al. 2009; Brede et al. 2010; Butenhoff et al. 2004a; Costa et al. 2009; De Silva et al. 2009; Dzierlenga et al. 2020; Fu et al. 2016; Gomis et al. 2016, 2017; Hanhijärvi et al. 1988; Kemper 2003; and others[c]
PFCAs	PFNA	months	days–months	--	--	years	Benskin et al. 2009; De Silva et al. 2009; Ohmori et al. 2003; Tatum-Gibbs et al. 2011; Zhang et al. 2013
PFCAs	PFDA	--	months	--	--	years	Ohmori et al. 2003; Zhang et al. 2013
PFCAs	PFUnDA	--	--	--	--	years–decades	Zhang et al. 2013
PFCAs	PFDoDA	--	months	--	--	--	Kawabata et al. 2017a
PFSAs	PFBS	hours	hours	hours-days	months	weeks–months	Chengelis et al. 2009a; Huang et al. 2019a; Lau et al. 2020; Numata et al. 2014; Olsen et al. 2009; Rumpler et al. 2016; Xu et al. 2020a
PFSAs	PFPeS	--	--	--	--	months	Xu et al. 2020a
PFSAs	PFHxS	weeks	days–weeks	months	years	years–decades	Benskin et al. 2009; Fu et al. 2016; Huang et al. 2019a; Kim et al. 2016; Li et al. 2018a; Numata et al. 2014; Olsen et al. 2007; Sundstrom et al. 2012; Worley et al. 2017; Xu et al. 2020a; Zhang et al. 2013

PFAS group	PFAS	Mouse	Rat	Monkey	Pig	Human	References
PFSAs	PFHpS	--	--	--	years	years	Numata et al. 2014; Xu et al. 2020a
PFSAs	PFOS[d]	weeks–months	weeks–months	months	years	years–decades	Benskin et al. 2009; Chang et al. 2012; Noker and Gorman 2003; De Silva et al. 2009; Fu et al. 2016; Gomis et al. 2017; Huang et al. 2019a; Kim et al. 2016; Li et al. 2018a; Numata et al. 2014; Olsen et al. 2007; Seacat et al. 2002; and others[e]
FASAs and derivatives	FOSA	--	days	--	--	--	Ross et al. 2012
FT-based substances	8:2 FTOH	--	hours	--	--	--	Fasano et al. 2006; Huang et al. 2019b
FT-based substances	5:3 Acid	--	weeks–months	--	--	months	Kabadi et al. 2020; Russell et al. 2015b
PFPAs	C6 PFPA	--	days	--	--	--	D'eon and Mabury 2010
PFPAs	C8 PFPA	--	hours–days	--	--	--	D'eon and Mabury 2010; Joudan et al. 2017
PFPAs	C10 PFPA	--	days	--	--	--	D'eon and Mabury 2010
PFPIAs	C6/C6 PFPiA	--	days	--	--	--	D'eon and Mabury 2010
PFPIAs	C6/C8 PFPiA	--	days	--	--	--	D'eon and Mabury 2010; Joudan et al. 2017
PFPIAs	C6/C10 PFPiA	--	days	--	--	--	D'eon and Mabury 2010
PFPIAs	C6/C12 PFPiA	--	days–weeks	--	--	--	D'eon and Mabury 2010
PFPIAs	C8/C8 PFPiA	--	days	--	--	--	D'eon and Mabury 2010; Joudan et al. 2017
PFPIAs	C8/C10 PFPiA	--	days–weeks	--	--	--	D'eon and Mabury 2010
PAPs	4:2 diPAP	--	days	--	--	--	D'eon and Mabury 2011
PAPs	6:2 diPAP	--	days	--	--	--	D'eon and Mabury 2011
PAPs	8:2 diPAP	--	days	--	--	--	D'eon and Mabury 2011
PAPs	10:2 diPAP	--	days	--	--	--	D'eon and Mabury 2011

PFAS group	PFAS	Mouse	Rat	Monkey	Pig	Human	References
Ether-PFAS (PFESAs)	6:2 Cl-PFESA	--	days	--	--	years–decades	Shi et al. 2016; Yi et al. 2021
Ether-PFAS (PFESAs)	6:2 H-PFESA	--	days	--	--	--	Yi et al. 2021
Ether-PFAS (PFECAs)	ADONA	hours	hours–weeks	hours	--	weeks	3M 2007a, 2008a, 2008b, 2008c, 2010; Harlan Laboratories Ltd 2010
Ether-PFAS (PFECAs)	EEA-NH4	--	hours	hours–days	--	--	AGC Chemical 2007a, 2007b
Ether-PFAS (PFECAs)	HFPO-DA	hours–days	hours–days	hours–days	--	--	DuPont 2008b, 2011; Gannon et al. 2016
Ether-PFAS (PFECAs)	PFO4DA	hours	--	--	--	--	Chen et al. 2021
Ether-PFAS (PFECAs)	PFO5DA	months	--	--	--	--	Chen et al. 2021

[a] Time frames: hours = up to 24 hours; days = >1 to 7 days; weeks = >7 to 31 days; months = >1 to 12 months; years = >1 year; decades = >10 years
[b] PFOA was also tested in dogs, with a half-life in the order of weeks.
[c] Kim et al. 2016; Kudo et al. 2002; Lau et al. 2005; Li et al. 2018a; Lieder et al. 2006; Lou et al. 2009; Numata et al. 2014; Ohmori et al. 2003; Olsen et al. 2003; Olsen et al.2007; Seals et al. 2011; Vanden Heuvel et al. 1991; Worley et al. 2017; Xu et al. 2020a; Zhang et al. 2013
[d] PFOS was also tested in rabbits, with a half-life in the order of months.
[e] Shi et al. 2016; Tarazona et al. 2016; Wong et al. 2014; Worley et al. 2017; Xu et al. 2020a; Zhang et al. 2013

7.2 Health effects

Although there is a vast amount of research on the health effects associated with PFAS, the majority of research is focused on PFCAs and PFSAs, particularly PFOA and PFOS. Fewer data exist for other PFAS, although research on these substances is increasing. Toxicological and epidemiological data currently exist for fewer than 50 individual PFAS. A number of international agencies and journal publications have reviewed the human health hazards associated with these PFAS (e.g., ATSDR 2021; ECHA 2022a, 2022b; EFSA 2020; Fenton et al. 2021). In contrast, limited or no data exist for the majority of PFAS, including many PFAS that are known to be present in commercial products or that have been found in the environment. These include C1 to C3 PFSAs and PFCAs, other FT-based substances (e.g., containing phosphorus or a thioether), cyclic PFAS, side-chain fluorinated polymers, perfluoropolyethers, or fluoropolymers.

In reviews on the hazards of PFAS, it has been suggested that fluoropolymers have unique properties, including insignificant impacts on human health. Consequently, it has been proposed that fluoropolymers be considered separately from other PFAS as “polymers of low concern” (PLC; Henry et al. 2018; Korzeniowski et al. 2022). Buck et al. (2011) define fluoropolymers as substances with a carbon-only polymer backbone with fluorine atoms directly attached to it. Henry et al. (2018) argued that fluoropolymers do not have reactive functional groups with high toxicity and that their physico–chemical properties (e.g., large molecular weight, low solubility) prevent bioavailability, bioaccumulation, and toxicity. Toxicity data for the fluoropolymer polytetrafluoroethylene (PTFE) appear to indicate a lack of effects, including systemic effects, under the conditions tested (see Table S5 in Henry et al. 2018; Lee et al. 2022). However, no toxicity data were identified for fluoropolymers other than PTFE; consequently, caution should be applied when discussing the lack of toxicity for the entire group of fluoropolymers. Furthermore, Lohmann et al. (2020) argue that not all fluoropolymers meet the OECD (2007) definition for polymers of low concern (for example, the fluoropolymer Nafion contains a reactive functional group). In addition, the authors give evidence that nanoparticles of similar molecular size have in fact been able to penetrate cell membranes and thus be bioavailable. Moreover, they point out that, while PTFE may be of low hazard, the PFAS processing aids used and released in the production of some fluoropolymers (e.g., salts of PFOA, PFNA, and HFPO-DA) have exhibited toxicity and this should be taken into consideration when evaluating overall hazard (Lohmann et al. 2020). Overall, it appears that there are complexities associated with fluoropolymers that require further consideration before the toxicity of these substances can be accurately assessed.

When examining the toxicity data available for PFAS other than fluoropolymers, it is evident that, on the basis of the available information, exposure to these substances has the potential to affect multiple systems and organs. To gain a better understanding of the key health endpoints, the Government of Canada commissioned a report to summarize the available data (Sanexen 2021). The purpose of the report was to provide an overview of the publicly available science and to highlight commonalities across the studied PFAS. It did not include a critical review of the individual studies (e.g., evaluation of study design, strengths, weaknesses, biases). The Government of Canada has reviewed the report in detail and noted that data on recurrent health

effects were available for 43 PFAS, including perfluorinated compounds (PFCAs, PFSAs), polyfluorinated compounds (FT-based substances, FASAs, and derivatives) as well as per/polyfluoroalkyl ether compounds (PFESAs, PFECAs). Although several PFAS subgroups (e.g., LC-PFCAs or LC-PFSAs, PFECAs) were well represented with a number of studies and health endpoints available for several compounds, other PFAS subgroups were limited to data for a single substance or were limited in terms of the amount and type of data available for each substance.

Table 4 provides an overview of the information available for the various PFAS groups and subgroups. Both toxicological data (studies in laboratory animal models) and epidemiological data (studies in humans) are available for most of the PFAS groups. The exceptions were for C1 to C3 PFSA and FT-based substances, for which only animal data were available, and for FASAs, for which only human data were available. Overall, and despite the lack of equivalency in the level of information between PFAS groups/subgroups, the main systems/organs/targets identified as being affected include the liver, immune system, kidney, reproduction, development, endocrine disruption (thyroid), the nervous system, and metabolism (lipids, glucose homeostasis, body weight). For most of these systems/organs/targets, recurrent effects were observed in both animal and human studies. The exception is for effects in the adrenal glands, which were reported in animal studies only.

While there are limitations to epidemiological studies—including the fact that the associations identified are not causal in nature—when they are combined with toxicological data from experimental animals, the findings are more compelling, and the overall evidence of effect is strengthened. The sections below provide an overview of the information available for each of the recurrent health endpoints (see Appendix E for supporting references). Although the data indicate that statistically significant effects or associations were identified for these endpoints, other studies may have found no such effect or association. These null findings are not detailed in the summaries below.

Table 4. Summary of the recurrent health effect endpoints examined in human and animal studies

PFAS groups	PFAS subgroups	Number of PFAS with data	Effect on body weight	Effect on kidney	Effect on immune system	Effect on liver (except serum lipids)	Effect on reproduc-tion (except ED)	Effect on development (except ED and neurotoxicity)	Effect on nervous system or neuro-development	Effect on endocrine system - ED during develop-ment	Effect on endocrine system - Reproductive hormones	Effect on endocrine system - Thyroid gland or hormones	Effect on endocrine system - Adrenal gland or hormones	Metabolic disruption - Serum lipids	Metabolic disruption - Glucose homeo-stasis
PFCAs	C4–C7	≤4	H + A +	**H ++** **A ++**	H ++ A +	H+ A ++	H + A +	**H ++** **A ++**	A ++	A +	H +	**H ++** **A ++**	--	A ++	H ++
PFCAs	≥C8	≤9	**H ++** **A ++**	**H ++** **A ++**	**H ++** **A ++**	**H ++** **A ++**	**H ++** **A ++**	**H ++** **A ++**	**H ++** **A ++**	**H ++** **A ++**	**H ++** **A ++**	**H ++** **A ++**	A ++	**H ++** **A ++**	**H ++** **A ++**
PFSAs	C1–C3	≤1	--	--	--	A +	A +	--	--	--	--	--	--	A +	A +
PFSAs	C4–C7	≤3	**H ++** **A ++**	H + A ++	**H ++** **A ++**	**H ++** **A ++**	H ++ A +	**H ++** **A ++**	H + A +	A +	H ++ A+	**H ++** **A ++**	A +	**H ++** **A ++**	H ++
PFSAs	≥C8	≤2	H + A +	H ++ A +	H + A +	H + A +	H + A +	H + A +	H + A +	H + A +	H + A +	H + A +	A +	H + A +	H + A +
FASAs and derivatives	FASA	≤1	H +	--	H +	--	H +	H +	H +	--	--	--	--	--	--
FASAs and derivatives	Derivatives	≤6	H + A +	H + A +	A +	A ++	H + A ++	A ++	--	--	--	H ++ A +	--	A ++	H +
FT-based substances	FTSA (n:2)	≤1	A +	A +	--	A +	--	--	--	--	--	--	--	--	--
FT-based substances	FTOH (n:2)	≤2	A ++	A ++	A ++	A ++	A +	A +	A +	--	--	A ++	--	A +	--
FT-based substances	FTCA (n:2 and n:3)	≤2	A +	A +	A +	A ++	--	--	--	--	--	A +	--	A +	--
Ether-PFAS	PFESA	≤2	A +	H +	--	H + A +	A +	H +	--	--	--	A +	--	H + A +	H +
Ether-PFAS	PFECA	≤12	A ++	**H ++** **A ++**	A ++	**H ++** **A ++**	A +	A ++	--	--	--	A ++	A ++	**H ++** **A ++**	A ++

A: animal data (statistically significant effect and/or adverse effect induced by PFAS); ED: endocrine disruption; H: human data (significant association with exposure to PFAS).

-- No retrieved data indicating a PFAS-induced effect (A) or an association with exposure to PFAS (H) (i.e., effect/association not observed, not evaluated, or not retrieved).

\+ Recurrent Effect in the target observed for a single PFAS within the subgroup (pale colors).

++ Recurrent Effect in the target observed for more than 1 PFAS within the subgroup (dark colors).

Bold Indicates cases where (++) were attributed to both human and animal data.

Source: Adapted from Sanexen (2021)

7.2.1 Liver

Effects in liver are one of the most investigated endpoints, and data have been reported in humans and/or animals for 33 PFAS. In epidemiological studies, exposure to PFOS and PFHxS was associated with an increased risk of certain liver diseases (e.g., non-alcoholic fatty liver disease, cholelithiasis, biliary duct disorders, lobular and portal inflammation, liver fibrosis). Changes in serum levels of enzymes and bilirubin were the most common biomarkers of liver damage investigated in both epidemiological and laboratory studies. Increased liver enzyme levels were reported for 8 PFCAs, 3 PFSAs, 2 FT-based substances, and 6 ether-PFAS, while inconsistent alterations to bilirubin levels were reported for 6 PFCAs, 3 PFSAs, 2 FT-based substances, and 4 ether-PFAS, indicating the possibility that bilirubin may not be a consistent biomarker for liver effects in these cases. In laboratory studies, liver weight and histopathological endpoints were often examined as evidence of hepatotoxicity. Increased liver weights and/or histopathological findings such as hepatocellular hypertrophy, hyperplasia, and necrosis were noted for 11 PFCAs, 4 PFSAs, 2 FASA derivatives, 5 FT-based substances, and 11 ether-PFAS. In addition, alterations to lipid homeostasis in the liver were examined in animal studies, and data were reported for 4 PFCAs, 3 PFSAs, and 4 ether-PFAS. Both increasing and decreasing levels of hepatic triglycerides and/or total cholesterol levels were reported. Currently, the relationship between changes in these parameters following PFAS exposure and lipid homeostasis is not clearly understood (Das et al. 2017).

7.2.2 Kidney

The long biological half-lives of certain PFAS are attributed to renal reabsorption processes while the concentration of PFAS in renal tissues and the related impacts on the kidney are of concern (Fenton et al. 2021). Adverse effects on the kidney have been reported in humans and/or animals for 29 PFAS. In epidemiological studies, exposure to PFBA, PFOA, PFHxS, and PFOS was associated with an increased risk of chronic kidney disease and/or gout. In addition, glomerular filtration rates were mostly decreased following exposure to 9 PFCAs, 3 PFSAs, and N-MeFOSA. Of note is that reverse causality is a possibility for this endpoint, meaning that decreased glomerular filtration (e.g., due to a pre-existing condition) may result in increased PFAS levels, as opposed to the increased levels of PFAS causing the decreased filtration rates. Biomarkers such as serum uric acid, blood urea nitrogen, and serum creatinine can provide an indication of renal function. These biomarkers were mostly increased in epidemiological and/or laboratory studies for 11 PFCAs, 3 PFSAs, and 5 ether-PFAS. In animal studies, altered kidney weights were reported for 6 PFCAs, 3 PFSAs, N-MeFOSE, 3 FT-based substances, and 3 ether-PFAS. For most PFAS, increased kidney weights were noted; however, for some PFAS, decreased kidney weights were also reported. Nephrotoxicity as indicated by histopathological findings in animal models included tubular hypertrophy, degeneration and/or necrosis/dilation, papilloma necrosis/fibrosis as well as cortical and/or medullary congestion. Such findings were reported for 5 PFCAs, 2 PFSAs, 4 FT-based substances, and 3 ether-PFAS.

7.2.3 Immune system

The immune system can be a sensitive target for environmental contaminants; indeed, immunotoxicity associated with PFAS exposure has been reported in human and/or animal studies for 23 PFAS. In epidemiological studies, the endpoints investigated were immunosuppression and immunoenhancement.

Immunosuppression mainly refers to reduced antibody responses to vaccination (e.g., rubella, tetanus, diphtheria) and to increased incidence of infectious diseases (e.g., throat/airway/ear infections, gastroenteritis, croup). Immunosuppression was noted in studies for 6 PFCAs, 3 PFSAs, and FOSA. In animal studies, immunosuppression referring mainly to decreased antibody response to antigens (T-cell-dependent or -independent antibody responses) was reported for PFOA, PFOS, and HFPO-DA. Reduced levels, proliferation, and/or activity of white blood cells was noted for 3 PFCAs, PFOS, 8:2 FTOH, and 2 ether-PFAS, and an increased incidence of infectious disease was noted for PFOS. Recent reviews, particularly for PFOS and PFOA, show epidemiological findings to be concordant with animal studies indicating the importance of immunosuppression as a key endpoint (Dewitt 2019; NTP 2016).

In terms of immunoenhancement, which refers to allergic sensitization and/or hypersensitivity responses (e.g., asthma, rhinitis, atopic dermatitis), this endpoint was reported in epidemiological studies for 7 PFCAs and 4 PFSAs. Changes in immune system organ weights and histopathological alterations have also been investigated in laboratory studies in relation to PFAS exposure. Studies have noted decreased spleen, thymus, and/or lymph node weights, often in association with histopathological findings (decreased size and/or cellularity, necrosis, and hyperplasia) in these organs and/or in the bone marrow. At least one of these findings was reported following exposure to 6 PFCAs, 2 PFSAs, N-EtFOSE, 3 FT-based substances, and 2 ether-PFAS.

7.2.4 Reproduction

Reproductive effects associated with PFAS exposure have been investigated in human and/or animal studies for 22 PFAS. In epidemiological studies, preeclampsia and/or pregnancy-induced hypertension were found to be associated with exposure to 2 PFCAs and 3 PFSAs. In addition, lower fecundability (i.e., the probability of conception in a menstrual cycle) and higher infertility (i.e., a time to pregnancy longer than 12 months) were related to exposure to 2 PFCAs and 2 PFSAs. Increased gestational weight gain was noted in epidemiological and/or animal studies for PFOA, PFOS, N-EtFOSAA, and HFPO-DA. Both laboratory and epidemiological studies have investigated the effects on reproductive hormones following PFAS exposure. Altered serum levels (increased or decreased) of estradiol, testosterone, progesterone, follicle-stimulating hormone, and/or prolactin were the most recurrent endpoints and were associated with exposure to 7 PFCAs and 3 PFSAs. In terms of male reproductive outcomes, abnormal sperm morphology, decreased semen volume, and decreased sperm motility, concentration, and/or count were noted in epidemiological and/or animal studies for 5 PFCAs, 3 PFSAs, and FOSA. In addition, altered reproductive organ weights (i.e., seminal vesicles, testes, and/or epididymides) were reported in animal studies for 4 PFCAs, 2 PFSAs, 2 FASA derivatives, 6:2 FTOH, and 2 ether-PFAS.

7.2.5 Development

Information on developmental toxicity associated with PFAS exposure was noted in human and/or animal studies for 23 PFAS. Different exposure scenarios were considered, including maternal exposure before or during gestation (i.e., *in utero* exposure), lactational exposure, postnatal exposure, or a combination of these. The most commonly investigated endpoints were prenatal and postnatal growth outcomes such as decreased birth weight, birth length, ponderal index, and head circumference. These outcomes were observed in epidemiological and/or animal studies for 9 PFCAs, 3 PFSAs, 2 FASAs and derivatives, 6:2 FTOH, and 4 ether-PFAS. Laboratory studies further noted increased prenatal and postnatal mortality for many of these same PFAS. In laboratory studies, delayed ossification and other skeletal variations (increased incidence of tail, sternal, and limb defects) were reported for PFOA, 2 PFSA, N-EtFOSE, 6:2 FTOH, and HFPO-DA. The occurrence of cleft palate was also noted following PFOS exposure. Delayed eye opening was a recurrent finding in animal studies for 4 PFCAs and 2 PFSAs. Alterations in the development of the reproductive system were noted in relation to exposure to 8 PFCAs, 4 PFSAs, and HFPO-DA. In epidemiological studies, this was related to altered anogenital distance, altered hormone levels, and changes to the mean age of puberty onset. In laboratory animals, the most recurrent reproductive findings included altered hormone levels, decreased Leydig cell development, altered ovarian function, altered anogenital distance, delayed puberty, and abnormal mammary gland development.

7.2.6 Endocrine function (thyroid)

Some PFAS may act as endocrine disruptors and, more specifically, may have effects on thyroid function. Effects on the thyroid and adrenal glands were reported in studies for 25 PFAS. In epidemiological studies, an increased risk of thyroid diseases (e.g., hyperthyroidism, hypothyroidism) was associated with exposure to PFOA, PFHxS, and PFOS. Alterations (increase and/or decrease) in the serum levels of thyroid-stimulating hormone, triiodothyronine, and thyroxine levels were the most recurrent evidence of PFAS endocrine disruption. These effects were noted in both epidemiological and laboratory studies and were observed in juvenile and adult populations as well as in pregnant women (epidemiological studies only). In laboratory studies, alterations to thyroid gland weight (mainly increases but also decreases) and/or adrenal gland weight were reported for 5 PFCAs, 3 PFSAs, 2 FT-based substances, and 2 ether-PFAS. Histopathological alterations to the thyroid gland (mainly hypertrophy and hyperplasia but also adenoma and altered colloids) were reported for 4 PFCAs, PFHxS, N-EtFOSE, 2 FT-based substances, and 2 ether-PFAS, whereas histopathological alterations to the adrenal glands (including hypertrophy, hyperplasia, necrosis, atrophy, and vacuolation) were reported for 2 PFCAs and HFPO-DA.

7.2.7 Nervous system

Effects on the nervous system have not been studied as widely as other endpoints. However, recurrent effects have been noted in humans and/or animals for 14 PFAS. Both neurodevelopmental effects and neurological effects (observed during adulthood) have been investigated. In terms of neurodevelopmental effects, epidemiological studies have examined outcomes in relation to 4 PFCAs, 2 PFSAs, and FOSA. The studies found that exposure to these PFAS was associated with mixed effects on behaviour (e.g., attention deficit hyperactivity

disorder, autism spectrum disorder) and cognition (e.g., learning, reading skills). In animal studies, neurodevelopmental effects such as behavioural deficits, altered spontaneous behavior, cognitive function, and/or altered motor activity in rodent offspring were reported for 3 PFCAs and 2 PFSAs. In terms of neurological effects, laboratory studies for 7 PFCAs, PFOS, and 6:2 FTOH identified neurotoxicity (including cachexia, lethargy, delay in bilateral pupillary reflex, and tonic convulsions in response to stimuli), impaired cognition, and/or impaired motor activity (including grip strength and locomotor activity) in animal models.

7.2.8 Metabolism and body weight

Some PFAS have a structure similar to fatty acids, which activate peroxisome proliferator-activated receptors (PPARs). Since PPARs regulate lipid and glucose metabolism, it is thought that PFAS may also have an effect on body weight regulation and the development of diabetes. Results of studies investigating these endpoints in humans and/or animals were reported for 31 PFAS. In epidemiological studies, an increased prevalence of gestational diabetes and/or increased levels of diabetes biomarkers (e.g., insulin resistance, serum levels of insulin and/or glucose) were reported during pregnancy for 6 PFCAs and 3 PFSAs. However, these outcomes were inconsistently observed in juveniles and (non-pregnant) adults exposed to PFAS. In laboratory studies, increased levels of diabetes biomarkers were reported in adult animals for 4 PFCAs, PFOS, and 4 ether-PFAS. Levels were also increased in dams and juveniles exposed to PFOS.

In terms of body weight, epidemiological studies in adults showed an increased incidence of obesity and/or obesity biomarkers (e.g., waist circumference, body mass index) in relation to exposure to 3 PFCAs, 3 PFSAs, and N-MeFOSAA. In children, the results were not as consistent, with body weights and/or obesity biomarkers sometimes increasing and sometimes decreasing following exposure to 6 PFCAs, 2 PFSAs, and FOSA. In animal studies, body weights were mostly decreased, although increased body weights were also reported for several PFAS, especially at low doses. Data were available for 9 PFCAs, 3 PFSAs, N-EtFOSE, 4 FT-based substances, and 4 ether-PFAS.

Alterations (mostly increases) in serum triglycerides and/or cholesterol levels were also noted in several epidemiological studies, including for 4 PFCAs, 3 PFSAs, and 5 ether-PFAS. Conversely, serum lipid levels were mostly decreased in animal studies for 8 PFCAs, 4 PFSAs, 2 FASA derivatives, 3 FT-based substances, and 6 ether-PFAS, which may be due to the large differences in exposure doses (Fragki et al. 2021).

7.2.9 Carcinogenicity

Using the Key Characteristics of Carcinogens framework for cancer hazard identification, Temkin et al. (2020) applied a weight of evidence approach (consideration of epidemiological data, *in vivo* data in animals, and *in vitro* data) to evaluate 26 PFAS. The authors found that multiple PFAS exhibited several of the key characteristics of carcinogens and that each of the 26 chemicals, which included long- and short-chain perfluoroalkyl carboxylates and sulfonates, fluorotelomer alcohols, polyfluoroalkyl phosphate esters, and fluoropolyether carboxylates, exhibited at least one characteristic. Well-studied PFAS, such as PFOA and PFOS, exhibit up to five key characteristics (e.g., induces oxidative stress, immunosuppressive, alters cell proliferation, exhibits epigenetic alterations). In addition, a recent study found that

concentrations of specific PFAS in the serum of US firefighters were linked with accelerated epigenetic age and locus-specific DNA methylation. These toxicity biomarkers are associated with many diseases, including cancer (Goodrich et al. 2021).

Although a number of epidemiological and animal studies have examined the association between exposure to PFAS and the occurrence of cancer, the data is limited primarily to PFOA and PFOS, with less data for a small number of other PFAS, including PFCAs, PFSAs, and FASAs. For the most part, no consistent associations were noted between exposure to PFAS and the risk of cancer. However, credible evidence of increases in kidney and testicular cancer has been noted following occupational and community exposure to PFOA. As a result, the International Agency for Research on Cancer (IARC) has classified PFOA as possibly carcinogenic to humans (Group 2B). Since the weight of evidence indicates that PFOA is not DNA-reactive, the mode of action is likely through a non-genotoxic mechanism (IARC 2017). Subsequent to this evaluation, the National Toxicology Program released the results of a study that examined the exposure of rats to PFOA over a 2-year period, including during gestation and lactation. The study results showed an increase in the numbers of liver and pancreatic tumours in male rats and an increase in the number of pancreatic tumours in female rats exposed to PFOA, compared to controls (NTP 2020).

7.3 Overview of the lowest observed adverse effect levels (LOAELs)

Table 5 provides a summary of the lowest doses at which adverse effects have been observed following oral exposure to PFAS in animal studies. With a focus on common endpoints of concern, data were found for 43 PFAS. The lowest observed adverse effect levels (LOAELs) refer to external experimental doses in mg/kg bw/day associated with statistically significant adverse changes for a given endpoint. The compilation of values is not exhaustive, particularly for data-rich PFAS where the focus was on the lower values. Toxicity studies in various animal models with various designs (e.g., dose regimens, study duration, statistics) were identified and considered. Since the determination of a LOAEL depends on the doses tested, the values reported should not be compared between substances without consultating the corresponding no observed adverse effect levels (NOAELs). Indeed, several LOAELs were also the lowest dose tested in a study (i.e., a NOAEL could not be determined). Furthermore, the lowest dose tested sometimes varied by more than an order of magnitude between studies.

To date, there has been no consensus among hazard assessors on the most sensitive endpoints in animal studies for any one PFAS. This has resulted in various endpoints being selected as points of departure for risk assessments and is in part responsible for the wide array of toxicological reference values seen across governments and organizations worldwide. Recent assessments have concluded that effects on the immune system, which were observed at the lowest serum PFAS levels in both animals and humans, are critical (EFSA 2020; US EPA 2022a, 2022b). However, the science is rapidly evolving and, as has been observed in the past, it is possible that new data may show effects on other endpoints at lower levels.

Table 5. Overview of the lowest LOAELs (lowest observed adverse effect levels) identified for various endpoints of concern following oral exposure to PFAS in laboratory animals

Target	Health endpoint	Range of LOAELs (mg/kg bw per day)	Number of PFAS[a]	References
Liver	Non-neoplastic histopathological lesions	0.01 to 300	20	3M 2008d; Blake et al. 2020; Butenhoff et al. 2002, 2009, 2012a; Caverly Rae et al. 2015; Chang et al. 2018; Chengelis et al. 2009; Covance Laboratories Inc. 2001; DuPont 2008a, 2008b, 2008c, 2008d, 2008e, 2010a, 2010b, 2010c, 2012, 2013a, 2013b; ECHA 2021a; Filgo et al. 2015; Gordon 2011; Hirata-Koizumi et al. 2012, 2015; IRDC 1978; Kato et al. 2015; Kirkpatrick 2005; Ladics et al. 2008; Loveless et al. 2008, 2009; Mukerji et al. 2015; NOTOX 1999; NTP 2019a; Perkins et al. 2004; Quist et al. 2015; Serex et al. 2014; Sheng et al. 2017; Stump et al. 2008; Takahashi et al. 2014; Wang et al. 2017b, 2019c, 2021; Xing 2016; Zhou et al. 2020
Liver	Neoplastic lesions	0.1 to 500	2	Butenhoff et al. 2012a; Caverly Rae et al. 2015; DuPont 2013b
Liver	Increased liver weight (sometimes concomitant with increased serum enzymes and/or altered liver lipid/glycogen contents)	0.002 to 300	26	3M 2001; Butenhoff et al. 2004b, 2012b; Chang et al. 2018; Chen et al. 2021; Conley et al. 2019, 2021; Covance Laboratories Inc. 1999, 2000; Das et al. 2008, 2015; Ding et al. 2009; Dong et al. 2009b; DuPont 2008a, 2008b, 2008c, 2008d, 2008e, 2009a, 2010c; Fang et al. 2012a; Frawley et al. 2018; Guo et al. 2019, 2021a, 2021b; Harris and Birnbaum 1989; Huck et al. 2018; Kawashima et al. 1995; Kennedy 1987; Kirkpatrick 2005; Lai et al. 2018; Lefebvre 2008; Lieder et al. 2009a; York 2003; Liu et al. 1996;

				Luebker et al. 2005a; Mertens et al. 2010; Miyata 2007; NCDPH 2018; NTP 2019a, 2019b; Rushing et al. 2017; Seacat et al. 2002; Sheng et al. 2018; Son et al. 2008; Wan et al. 2014; Wang et al. 2015b; Wolf et al. 2010; Woodlief et al. 2021; Wu et al. 2018; Xie et al. 2009; Zhang et al. 2008, 2018b; Zheng et al. 2017; Zhong et al. 2016
Kidney	Increased kidney weight and/or altered clinical chemistry	0.13 to 1000	18	Asahi Glass 2006; Blake et al. 2020; Butenhoff et al. 2004b, 2009; Chengelis et al. 2009; Covance Laboratories Inc. 1999; Ding et al. 2009; Dong et al. 2009; DuPont 2008a, 2008b, 2008c, 2008d, 2008e, 2009a, 2010a, 2010b, 2010c, 2012, 2013a; ECHA 2021a; Gordon 2011; Hirata-Koizumi et al. 2012, 2015; Kato et al. 2015; Kirkpatrick 2005; Loveless 2009; Miyata 2007; Mukerji et al. 2015; NCDPH 2018; NOTOX 1999; NTP 2019a, 2019b; Serex et al. 2014; Stump et al. 2008; Takahashi et al. 2014; Xing et al. 2016
Kidney	Histopathological lesions	5 to 300	5	Caverley Rae et al. 2015; DuPont 2010a, 2010b, 2010c, 2013b; Klaunig et al. 2015; Kirkpatrick 2005; ECHA 2021b; Ladics et al. 2008; Lieder et al. 2009a; York 2003
Immune function	Altered immune response (reduced antibody response to an antigen, reduced resistance to disease, and/or altered cytokine response)	0.0004 to 100	5	Bodin et al. 2016; DeWitt et al. 2016; Dong et al. 2009; 2011; Fair et al. 2011; Guruge et al. 2009; Peden-Adams et al. 2008; Rushing et al. 2017; Wang et al. 2019c; 2021; Zhong et al. 2016
Immune function	Histopathological lesions or altered splenic	0.03 to 315	11	Covance Laboratories Inc. 2002; Fang et al. 2008; Frawley et al. 20018; Griffith and Long 1980;

	cell subpopulations			Guo et al. 2021c; Hirata-Koizumi et al. 2015; Kato et al. 2015; Kirkpatrick et al. 2005; Rushing et al. 2017; Son et al. 2009; Woodlief et al. 2021; Zhong et al. 2016
Immune function	Decreased spleen and/or thymus weights	1 to 125	9	DeWitt et al. 2016; DuPont 2008a, 2008b, 2008c, 2008d, 2008e, 2009b, 2012; Fang et al. 2009, 2010; Kato et al. 2015; Kirkpatrick 2005; Lieder et al. 2009b; Loveless et al. 2008; NTP 2019a, 2019b; Rushing et al. 2017; Yang et al. 2001; Zhong et al. 2016
Immune function	Reduced globulin levels, increased A/G ratio, and/or reduced immunoglobulin G1 level	0.2 to 250	7	Caverly Rae et al. 2015; DuPont 2007, 2008a, 2008b, 2008c, 2008c, 2008d, 2008e, 2013b; Lefebvre et al. 2008; Loveless et al. 2009; NTP 2019a, 2019b
Immune function	Altered white blood cell counts	1 to 100	2	DuPont 2013a; Gordon 2011
Reproduction	Altered male reproductive system	0.01 to 500	14	ATSDR 2021; Argus Research Laboratories Inc. 1999a; Covance Laboratories Inc. 1999; DuPont 2008a, 2008b, 2008c, 2008d, 2008e, 2013a; Feng et al. 2009, 2010; Health Canada 2006; Hirata-Koizumi et al. 2015; Kato et al. 2015; Li et al. 2018c; Loveless et al. 2009; Miyata et al. 2007; Mukerji et al. 2015; NTP 2019a; Serex et al. 2014; Shi et al. 2007, 2009a; Singh and Singh 2018, 2019b; Yan et al. 2021; Zhou et al. 2018, 2020
Reproduction	Altered female reproductive system	0.2 to 1000	7	Cao et al. 2020; Chen et al. 2017; DuPont 2008a, 2008b, 2008c, 2008d, 2008e, 2013; Fair et al. 2011; Hirata-Koizumi; Kato et al. 2015; Miyata 2007; Mukerji et al. 2015; NTP 2019b; Wang et al. 2018a

Reproduction	Altered serum levels of reproductive hormones (testosterone, estradiol, LH, FSH, and/or progesterone)	0.2 to 200	7	Biegel et al. 2001; Cao et al. 2020; Chen et al. 2019; Cook et al. 1992; Feng et al. 2009; Li et al. 2018c; Liu et al. 1996; NTP 2019a; Seacat et al. 2002; Shi et al. 2007, 2009a, 2009b; Singh and Singh 2019b; Yan et al. 2021; Zhao et al. 2010
Reproduction	Adverse outcomes during gestation and/or lactation	0.4 to 1000	10	Argus Research Laboratories Inc. 1999a, 1999b, 1999c, 2000; Blake et al. 2020; Case et al. 2001; Chang et al. 2018; Das et al. 2008; DuPont 2013a; Hirata-Koizumi et al. 2012; Kato et al. 2015; Lee et al. 2015; Luebker et al. 2005b; Mukerji et al. 2015; O'Connor et al. 2014; Riker Laboratories Inc 1981; White et al. 2011; Wolf et al. 2010
Development	Reduced postnatal survival	0.3 to 1.6	4	Abbott et al. 2007; Butenhoff et al. 2004b; Chen et al. 2012; Luebker et al. 2005b; Stump et al. 1997; White et al. 2011; Wolf et al. 2010; Xia et al. 2011
Development	Altered prenatal and/or postnatal growth (low birth weight, reduced body weight gain, delayed eye opening, reduced ossification, skeletal alterations)	0.3 to 1000	14	Argus Research Laboratories Inc. 1999d, 1999e, 1999f; Asahi Glass 2014; Das et al. 2008, 2015; DuPont 2010c; Feng et al. 2017; Gordon 2011; Harris and Birnbaum 1989; Hazleton Laboratories America Inc. 1983; Hirata-Koizumi et al. 2012, 2015; Hu et al. 2010; Iwai and Hoberman 2014; Koskela et al. 2016; Lau et al. 2006; Loveless et al. 2009; Loveless et al. 2009; Luebker et al. 2005a, 2005b; Onishchenko et al. 2011; Riker Laboratories Inc. 1980; Rogers et al. 2014; Takahashi et al. 2014
Development	Altered development of the reproductive system (altered sexual hormones,	0.01 to 200	8	Conley et al. 2019; Das et al. 2015; Feng et al. 2017; Lau et al. 2006; Li et al. 2021c, 2021d; Macon et al. 2011; Ramhøj et al. 2018, 2020; Singh and Singh 2019b; Song et al. 2018; Tucker

	delayed puberty, decreased weight and/or function of male organs, altered function/morphology of female organs)			et al. 2015; Zhang et al. 2021; Zhong et al. 2016
Development	Altered thyroid hormones	0.4 to 200	3	Feng et al. 2017; Lau et al. 2003; Luebker et al. 2005a; Ramhøj et al. 2020
Development	Increased fetal/pup liver weight(s) and/or metabolic alterations (altered serum cholesterol, glucose, insulin and/or leptin level, increased body weight, reduced fetal liver glycogen accumulation)	0.01 to 10	6	Chang et al. 2018; Conley et al. 2019, 2021; Das et al. 2015; Harris and Birnbaum 1989; Hines et al. 2009; Quist et al. 2015; Stump et al. 2008; Wan et al. 2014; Zhong et al. 2016
Endocrine	Adrenal gland (altered weight(s), increased cortisol or corticosterone, histopathological changes)	0.01 to 100	8	3M 2007b; DuPont 2008a, 2008b, 2008c, 2008d, 2008e, 2010a, 2010b, 2010c; Fang et al. 2008, 2009; Gordon 2011; Hadrup et al. 2016; Hirata-Koizumi et al. 2015; Kato et al. 2015; NTP 2019a, 2019b;
Endocrine	Thyroid gland (altered weight(s), altered T3, T4 and/or TSH, histopathological changes)	0.1 to 125	18	3M 2007b; Butenhoff et al. 2002, 2009, 2012a, 2012b; Cao et al. 2020; Conley et al. 2019, 2021; Covance Laboratories Inc. 2001; DuPont 2007, 2012; ECHA 2021b; Feng et al. 2017; Gordon 2011; Harris et al. 1989; Hirata-Koizumi et al. 2015; Hong et al. 2020; Kirkpatrick 2005; Ladics et al. 2008; Lau et al. 2003; Loveless et al. 2009; Luebker et al. 2005a; NTP 2019a, 2019b; Ramhøj et al. 2018, 2020; Seacat

				et al. 2002; Serex et al. 2014; Thibodeaux et al. 2003; Wang et al. 2018a; Yu et al. 2009
Nervous system	Decreased grip strength, decreased motor activity, alterations in the dopaminergic system, delayed pupillary reflex, hypoactivity, and prostration	0.5 to 150	7	Butenhoff et al. 2012b; Griffith et al. 1980; Hirata-Koizumi et al. 2015; Kato et al. 2015; Kawabata et al. 2017b; Miyata 2007; Salgado et al. 2016
Nervous system	Neurodevelopmental alterations (spontaneous and/or cognitive behaviour, alteration in the hippocampus)	0.3 to 9.2	3	Goulding et al. 2017; Johansson et al. 2008; Koskela et al. 2016; Mshaty et al. 2020; Onishchenko et al. 2011; Viberg et al. 2013; Wang et al. 2015c; Zeng et al. 2011
Metabolism and body weight	Effects on glucose homeostasis	0.01 to 1000	12	Bodin et al. 2016; Chen et al. 2021; Ding et al. 2009; Fang et al. 2012b; Gordon 2011; Hines et al. 2009; Hirata-Koizumi et al. 2012; Huck et al. 2018; Kato et al. 2015; Lai et al. 2018; NCDPH 2018; Serex et al. 2014; Wan et al. 2014; Wu et al. 2018; Zheng et al. 2017; Zhou et al. 2020
Metabolism and body weight	Increased serum lipids	0.01 to 125	6	Butenhoff et al. 2002; Chen et al. 2021; Conley et al. 2021; Huck et al. 2018; Shi et al. 2007, 2009; Wu et al. 2018
Metabolism and body weight	Decreased serum lipids	0.01 to 1000	23	Covance Laboratories Inc. 1999, 2001, 2002; Bijland et al. 2011; Blake et al. 2020; Butenhoff et al. 2012; Chang et al. 2018; Chengelis et al. 2009; Conley et al. 2019, 2021; Ding et al. 2009; DuPont 2009a, 2010a, 2010b, 2010c, 2012, 2013a; ECHA 2021a; Fang et al. 2012a; Gordon 2011; Hirata-Koizumi et al. 2012; Kato et al. 2015; Kirkpatrick 2005; Ladics et al. 2008; Lai et al. 2018;

				Loveless et al. 2008, 2009; Luebker et al. 2005a; NCDPH 2018; NTP 2019a, 2019b; Quist et al. 2015; Seacat et al. 2002; Sheng et al. 2018; Singh and Singh 2018; Takahashi et al. 2014; Wang et al. 2017b; Wu et al. 2018; Zhang et al. 2018b; Zhou et al. 2020
Metabolism and body weight	Increased body weight	0.01 to 100	6	Blake et al. 2020; Chen et al. 2021; Hines et al. 2009; Loveless et al. 2009; Zhang et al. 2018b
Metabolism and body weight	Decreased body weight	0.4 to 1000	18	Argus Research Laboratories Inc. 1998, 1999a, 1999b, 1999d; Asahi Glass 2014; Blake et al. 2020; Case et al. 2001; Caverly Rae et al. 2015; Conley et al. 2019, 2021; Das et al. 2015; Ding et al. 2009; Dong et al. 2009; DuPont 2009b, 2012, 2013b; ECHA 2021b; Fang et al. 2009; Frawley et al. 2018; Griffith and Long 1980; Hadrup et al. 2016; Harris and Birnbaum1989; Hazleton Laboratories America Inc. 1983; Hirata-Koizumi et al. 2012, 2015; Kato et al. 2015; Kawabata et al. 2017b; Kawashima et al. 1995; Ladics et al. 2008; Lee et al. 2015; Lefebvre et al. 2008; Loveless et al. 2008, 2009; Luebker et al. 2005a; Mukerji et al. 2015; NOTOX 1999; NTP 2019a, 2019b, 2020; O'Connor et al. 2014; Permadi et al. 1993; Sheng et al. 2018; Shi et al. 2007, 2009; Stump et al. 2008; Takahashi et al. 2014; Wang et al. 2015b, 2021; Xie et al. 2009; Xing et al. 2016

A/G: albumin/globulin; FSH: follicle-stimulating hormone; LH: luteinizing hormone; T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone

[a] The number of PFAS represents the number of different substances for which data have been found. There may be more than one study with an identified LOAEL for a given PFAS.

Source: Sanexen (2021)

7.4 Mode of action

The mechanisms of action for PFAS-induced effects are not well understood. Many of the different effects induced by PFAS are believed to be mediated in part by the activation of peroxisome proliferator-activated receptor alpha (PPARα), which modulates lipid and glucose homeostasis, cell proliferation and differentiation, and inflammation. However, studies in animals in which the expression of PPARα has been removed have also shown adverse effects for some endpoints such as liver steatosis (Das et al. 2017) and developmental toxicity in mice (Abbott et al. 2009), suggesting that mechanisms other than PPARα activation are also involved. It is more likely that multiple nuclear receptors, including constitutive activated/androstane receptor (CAR), play a role in mediating PFAS-induced effects in the various target organs (Elcombe et al. 2010). In high-throughput *in vitro* studies, the US EPA's Tox21 data set shows that short- and long-chain PFCAs, PFSAs, and FTOHs can interact with around two dozen different nuclear receptors, with the number of receptors varying depending on the individual PFAS (Goodrum et al. 2021).

7.5 Mixtures and cumulative effects on human health

On the basis of environmental sampling and biomonitoring data, it is evident that humans are typically exposed to multiple PFAS. Despite a lack of toxicity data for many PFAS, it is also evident that studied PFAS share effects on similar endpoints (e.g., liver, immune system, thyroid, serum lipids). Given the combined exposure to multiple PFAS and the similarity of affected endpoints, there are concerns for the cumulative effects of PFAS (ECHA 2022a). Most toxicology and epidemiology studies have evaluated the effects associated with exposure to a single PFAS, but though this approach is useful in providing robust, specific, and unbiased estimates of effect, these studies are not typically designed to assess the potential for interaction, non-additivity of effects, or cumulative effects at lower doses. The hazards of exposure to PFAS mixtures are largely unknown. A limited number of *in vivo* and *in vitro* studies have evaluated the interactive effect of multiple PFAS on different endpoints (see Ojo et al. 2021 for a summary). Antagonistic, synergistic, and additive effects have all been observed in different studies and may be dependent on the species, dose levels, dose ratios, duration of exposure, and mixture components (Ojo et al. 2021). The complexity of these findings demonstrates the importance of considering grouping strategies and frameworks (Cousins et al. 2020b; Goodrum et al. 2021) and incorporating NAM when evaluating the toxicity of PFAS mixtures. Given that the occurrence of synergisms and antagonisms are relatively infrequent in mixture assessments (Martin et al. 2021), a default application of dose-additivity can be applied even if the similarity of the components is unknown (Martin et al. 2021). Adopting dose-additivity as a default when conducting a hazard or risk assessment has been considered a precautious approach that better reflects real world exposures as compared to single compound assessments (Backhaus and Faust 2012).

Epidemiology studies have traditionally been limited with respect to the study of chemical mixtures (e.g., mixtures of multiple PFAS) because many of the individual chemicals are correlated with one another (i.e., people exposed to higher levels of one are often also exposed to higher levels of another). This makes it difficult to identify unique contributions of individual chemicals or to examine cumulative effects (Braun et al. 2016). In recent years, several novel

statistical tools have been developed to overcome these limitations (Bobb et al. 2018; Carrico et al. 2015; Keil et al. 2019). Using these novel and continually emerging tools, epidemiologists are beginning to provide evidence for the cumulative health effects of exposure to PFAS mixtures (Rosato et al. 2022). This work is also expected to help identify whether there are individual PFAS within a mixture that may be the “bad actors” driving a mixture effect. An ongoing challenge in this area is the identification of important statistical mixtures—that is, mixtures of PFAS to which humans are actually exposed—as opposed to those for which biomonitoring data are correlated for other reasons (e.g., shared physiological processes, such as distribution and excretion pathways).

7.6 New approach methodologies (NAMs) for human health hazard

NAMs (described previously in section 6.2.5) provide a time and resource efficient alternative to traditional animal testing and are increasingly being used to provide hazard and risk information for chemical prioritization and human health risk assessment, reducing the reliance on mammalian models. Recently, frameworks outlining fit-for-purpose criteria to evaluate and achieve credibility in the use of NAMs in regulatory contexts have been developed to address data-poor chemicals (such as PFAS) and establish confidence in the scientific underpinning of NAMs among international stakeholders (Parish et al. 2020).

The utility of screening thousands of chemicals using high-throughput *in vitro* toxicity testing (US EPA 2021c) has been demonstrated under the existing toxicity forecasting (ToxCast) program (Judson et al. 2010; Reif et al. 2010; US EPA 2015) and increasingly through collaborative efforts such as the Accelerating the Pace of Chemical Risk Assessment (APCRA) initiative (Paul Friedman et al. 2020). Multiple PFAS are currently listed within the ToxCast chemical inventory, which reveals characteristics that could be used to identify PFAS on the basis of their potential for immunotoxicity (Naidenko et al. 2021) or carcinogenicity (Singh and Hsieh 2021).

PFAS (with the exception of PFOS and PFOA) are largely considered to be data-poor, making this group a suitable candidate for high-throughput screening (HTS) and NAM-based approaches in order to gain a better understanding of distinct features across the class. NAMs have been used to generate information using HTS techniques for related subsets of chemicals with varied characteristics (i.e., physicochemical and structural properties) and used to model and characterize hazards, such as for the purpose of read-across (Kuseva et al. 2021). Implementing *in vitro* and *in silico* analyses to investigate mechanistic properties of PFAS has indicated direct interaction with the nuclear receptor peroxisome proliferator activated receptor (PPAR) and other transcription factors (Almeida et al. 2021; Azhagiya Singam et al. 2020; Behr et al. 2020; Houck et al. 2021; Ojo et al. 2020). However, PPAR activation alone does not fully explain the toxicity of PFAS. Additional mechanisms leading to effects such as disrupted cholesterol metabolism and regulation, immunotoxicity, and carcinogenicity have also been identified as playing a role, wherein NAMs are being developed to identify *in vitro* proxies to characterize and quantify these outcomes (Naidenko et al. 2021; Singh and Hsieh 2021). Government of Canada efforts to use NAMs to fill data gaps for PFAS are further described in section 8.1.2.

8 Domestic and international actions on PFAS

KEY POINTS ON DOMESTIC AND INTERNATIONAL ACTIONS ON PFAS

- The manufacture, use, sale, offer for sale, and import of certain PFAS (PFOS, PFOA, long-chain PFCAs, and their salts and precursors) and products that contain them are prohibited in Canada through regulations under the *Canadian Environmental Protection Act*, 1999, with a limited number of exemptions. However, other PFAS are not prohibited and could be used as alternatives to prohibited PFAS.
- New PFAS that are manufactured or imported into Canada are assessed and risks are managed as required through the *New Substances Notification Regulations*.
- The Government of Canada is actively researching the environmental and health impacts of PFAS, including the use of new approach methodologies to address multiple PFAS simultaneously.
- Environmental and human monitoring and surveillance programs are ongoing, in addition to specific initiatives to address subpopulations who may be more susceptible or highly exposed, including pregnant women and children, First Nation, Metis and Inuit populations, and firefighters.
- Targeted and non-targeted approaches have the potential to contribute to the characterization of environmental profiles, environmental exposures, and health effects.
- Future research will include studies of the effects of single PFAS and real-life mixtures on both ecological and human health endpoints.
- Additional action to address PFAS in Canada is taking place through initiatives such as the Federal Contaminated Sites Action Plan and guidelines for soil and drinking water quality.
- The Stockholm Convention on Persistent Organic Pollutants is an important international agreement that requires that measures be taken to prohibit or restrict a number of PFAS, including PFOA, PFOS, and PFHxS. The listing of LC-PFCAs is also being considered.
- Many other jurisdictions, including the United States and the European Union, are taking specific action on PFAS.

8.1 Domestic activities

8.1.1 Risk assessment and management under CEPA

In Canada, 3 well-defined subgroups of PFAS have been assessed under CEPA. They have been found to be of concern for the environment and therefore have been added to Schedule 1 of CEPA:

- Perfluorooctane sulfonate and its salts and precursors (PFOS) (EC 2006; HC 2006);
- Perfluorooctanoic acid and its salts and precursors (PFOA) (EC, HC 2012); and
- Long-chain perfluorocarboxylic acids and their salts and precursors (LC-PFCAs) (EC 2012).

These Schedule 1 substances capture entire subgroups based on moieties of concern.

A 2006 Risk Management Strategy for PFOS stated that the ultimate environmental objective was to reduce concentrations of PFOS in the Canadian environment to the lowest level possible (Government of Canada 2006). In 2008, the *Perfluorooctane Sulfonate and Its Salts and Certain Other Compounds Regulations* were published to prohibit the manufacture, import, sale, and use of PFOS, with a limited number of exemptions to allow for the transition to alternatives (Government of Canada 2008). In 2009, PFOS and its salts were added to the Virtual Elimination List under CEPA.

In 2010, the Government of Canada initiated an *Environmental Performance Agreement respecting PFCAs and their Precursors in Perfluorochemical Products Sold in Canada*. Over the term of this voluntary 5-year agreement, the four participating companies met their commitment to eliminate residual PFOA, residual LC-PFCAs, and residual precursors from their perfluorochemical products sold in Canada.

The manufacture, use, sale, offer for sale, and import of PFOA, LC-PFCAs, their salts and precursors, and products that contain them have been prohibited since 2016 under the PCTSR, with a limited number of exemptions (Canada 2012a). For example, PFOA and LC-PFCAs in certain AFFF for limited uses and manufactured items are exempt. PFOS was also added to the regulations in 2016, which maintained the regulatory requirements of the *Perfluorooctane Sulfonate and Its Salts and Certain Other Compounds Regulations* and removed certain exemptions. As a result, the *Perfluorooctane Sulfonate and Its Salts and Certain Other Compounds Regulations* were repealed. The PCTSR currently address 94 PFAS identified as being present in Canadian commerce through the DSL, as well as other PFAS for which the presence in Canada is unknown.

In 2018, a consultation document was published on proposed amendments to the PCTSR (Government of Canada 2018). The proposed regulatory approach would be to continue to phase out the use of the toxic substances currently controlled by the regulations. Some exemptions were initially available for PFOS, PFOA, and LC-PFCAs to allow specific market sectors to transition to using alternatives. The next phase of risk management for these substances will be to remove or provide a time limit for the remaining exemptions. Comments and information received in response to the consultation document were considered in the development of proposed Regulations, which were published on May 14, 2022, in the *Canada Gazette*, Part I (Canada 2022a).

In addition, Health Canada and Environment and Climate Change Canada are responsible for administering the *New Substances Notification Regulations (Chemicals and Polymers)* and the *New Substances Notification Regulations (Organisms)* (NSNR). This set of regulations ensure that new substances (chemicals, polymers, and living organisms not listed on the DSL) are assessed for potential risks to human health and the environment and that, if required, control measures are put in place before they are imported into or manufactured in Canada. PFAS are not grouped when they are assessed under the NSNR; each new substance is notified to the government at a different point in time and is individually evaluated for potential risks to the environment and the general public originating from industrial and other relevant uses (for example, consumer uses, cosmetics, pharmaceuticals). Since 1994, about one-third of

approximately 270 new PFAS were subject to risk management measures under the new substances regime to mitigate the risks to human health and/or the environment. These included Ministerial prohibitions (Canada 2004) and Ministerial Conditions (Canada 1996). A Ministerial Condition is a control measure imposed on a new substance to minimize a suspected risk to human health or the environment, in response to a suspicion that the substance may meet the criteria for "toxic" under CEPA. Substances subject to Ministerial Conditions are not eligible for addition on the DSL and must be notified under the new substances notification regime whenever a new notifier wishes to import or manufacture the substance.

A new substance assessment takes into consideration potential risks concerning the notified activities as well as any other possible activities involving the substance. When there is suspicion that a significant new activity (SNAc) may result in the substance becoming toxic, the SNAc provisions of CEPA (see section 85 of CEPA) can be applied to a new substance with the publication of a SNAc Notice in the *Canada Gazette*, Part I. A SNAc Notice describes activities that may result in a significantly greater quantity or concentration of the new substance in the environment, or a significantly different manner or circumstances of exposure to the new substance. Under CEPA, a new substance not on the DSL, or an existing substance on the DSL, may be subject to a SNAc. A SNAc Notice applies to anyone using the substance. Any person wishing to engage in a significant new activity in relation to the substance is required to submit a Significant New Activity Notification (SNAN) to the Minister of the Environment containing all the information prescribed in the Notice prior to using the substance for the proposed activity. After the complete information is received, the Minister of the Environment and the Minister of Health will conduct risk assessments of the substance in relation to the proposed significant new activity within the timelines set out in the Notice. For new substances not on the DSL, a SNAc Notice allows the intended use of the substance described in the New Substances Notification. A new substance subject to a SNAc may become eligible for listing on the DSL. Until the new substance is added to the DSL, other persons must continue to notify the manufacture or import of the new substance as specified by the NSNR.

8.1.2 Planned and future research, monitoring, and surveillance

8.1.2.1 Ecological

Canadian government research has been ongoing since the early 2000s and has been critical in informing early regulatory action in Canada and internationally. Some recent examples of Government of Canada research projects that have garnered preliminary data include 1) a research project on LC-PFCA, PFOS, and PFOA and novel PFAS (zwitterionic and cationic PFAS) in the St. Lawrence River freshwater food web (fish, invertebrates, aquatic plants, water, and sediment); 2) a research project on LC-PFCAs, PFOS, PFOA, and other PFAS (fluorotelomer acids, perfluoropolyether carboxylates, perfluoropolyether sulfonates, chlorine-substituted perfluoroalkyl acids) in wastewater influent, effluent, and Lake Ontario sediment cores; and 3) a field-based study on the accumulation of LC-PFCAs, PFOS, and PFOA in freshwater fish and mussels in wastewater effluent-receiving environments. A study to examine the toxicity and bioaccumulation of 4 short-chain (C4 and C6) perfluoroalkyl substances (2 PFCAs and 2 PFSAs) in 3 freshwater species (snail, amphipod, and frog) has also been completed, with data analysis currently in its final stages. The main objective of this study was

to determine if the size (chain length) or the carboxylic or sulfonic acid moiety of these compounds affected toxicity and bioaccumulation in aquatic organisms. In addition, several effects-based projects began in the summer/fall of 2019. These projects encompass bioaccumulation, biomagnification, acute and chronic toxicity, multi-generational effects, and fish metabolism.

In addition to discrete research projects, the Government of Canada conducts extensive monitoring in various ecosystems and biota as described in section 4.2. Ongoing monitoring programs include air monitoring in Alert, Nunavut, the Great Lakes Basin, and at various sites through the GAPS network; water quality monitoring in transboundary waters and collection of fish tissues from water bodies throughout Canada; collection of seawater and animal tissues (polar bears, ringed seals, and Arctic char) or eggs (seabirds) in Arctic and Subarctic locations as part of the NCP core EMR projects; monitoring of fish and wildlife across Canada as part of research and monitoring programs under CMP; and monitoring of influent, effluent, and solids residuals from municipal WWTPs.

Government of Canada researchers have also published numerous review papers on PFAS in relation to ecotoxicology (summarized in Ankley et al. 2021), research priorities to achieve sustainable environmental quality (Fairbrother et al. 2019), oceans (Muir and Miaz 2021), the Arctic (Muir et al. 2019; Muir and de Wit 2010), marine mammals (Fair and Houde 2018), and wildlife (De Silva et al. 2021; Houde et al. 2011).

Future Government of Canada work is planned to generate transcriptomic, as well as proteomic and lipidomic, dose-response data for zebrafish embryos and adults exposed to single PFAS, simple mixtures, and real-world mixtures. This proposed research is relevant to other ecological species and to human health; Government of Canada researchers have shown how transcriptomic data from zebrafish embryo assays can be linked to AOPs to make inferences about cross-species apical effects that could result from exposure (Xia et al. 2021). Furthermore, improvements in both targeted and non-targeted chemical analyses (reviewed in De Silva et al. 2021), paired with passive sampling techniques and NAM assays, have the potential to contribute to the characterization of PFAS mixtures that may be found in the environment. Finally, several PFAS have been included in Version 2 of the Ecological Risk Classification of organic substances (ERC2; ECCC 2022). ERC2 is a high-throughput prioritization method that uses many sources of NAM data, including *in silico*, *in chemico*, and *in vitro* data, to complement traditional *in vivo* sources.

8.1.2.2 Human health

The Government of Canada has been actively carrying out research on the effect of PFAS exposure on the health of Canadians since 2008. This includes laboratory-based research evaluating the health risk posed by PFAS, including PFCAs, PFSAs, fluorotelomers, and sulfonamides (Curran et al. 2008; Dong et al. 2016; Lefebvre et al. 2008; Reardon et al. 2021; Rowan-Carroll et al. 2021), and epidemiological research evaluating the potential effects of PFAS (PFOA, PFOS, PFHxS) exposure during pregnancy on both maternal and child health outcomes, such as gestational weight gain, gestational hypertension, pre-eclampsia, gestational diabetes, infertility, low birth weight, and newborn markers of immune system development,

androgenic endocrine disruption, and metabolic function (see Arbuckle et al. 2020; Ashley-Martin et al. 2015, 2016, 2017; Borghese et al. 2020; Shapiro et al. 2016; and Vélez et al. 2015). Additionally, toxicological research to advance hazard characterizations for PFAS congeners that are not well studied (i.e., PFUdA) is being planned to increase knowledge on structure activity relationships between short- and long-chain PFAS.

To continue to improve the understanding of the PFAS class, the Government of Canada is leading an initiative in collaboration with academic partners under the Accelerating the Pace of Chemical Risk Assessment program (US EPA 2021d) to demonstrate the applications of changes in gene expression as Points Of Departure for chemical prioritization and hazard characterization. This case study first developed a bioinformatics pipeline to streamline data processing and derive transcriptomic points of departure (tPODs) for a subset of PFAS testing in human liver microtissues. Secondly, the analyses correlated chemical potency in subcategorized PFAS with carbon chain-length and enabled chemical ranking on the basis of potency (i.e., potential to induce liver effects) using gene expression data (Reardon et al. 2021; Rowan-Carroll et al. 2021). *In vitro* derived estimates for PFOS and PFOA were found to be more protective when compared to traditional apical PODs, and common underlying mechanisms of PFAS-induced liver perturbations were identified through altered cholesterol biosynthesis and lipid metabolism, as well as PPARα activation (Rowan-Carroll et al. 2021). Further investigations under this initiative are underway to further evaluate key endpoints used as categorization targets for future PFAS screening, including the development and validation of NAMs such as 3D liver spheroid model and zebrafish embryo model.

In addition, the Government of Canada is conducting laboratory research to reveal the mechanisms underlying the suppression of antibody production using mouse models and the effects of low dose exposure to PFOA and PFOS on the toxicokinetics in male rats. Research is also ongoing to model the dose-response behaviour of various PFAS in the Canadian population. The research efforts between the Government of Canada and international partners are generating high-throughput toxicokinetic data to extrapolate animal dose responses and *in vitro* biological concentrations response into daily population exposure levels. In parallel, laboratory activities have been initiated to investigate potential markers of immune suppression from animal studies that can be identified in humans. This knowledge gathering will support the development of toxicokinetic models, providing both regulators and scientists with tools to predict exposure across different PFAS and identify potential markers of altered immune functions.

Government of Canada research laboratories have also been focused on improving analytical detection methods for measuring PFAS properties in different exposure media. Analytical methods were developed to characterize a broad range of PFAS using standard analytical or suspect screening approaches. These methods are being applied for various environments and media such as blood, human milk, umbilical cord blood, drinking water, food, and house dust (Kubwabo et al. 2004, 2005, 2013; Monroy et al. 2008; Rawn et al. 2022a, 2022b). These detection methods have proven to be important for standardizing the measurement of PFAS in environment and population surveys.

To help characterize and understand PFAS exposure and effects on subpopulations who may be more susceptible or highly exposed and at various life stages, a number of studies are underway, many of which are leveraging the MIREC Research Platform. Research has been initiated to investigate the associations between self-reported prenatal and postpartum personal care product use (i.e., cosmetics, lotions, hair products) and PFAS concentrations in the first trimester, human milk, and infant formula. Given that PFAS may alter immune function, research is also underway to characterize PFAS concentrations during pregnancy and the resulting maternal and child antibody response to common vaccines (i.e., measles, mumps, rubella, and varicella). Analysis of an additional suite of 40 PFAS (including legacy, alternative, replacement, and precursor compounds) is underway in women 10 years postpartum, and research into the health effects of exposure to these PFAS is forthcoming. Additionally, an analysis of PFAS is underway in a sample of women from the CARTaGENE cohort in Quebec. Related research will examine associations with longitudinal health indicators, starting with the age at menopause onset. Using data from the CHMS, future work could also explore exposure to PFAS, health outcomes, and several factors of vulnerability (e.g., age, socioeconomic status, racial/cultural origin).

Monitoring and surveillance activities, such as those conducted through the CHMS, and the MIREC longitudinal study, are continuing to collect and analyze biospecimens for historical and replacement PFAS and their precursors and metabolites (more detail can be found in section 5). Additionally, environmental exposures to PFAS have been monitored through the Canadian House Dust Survey, the Total Diet Study, and the Canadian Drinking Water Survey. Similarly, research funded by the Northern Contaminants Program is also providing information on PFAS exposures in Northern First Nations, Metis, and Inuit communities. More detail can be found in section 5.

In support of characterizing the exposure to PFAS of a potentially highly exposed occupational group, the Government of Canada is conducting research and monitoring of firefighters' levels of exposure to chemicals, including PFAS, as a part of Canada's actions to help protect firefighters from harmful chemicals (Helping to protect firefighters from harmful chemicals - Canada.ca). Firefighters' exposure to chemicals is being monitored through various collaborative research projects, including studies involving blood and urine samples, and collection of skin wipes. These research and monitoring activities are contributing to the identification of best practices for firefighters to reduce harm to them.

The Government of Canada plans to focus on the chemical hazards and occupational and combined exposures specific to firefighters. This will include expanding existing human biomonitoring initiatives and developing a plan for long-term monitoring and surveillance of this population.

Ongoing priorities for research related to PFAS under Canada's CMP include characterizing immunotoxicity, hepatotoxicity, and neurotoxicity (including using NAM) associated with exposure to 23 priority PFAS as well as environmentally relevant PFAS mixtures. Additional analysis of biomonitoring data will also be necessary to characterize environmental exposure

and effects, including chemical identification using targeted, suspect screening, and non-targeted analytical methods.

8.1.3 Guidelines for protection of human health and the environment

A number of guidelines for the protection of human health and the environment have been developed by the Government of Canada (i.e., Federal Environmental Quality Guidelines) or through the Canadian Council of Ministers of the Environment (CCME; i.e., Canadian Environmental Quality Guidelines).

Federal Environmental Quality Guidelines are available for PFOS in surface water for the protection of aquatic life as well as for fish tissue, wildlife diet for mammalian and avian consumers of aquatic biota, and bird eggs (ECCC 2018). Canadian Soil and Groundwater Quality Guidelines (SQGs and GWQGs) are also available for PFOS for the protection of human health and the environment (CCME 2021b). These guidelines include a number of exposure pathways, including ecological pathways, drinking water, off-site migration, and the protection of groundwater.

Canadian Drinking Water Quality Guidelines are available for PFOS and PFOA (HC 2018a, 2018b). In the absence of Canadian Drinking Water Quality Guidelines for PFAS other than PFOS and PFOA, Health Canada has developed drinking water screening values (DWSVs) for 9 select PFAS.[5] These drinking water quality guidelines and screening values for PFAS are used to assess potable groundwater or surface water at federal contaminated sites and are used by provinces and territories to manage drinking water in their regions (HC 2022). In close collaboration with the Federal-Provincial-Territorial Committee on Drinking Water, the Government of Canada is using a group approach to review the PFAS drinking water guidelines and screening values. In February 2023, a consultation document was published on a proposed objective that will recommend a single treatment-based value for a group of PFAS in drinking water (HC 2023b).

In the absence of Canadian SQGs for other PFAS at this time, Health Canada has developed soil screening values (SSVs) on the basis of human direct contact with soil for 10 select PFAS[6] (HC 2022). These SSVs are based on readily available scientific studies. They are not subject to the extensive review completed for the CCME SQGs, which undergo internal peer review and public consultation prior to CCME approval. These SSVs for PFAS are used to assess soil at federal contaminated sites. In addition, given the uncertainties associated with the assessment of PFAS contamination, a precautionary approach is warranted. Further work is ongoing to investigate the feasibility of assessing PFAS at contaminated sites as a class or group.

[5] Water Talk - Perfluoroalkylated substances in drinking water

[6] Perfluorooctanoic acid (PFOA), perfluorobutanoate (PFBA), perfluorobutane sulfonate (PFBS), perfluorohexane sulfonate (PFHxS), perfluoropentanoate (PFPeA), perfluorohexanoate (PFHxA), perfluoroheptanoate (PFHpA), perfluorononanoate (PFNA), 6:2 fluorotelomer sulfonate (6:2 FTS), and 8:2 fluorotelomer sulfonate (8:2 FTS).

The development of environmental quality guidelines for PFOA for surface water, soil, and groundwater is currently under consideration.

Provinces and territories develop guidelines that respond to needs within their jurisdictions to address sites on provincial/territorial lands and sites on private properties, including industrial facilities. Through the *Contaminated Sites Regulation*, British Columbia has developed guidelines for PFOA for the protection of human health as well as for PFOS and PFBS for the protection of the environment and human health (Government of British Columbia, 1996). In addition, Ontario has published Toxicity Reference Values for PFOS and PFOA in its May 2021 publication of *Human Health Toxicity Reference Values (TRVs) Selected for Use at Contaminated sites in Ontario* (OMECP 2021). These are by contrast lower than the TRVs developed by Health Canada (2018a, 2018b) for PFOS and PFOA, respectively. For the assessment and remediation of potentially contaminated sites in the 4 Atlantic Provinces, the governments of these provinces have adopted Health Canada and British Columbia's screening levels and guidelines for drinking water and soil in the publication of the *Atlantic RBCA Environmental Quality Standards and Pathway Specific Standards* (APIRI 2021).

8.1.4 Contaminated sites

Federal contaminated sites are located on land owned or leased by the federal government or on land where the federal government has accepted responsibility for the contamination. The Federal Contaminated Sites Inventory shows more than 23 000 suspected, active, and closed federal contaminated sites, of which there are over 100 sites with confirmed or suspected PFAS contamination (see Figure 3 in section 2.3). The most common sources of PFAS at federal contaminated sites are associated with the use of AFFF and include activities such as firefighting training and the maintenance of firefighting equipment. The Government of Canada continues to take action through the Federal Contaminated Sites Action Plan (FCSAP) to reduce environmental and human health risks from known federal contaminated sites.

Environment and Climate Change Canada, Fisheries and Oceans Canada, and Health Canada are science-based expert support departments in the FCSAP program, providing guidance, training, and advice for the assessment of ecological and human health risks at federal contaminated sites relevant to their mandates. For example, Fisheries and Oceans Canada has supported the development of reports that provide relevant information on PFOS, including the *Federal Contaminated Sites Action Plan (FCSAP): Ecological Risk Assessment Guidance* (DFO 2022) and the *Guidance for Assessing and Managing Aquatic Contaminated Sites in Working Harbours, Version 1.1* (ECCC 2021). Health Canada has prepared a *Human Health Risk Assessment (HHRA) Framework for Federal Sites Impacted with Per- and Polyfluoroalkylated Substances* (HC 2019b) to provide direction in conducting human health risk assessments at federal sites that have been impacted by PFAS associated with past and/or current use of AFFF. This framework is considered "evergreen" and will be updated on the basis of the evolving science in this area to remain current.

Available guidelines and screening values (see section 8.1.3) can be used for contaminated sites to evaluate risks to human health and the environment and to establish remediation objectives (CCME 2021b; HC 2022). Guidelines and screening values are only available for a

small number of PFAS and for specific pathways, and thus are not protective of all human exposure or ecological pathways for all PFAS that may be detected at a site. This presents challenges for risk assessment and risk management at contaminated sites. For example, existing environmental and drinking water guidelines were not developed to be protective of the fish consumption by human pathway; thus, additional media-specific investigation (i.e., analysis of fish tissue) may be needed to assess the risks associated with fish consumption.

There are numerous technical challenges associated with assessment, remediation (refer to section 3.2.6), and risk management activities at contaminated sites. The disposal of PFAS-impacted waste from PFAS-contaminated sites requires special consideration given the long-term ("forever") presence of this class of contaminants. The current analytical suite for environmental samples at commercial laboratories includes a small percentage of the known PFAS overall and those found specifically in AFFF. Therefore, the current analytical capacity only captures a small number of PFAS found at sites impacted by AFFF. The current approach of considering a small number of the known PFAS individually at contaminated sites has its limitations and results in uncertainty with respect to the assessment, remediation, and management of PFAS-contaminated sites. Given these challenges of managing sites contaminated with PFAS (from AFFF and other sources), considering PFAS as a class would reduce uncertainty and enable a more comprehensive and precautionary approach to be taken for the assessment, remediation, and management of PFAS-contaminated sites.

Where potential ecological or human health risks are identified at PFAS-contaminated sites, action may be necessary to eliminate or reduce exposure to PFAS. Such actions may include: the provision of alternative drinking water sources (i.e., bottled water), installation of water treatment systems, implementation of food consumption advisories, and remediation of specific areas of the site to remove PFAS hot spots/source areas. Long-term monitoring and management of PFAS-impacted sites is essential as environmental conditions affecting the migration or transformation of PFAS precursors may change, the analytical suite of PFAS may expand, and environmental guidelines may be revised. Moreover, there is need to verify that mitigation measures are indeed reducing exposure as planned.

8.1.5 Waste management

In Canada, waste management operations are most often dealt with at the provincial and territorial level. These jurisdictions therefore regulate the approval, licensing, and monitoring of waste treatment and disposal facilities, including municipal solid waste and hazardous waste. The collection, recycling, composting, and disposal of waste is managed by municipal authorities. The Government of Canada is responsible for the control of waste management activities on federal lands and the international and interprovincial movement of hazardous waste and hazardous recyclable materials. The Government of Canada can also apply its authorities under CEPA and other applicable laws to waste management when there is a potential for release of toxic substances (based on their inclusion on Schedule 1 of CEPA) to the air, land, or water (CCME 2014).

Most provinces and territories have regulations in place to control waste management operations and/or facilities. Some jurisdictions choose to have all of their requirements outlined

in a regulation, while others prefer to refer to a standard or guidance document in the regulations. However, the level of detail or the depth of the requirements included vary significantly across Canada. In addition, no specific requirements for the acceptance and/or disposal of waste containing PFAS are identified in any of the regulations and/or standards in place in the provinces and territories, and PFAS compounds in MSW landfills do not appear to be monitored at the provincial/territorial level in Canada.

8.1.6 Great Lakes Water Quality Agreement

Under the Great Lakes Water Quality Agreement (GLWQA), Canada and the United States have agreed to protect human health and the environment through cooperative and coordinated measures to reduce the anthropogenic release of chemicals of mutual concern (CMCs) into the waters of the Great Lakes. Under the GLWQA, the Parties have agreed to adopt, as appropriate, the principles of virtual elimination and zero discharge for releases and control of CMCs. The Government of Canada published Canada's Great Lakes Strategy for PFOS, PFOA, and LC-PFCAs in 2022 (ECCC 2022). The document outlines risk mitigation and management actions to further protect the Great Lakes from these substances.

Through the Great Lakes Protection Initiative, the Government of Canada takes action to address the most significant environmental challenges affecting Great Lakes water quality and ecosystem health by delivering on Canada's commitments under the GLWQA. To support the goal of reducing releases of harmful chemicals, the Government provides funding to projects seeking to increase participation in the application of measures that go beyond regulatory compliance to reduce releases of CMCs (including PFOS, PFOA, and LC-PFCAs) by developing, implementing, assessing, and promoting the use of innovative approaches.

8.1.7 Ozone-depleting Substances and Halocarbon Alternatives Regulations

The *Ozone-depleting Substances and Halocarbon Alternatives Regulations* (ODSHAR) under CEPA set out rules on the import, export, and manufacture of certain ozone-depleting substances (ODS) and products containing, or designed to contain, ozone-depleting substances. The regulations also set out rules concerning halocarbon alternatives. Hydrofluorocarbons (HFCs), hydrochlorofluorocarbons (HCFCs), and chlorofluorocarbons (CFCs) are substances covered by the ODSHAR that are in most cases also considered PFAS under the OECD definition.

HFCs are replacements for ODS and are potent greenhouse gases, with some having global warming potentials hundreds to thousands of times greater than that of carbon dioxide. The ODSHAR mandates a reduction of domestic HFC consumption by 85% from baseline by 2036.

HFCs are imported into Canada in bulk for use in the manufacture, servicing, and maintenance of refrigeration and air-conditioning equipment, as blowing agents in the manufacture of foam products, and as a propellant in aerosol products. As an alternative to HFCs, the industry has been transitioning to hydrofluoroolefins (HFOs) for some applications as they have a much lower global warming potential. HFOs are not regulated under the ODSHAR but are considered as PFAS under the definition of the OECD.

Tables 3 and 4 of the ODSHAR include some PFAS (HCFCs and HFCs) that were regulated under the NSNR but for which risk management was rescinded when they became subject to the ODSHAR.

8.2 International activities

A growing number of jurisdictions, including the European Union and some states in the United States, are addressing or proposing to address PFAS as a class. The Government of Canada works with other governments through a number of initiatives including the Stockholm Convention on Persistent Organic Pollutants, the OECD, and tri-laterally with the US EPA and ECHA on the APCRA initiative to collaborate and discuss scientific and regulatory needs. Information about certain key international actions are provided below for context.

8.2.1 Stockholm Convention on Persistent Organic Pollutants (POPs)

The Stockholm Convention on Persistent Organic Pollutants (POPs) aims to protect human health and the environment from substances that are of global concern. POPs listed to the Convention are persistent, bioaccumulative, undergo long-range transport, and lead to significant adverse human health and/or environmental effects. The Convention requires Parties to eliminate or severely restrict the production, use, import, and export of intentionally produced POPs and to implement measures to reduce unintentionally produced POPs. In addition, stockpiles and wastes containing POPs must be managed and disposed of in a safe, efficient, and environmentally sound manner. The Stockholm Convention has assessed and listed PFOS, its salts, and perfluorooctane sulfonyl fluoride (PFOSF) in 2009; PFOA, its salts, and PFOA-related compounds in 2019; and PFHxS, its salts, and PFHxS-related compounds in 2022.

In 2021, the Government of Canada nominated long-chain PFCAs to the Stockholm Convention. At the 18th meeting of the POPs Review Committee (September 26 to 30, 2022), it was decided to adopt the Risk Profile and advance to the Risk Management Evaluation stage of the listing process (POPRC 2022).

8.2.2 OECD Global Perfluorinated Chemicals Group

The OECD Global Perfluorinated Chemicals Group considers the development, facilitation, and promotion of international stewardship programs and regulatory approaches to reduce emissions of PFAS that are present in products.

The OECD has developed a Portal on PFAS to facilitate information exchange and to support the global transition towards safer alternatives. Through this Portal, governments and industries can share information on activities related to regulatory and stewardship efforts, updates on scientific developments, new technologies, available alternatives, and PFAS-related events. In 2017, the OECD developed a non-exhaustive list of 4730 PFAS, including Chemical Abstract Service registry numbers, as part of a new Comprehensive Global Database on PFAS. The compilation of the list utilized publicly accessible information sources, including lists from national or international regulatory bodies, public national/regional inventories of chemicals and chemicals in specific uses, national/regional inventories of chemicals subject to specific regulations, and scientific databases. Canada, the United States, and the European Union were

major contributing sources of PFAS data to the database (OECD 2018a). As indicated in section 1.1 (Chemical Scope), this organization also authored the reference and guidance document *Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance* (OECD 2021).

8.2.3 United States of America

In October 2021, a government-wide approach[7] to address current and future PFAS contamination was announced, which included the *US EPA PFAS Strategic Roadmap* (US EPA 2021e), designed to guide the agency's activities on PFAS through to 2024. Under the roadmap, the US EPA has proposed to take a number of actions including measures under their new chemicals program, adding certain PFAS to their Toxics Release Inventory, and proposing a data gathering rule. The US EPA also recently published its *National PFAS Testing Strategy*, which uses a stepwise testing approach to identify and select candidate PFAS for further testing by developing categories of PFAS on the basis of similarities in structure, physicochemical properties, existing toxicity data, and current manufacturing implications (US EPA 2021f). The information from these candidates may be extrapolated to characterize the hazard potential of their broader corresponding group.

The US approach also includes actions by the Department of Defense to address their PFAS-contaminated sites, by the Food and Drug Administration to expand testing of the food supply, by the Department of Agriculture to support research, by the Department of Homeland Security to inventory their PFAS uses and releases and to consider actions related to emergency responders. Research by a number of other US agencies was announced. These agencies have also established the Interagency Policy Committee on PFAS, which will work to coordinate and help develop new policy strategies to support research, remediation, and removal of PFAS in communities across the country.

The United States also has a number of actions that address PFAS in drinking water, such as the *Fifth Unregulated Contaminant Monitoring Rule* to collect new data on 29 PFAS in drinking water (US EPA 2021g), and is moving forward with developing a national primary drinking water standards under the *Safe Drinking Water Act for PFOA and PFOS*.

In 2016, the US FDA revoked a number of authorizations for LC-PFAS in food packaging. A voluntary phase-out of 6:2 FTOH was announced by the FDA in 2020. Beginning in 2021, the three remaining manufacturers agreed to a 3-year phase-out of sales of compounds containing 6:2 FTOH as a food contact substance. In 2019, a fourth manufacturer discontinued US sales of food contact materials that contain 6:2 FTOH. In an effort to help federal purchasers identify and procure environmentally preferable products and services, the US EPA (2022) recommends the Biodegradable Products Institute's (BPI) certification standard of 100 ppm total fluorine for food service ware (containers, cutlery, dishware) and trash bags. The BPI certification scheme states that organic fluorinated chemicals, such as PFAS, cannot be present in formulas for BPI

[7] FACT SHEET: Biden-Harris Administration Launches Plan to Combat PFAS Pollution

Certified items.[8] The 100 ppm limit acknowledges that PFAS may be incorporated into some products unintentionally.

At the state level, contamination of drinking water has led many states including Arkansas, California, Colorado, Illinois, Indiana, Kentucky, Maine, Maryland, Louisiana, Michigan, Minnesota, Nevada, New Hampshire, Vermont, Washington, West Virginia, and Wisconsin to prohibit the use of firefighting foams (AFFF) containing any type of PFAS (Safer States 2021). Many states have also taken action to prohibit the use of PFAS in food packaging including Maine, New York, Minnesota, Vermont, and Washington.

Some states have taken broader measures on PFAS, for example:

- California
  - Prohibition of the use of all PFAS in products for juveniles (under 12 years old) by 2023 (State of California 2021a)
  - Prohibition of the use of all PFAS in certain food packaging and imposition of disclosures for cookware by 2023 (State of California 2021b)
  - Prohibition of all PFAS from cosmetics by 2025 (State of California 2022)
- Maine
  - Reporting and removal of most PFAS in products will start in 2023 with a complete ban of all non-essential uses by 2030 (State of Maine 2021)
- Vermont
  - Prohibition of PFAS from consumer products (carpets, rugs, aftermarket treatments, and ski waxes) and food packaging by 2024 (State of Vermont 2021)
- Maryland
  - Prohibition of 13 PFAS from cosmetics by 2025 (State of Maryland 2021)

8.2.4 European Union

Like Canada, the European Union (EU) and its member States, except for Italy, are Parties to the Stockholm Convention on POPs.

Restrictions are currently in place in the EU for PFOS and PFOA, while restrictions on LC-PFCAs (European Commission 2021) will be coming into force in phases from 2023 through 2025. In addition, the EU is currently evaluating restrictions on PFHxA[9] and PFHxS.[10]

Certain PFAS are listed on the EU's *Registration, Evaluation, Authorisation and Restriction of Chemicals* (REACH) list of Substances of Very High Concern (SVHCs), including PFBS[11] and HFPO-DA (the ammonium salt of HFPO-DA is commonly known as GenX).[12]

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[8] BPI - Fluorinated Chemicals

[9] Registry of restriction intentions until outcome - Undecafluorohexanoic acid (PFHxA), its salts and related substances

[10] Registry of restriction intentions until outcome - Perfluorohexane-1-sulphonic acid, its salts and related substances

[11] Registry of SVHC intentions until outcome - Perfluorobutane sulfonic acid (PFBS) and its salts

[12] MSC unanimously agrees that HFPO-DA is a substance of very high concern

In October 2020, the European Commission published a plan entitled *Chemical Strategy for Sustainability Towards a Toxic-Free Environment* (European Commission 2020b), which outlines their intent to ban all PFAS as a group in firefighting foams as well as in other uses, allowing their use only where they are essential for society. This objective is based upon the large number of cases of contamination of soil and water, including drinking water, the unacceptable risks to both the environment and human health, and the related societal and economic costs. Other measures that the EU has committed to include working on PFAS through international fora and under other legislation on water, sustainable products, food, industrial emissions, and waste; supporting research and innovation for remediating PFAS contamination, and developing safe substitutes to PFAS.

In January 2022, ECHA submitted a proposal for an EU-wide restriction on all PFAS in firefighting foams for consideration by the scientific Committees for Risk Assessment and Socio-Economic Analysis and for comment.[13]

The EU has also published a PFAS restriction proposal that aims to reduce PFAS emissions into the environment; this proposal started a 6-month consultation on 22nd March 2023 (ECHA 2023).

8.2.5 Australia and New Zealand

Like Canada, Australia and New Zealand are Parties to the Stockholm Convention on POPs.

Australia does not generally ban or restrict industrial chemicals at the federal level; rather, these risk management actions fall under the jurisdiction of the state or territory. In 2018, South Australia banned fluorinated firefighting foams with a transition period, which ended January 2020. The Australian government has developed drinking water quality and recreational water guidance values for PFOS, PFOA, and PFHxS. The PFAS National Environmental Management Plan (Heads of EPA Australia and New Zealand 2020) provides the federal, state, and territory governments with a risk-based framework for the regulation of PFAS-contaminated sites and materials, and an intergovernmental agreement provides further specific guidance on actions as PFAS-contaminated sites (Council of Australian Governments 2020). The Australian government is also supporting research into PFAS exposure, health effects, and new remediation treatments.

In New Zealand, both PFOS and PFOA were banned in 2006, with an exemption for use in firefighting foams. However, since 2020, the import, manufacture, and use of PFOS and PFOA have been banned without any exemptions.

8.2.6 International scientific statements

Various groups of academic and government scientists and international bodies have issued statements proposing recommendations related to the current state of science, regulation, and environmental release of PFAS. The Helsingør, Madrid, and Zürich Statements are short

[13] Registry of restriction intentions until outcome - Per- and polyfluoroalkyl substances (PFAS)

publications resulting from expert meetings regarding PFAS (Scheringer et al. 2014; Blum et al. 2015; Ritscher et al. 2018). Signatories to these statements consist of a significant number of scientists, largely from international academic institutions.

The *Helsingør Statement on poly- and perfluorinated alkyl substances (PFASs)* (Scheringer et al. 2014) described the ubiquity of PFAS in the environment, lack of information on them, potential risks of the transition from regulated PFAS to fluorinated alternatives, lack of current regulatory oversight for fluorinated alternatives, and potential risks resulting from increasing exposure due to the stability of PFAS and perfluorinated transformation products in the environment. The Statement also called for the restriction of PFAS to essential applications only. The *Madrid Statement on Poly- and Perfluoroalkyl Substances (PFASs)* (Blum et al. 2015) built upon the concerns outlined in the Helsingør Statement, calling on the international community to limit PFAS production and use, and made specific recommendations to scientists, governments, chemical and product manufacturers, businesses and organizations, and consumers. The *Zürich Statement on Future Actions on Per- and Polyfluoroalkyl Substances (PFASs)* (Ritscher et al. 2018) also echoed the concerns of the two aforementioned statements, making a series of recommendations to help reduce and restrict the use of PFAS.

Taken as a whole, the statements describe challenges related to assessing and managing human and ecological exposure to the extensive class of PFAS and concerns about short-chain replacements for long-chain PFAS. Recommendations have been issued on cooperative actions and strengthening the science-policy approaches regarding PFAS. Many of these elements speak to taking a preventative and precautionary approach for this class of substances.

9 Findings

KEY POINTS ON FINDINGS

- PFAS have extreme environmental persistence and long-range transport properties, which are resulting in widespread long-term exposure.
- Multiple PFAS are widely present and co-occur in the environment, wildlife, and humans across Canada, including in remote regions such as the Arctic and Subarctic.
- Certain well-studied PFAS have been shown to bioaccumulate and are associated with hazardous effects in various organisms, including humans.
- PFAS are very challenging to remove from different environmental media. Due to the poorly reversible contamination of most environmental compartments, accumulation of PFAS within humans, biota, and the environment will continue to increase in the absence of intervention.
- While a small number of PFAS have received the majority of study, there is a growing body of evidence suggesting that concerns identified for these well-studied substances are more broadly applicable than previously believed. Additionally, cumulative effects from co-exposure may occur.
- Chemicals management of PFAS is difficult due to the large number of substances implicated and the exceptionally wide range of associated uses.
- As research to fully address the gaps in information for less-studied PFAS cannot realistically be conducted in a time frame that prevents further environmental releases,

a precautionary, class-based approach to addressing PFAS is needed to protect the environment and people from anticipated adverse effects.

The large number of substances (section 1) and wide spectrum of associated uses (section 2.1) within the broad PFAS class are challenging from a chemicals management standpoint. The use of large quantities of PFAS in a very wide range of applications, including but not limited to food packaging, drugs, cosmetics, textiles, vehicles and electronics, industrial lubricants, and AFFF, continues to add to environmental loading and human exposure. In combination with their extreme stability or transformation to other stable PFAS, the net effect of continued environmental release is that both direct human and environmental exposure will occur on a long-term basis. The result of this irreversible or at best poorly reversible contamination (ECHA 2022a) will be the continued accumulation of PFAS within humans, biota, and the environment.

Exposure to PFAS is further magnified by these substances' mobility (section 3.2.4) and long-range transport potential (section 3.2.5). As certain neutral PFAS are highly mobile in air (e.g., fluorotelomers) and ionized forms are mobile in water (e.g., PFAAs), PFAS can be transported over long distances and dispersed over large areas, resulting in global distribution. Additionally, some shorter-chain PFAS adopted in place of prohibited long-chain PFAS have proven to be even more mobile on a local scale, potentially implicating transfer to food crops and drinking water.

The combination of the extreme persistence, mobility allowing local migration, and long-range transport potential of PFAS in the environment has resulted in widespread PFAS exposure in a variety of ecosystems across Canada, as well as in biota and humans as supported by available monitoring data (sections 4 and 5). Environmental concentrations are highest in proximity to sources of release but are also of concern in remote regions far removed from areas of production and use, including the Canadian Arctic and Subarctic, due to long-range transport including in rainwater (section 4.1). Canadian human biomonitoring surveys have noted the near ubiquity of PFOS and PFOA in human plasma (section 5.4), indicating their ongoing presence. Additionally, certain PFAS have been found in significantly higher concentrations in certain Indigenous or northern communities compared with the rest of the Canadian population. Furthermore, certain shorter-chain PFAS with relatively rapid elimination in humans have shown high detection frequencies in humans in some international human biomonitoring data sets (e.g., Poothong et al. 2017), also suggesting ongoing exposure. As monitoring has and continues to be focused on a relatively small fraction of the existing PFAS, the full extent of exposure to PFAS is unknown.

Although data have largely been generated for a limited suite of well-studied substances, there is a growing body of evidence linking certain PFAS to toxic effects in both wildlife and humans. Data for wildlife are largely focused on a small group of species (e.g., fish, aquatic invertebrates; section 6); however, PFAS have been shown to bioaccumulate and cause toxicological effects in various organisms. Apical (e.g., growth, reproduction, development) and mechanistic (e.g., immunotoxicity, neurotoxicity) endpoint effects have been reported in the literature, with some species being more susceptible to harm. For instance, PFAS have been reported to possess a

high potential for biomagnification in air-breathing organisms (e.g., mammals, birds), which can increase the likelihood of adverse effects. Some PFAS have also been shown to be readily absorbed in humans, and can accumulate due to slow elimination and/or ongoing exposure. Similar to patterns of toxicity observed in wildlife, effects have been noted in multiple human systems and organs including the liver, immune system, reproduction, development, endocrine disruption (thyroid), and metabolism (section 7).

Despite the fact that the majority of substances and groups within the PFAS class are data poor, concerns surrounding the well-studied PFAS have frequently led to regulatory attention (section 8). For example, in Canada, PFOS, PFOA, and LC-PFCAs have all been concluded toxic under CEPA and have been prohibited (with a limited number of exemptions). Internationally, PFOS and PFOA have been listed, and LC-PFCAs (along with their salts and related compounds) have been nominated for listing as Persistent Organic Pollutants under the Stockholm Convention. Due in part to various regulatory actions worldwide on PFOA and PFOS, other PFAS (e.g., SC-PFCAs, SC-PFSAs) have been introduced as replacements. Initially, shorter-chain replacement substances were thought to have an overall lower bioaccumulation and toxicity potential on the basis of standard toxicity test results for freshwater aquatic test species such as fish, daphnia, and algae. However, concerns are increasingly being identified for a number of individual and/or groups of short-chain PFAS as they become more data rich and as data for other species, including mammals, become available. Recently, PFHxS (used in some cases as a substitute for PFOS, as well as in other applications) along with its salts and related compounds has been accepted for addition to the Stockholm Convention. Another replacement, PFBS, has been identified as a Substance of Very High Concern under REACH, as has HFPO-DA, its salts and its acyl halides (the ammonium salt of HFPO-DA is commonly known as GenX). In certain applications, these substances are used as replacements for PFOS and PFOA, respectively.

Despite these developments, significant gaps in information for the majority of PFAS remain. Although information on some other PFAS is becoming available (e.g., ECCC 2023), conducting the research to fully address the gaps in information to characterize the large and constantly increasing number of PFAS on a substance-by-substance or group-by-group basis would require an extremely long timeframe, during which exposures to humans and the environment would continue to increase, and new PFAS may be created or used in Canada. Filling data gaps in a sufficiently short time frame to appropriately address these substances through traditional approaches is not a feasible way to prevent ongoing and long-term future exposure.

Additionally, while laboratory studies have typically involved individual PFAS, environmental sampling and biomonitoring results indicate concurrent exposure of humans and biota to multiple PFAS. Many commercial precursors can transform to stable acids, further contributing to this combined exposure. Currently, the hazards of exposure to multiple PFAS are largely unknown, and the limited studies that have examined interactive effects have yielded complex results, including synergism, antagonism, and additivity, depending on the experimental conditions. Given the likelihood of concurrent exposure to multiple PFAS and the potential for cumulative effects, managing these substances as a class of compounds has received much attention (e.g., Bil et al. 2021; ECHA 2023; ECHA 2022a; EFSA 2020; HBM4EU 2019).

Addressing PFAS as a class of chemicals would also reduce the chance of regrettable substitution, support more holistic research and monitoring programs, and provide an opportunity to decrease future PFAS release to the environment.

The most efficient method to reduce PFAS concentrations in many receiving media, and the only method to reduce PFAS concentrations in ambient environmental media, continues to be upstream management and minimization. Accordingly, scientists, regulators, and other international organizations have increasingly advocated or undertaken new approaches to addressing PFAS (section 8.2). Debates on how to best define the scope of PFAS are appearing in the scientific literature (e.g., Kwiatkowski et al. 2020, 2021; Singh and Papanastasiou 2021). Recognizing the current state of the available science and ongoing environmental release of PFAS, various groups of academic and government scientists have also issued statements (e.g., Helsingør [Scheringer et al. 2014]; Madrid [Blum et al. 2015]; Zürich [Ritscher et al. 2018]), proposing approaches that include calls for the use of precaution and restrictions on the uses of PFAS. Among the international community, the United States has recently announced a government-wide approach to address current and future PFAS contamination. In support of this initiative, a group of 67 experts issued a letter to the US EPA advocating for a class-based approach to the regulation of PFAS and the elimination of new and non-essential uses (Birnbaum et al. 2021). Additionally, the EU has published a PFAS restriction proposal that started a 6-month consultation on 22nd March 2023 (ECHA 2023). The underlying context of this approach is the application of precaution due to the scale of current scientific uncertainty surrounding lesser-studied PFAS.

As a result of the extreme persistence of PFAS (increasingly referred to as “forever chemicals”), their potential for bioaccumulation in organisms and biomagnification through the food chain, their ability to move locally and over long ranges, and challenges in their remediation from contaminated sites and impossibility of their removal from the broader environment, environmental concentrations and uptake by humans and other biota will increase in the absence of intervention. While there are considerable challenges to understanding the characteristics of substances across the range of PFAS structures, there is a growing body of evidence suggesting that concerns identified for well-studied PFAS are more broadly applicable than previously believed. Additionally, recent studies suggesting the widespread environmental presence of and combined exposure to multiple PFAS, detection of novel PFAS in the environment, and a lack of understanding of cumulative effects suggest that the potential for adverse effects indicated by studies focusing on individual or limited suites of PFAS may be underestimated.

While there is limited information available across the class of PFAS, the following is known on the basis of current information:

- The broad use of PFAS and their ubiquitous presence in the environment have resulted in continuous environmental and human exposure to multiple PFAS as supported by both environmental monitoring and human biomonitoring studies, including higher exposures in certain human subpopulations.

- Environmental concentrations of PFAS are expected to continue to increase due to ongoing entry to the environment as PFAS are both extremely persistent in the environment and mobile, possessing local and long-range-transport capabilities.
- Well-studied PFAS can adversely affect multiple systems and organs in both humans and wildlife. Recent information demonstrates human health effects at lower levels than indicated by previous studies.
- Some well-studied PFAS have demonstrated the potential to bioaccumulate and biomagnify in food webs to an extent that can cause adverse effects in biota, even at low environmental concentrations.
- Potential for cumulative exposure and effects are important considerations as most human and wildlife exposures are to an unknown mixture of PFAS.

Despite uncertainties associated with understanding the characteristics of substances across the range of PFAS structures from toxicological, epidemiological and monitoring datasets that are focused on a limited number of PFAS, there is a growing body of evidence suggesting that concerns identified for well-studied PFAS are more broadly applicable than previously believed. Similarly, while the specific hazards associated with mixtures of PFAS are largely unknown, there are many potential sources of PFAS that can lead to exposure and it is reasonable to assume that cumulative effects may occur from exposure to multiple PFAS.

Consistent with application of precautionary assumptions that are protective of human health and the environment when addressing gaps in information, it is necessary to anticipate that hazardous properties identified for PFAS that have been well studied may also be inherent in other substances in the class, and that combined exposure to multiple PFAS increases the likelihood of detrimental impacts.

Owing to the extreme persistence of these substances, impacts on the environment are expected to increase if entry to the environment continues. On the basis of what is known about well-studied PFAS and the potential for other PFAS to behave similarly, it is proposed that the class of PFAS meets the criteria under paragraph 64(*a*) of CEPA as these substances are entering or may enter the environment in a quantity or concentration or under conditions that have or may have immediate or long-term harmful effects on the environment or its biological diversity. However, it is proposed to conclude that the class of PFAS does not meet the criteria under paragraph 64(*b*) of CEPA as these substances are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends.

Owing to the widespread use of PFAS combined with their ubiquitous presence in the environment, humans are continuously exposed to multiple PFAS, which have the potential to cause adverse effects of concern. On the basis of what is known about well-studied PFAS and the potential for other PFAS to behave similarly, and on the expectation that combined exposures to multiple PFAS increase the likelihood of detrimental impacts, it is proposed that the class of PFAS meets the criteria under paragraph 64(*c*) of CEPA as these substances are entering or may enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that the class of PFAS meets one or more of the criteria set out in section 64 of CEPA.

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11 Appendix A: Frequently used PFAS acronyms

Table A-1. Frequently used PFAS acronyms in the State of PFAS Report

Subgroup	CAS RN	Acronym[a]	Name
Perfluorocarboxylic acid (PFCA)	375-22-4	PFBA (C4)	Perfluorobutanoic acid
PFCA	2706-90-3	PFPeA (C5)	Perfluoropentanoic acid
PFCA	307-24-4	PFHxA (C6)	Perfluorohexanoic acid
PFCA	375-85-9	PFHpA (C7)	Perfluoroheptanoic acid
PFCA	335-67-1	PFOA (C8)	Perfluorooctanoic acid
PFCA	375-95-1	PFNA (C9)	Perfluorononanoic acid
PFCA	335-76-2	PFDA (C10)	Perfluorodecanoic acid
PFCA	2058-94-8	PFUnDA (C11)	Perfluoroundecanoic acid
PFCA	307-55-1	PFDoDA (C12)	Perfluorododecanoic acid
PFCA	72629-94-8	PFTrDA (C13)	Perfluorotridecanoic acid
PFCA	376-06-7	PFTeDA (C14)	Perfluorotetradecanoic acid
PFCA	67905-19-5	PFHxDA (C16)	Perfluorohexadecanoic acid
PFCA	16517-11-6	PFOcDA (C18)	Perfluorooctadecanoic acid
Perfluorosulfonic acid (PFSA)	NA	PFEtS (C2)	Perfluoroethane sulfonic acid
PFSA	423-41-6	PFPrS (C3)	Perfluoropropane sulfonic acid
PFSA	375-73-5	PFBS (C4)	Perfluorobutane sulfonic acid
PFSA	2706-91-4	PFPeS (C5)	Perfluoropentane sulfonic acid
PFSA	355-46-4	PFHxS (C6)	Perfluorohexane sulfonic acid
PFSA	375-92-8	PFHpS (C7)	Perfluoroheptane sulfonic acid
PFSA	1763-23-1	PFOS (C8)	Perfluorooctane sulfonic acid
PFSA	335-24-0	PFECHS (C8)	Perfluoroethylcyclohexane sulfonic acid
PFSA	68259-12-1	PFNS (C9)	Perfluorononane sulfonic acid
PFSA	335-77-3	PFDS (C10)	Perfluorodecane sulfonic acid
PFSA	79780-39-5	PFDoS (C12)	Perfluorododecane sulfonic acid
Perfluoroalkyl phosphonic acid (PFPA)	40143-76-8	C6 PFPA	Perfluorohexyl phosphonic acid
PFPA	40143-78-0	C8 PFPA	Perfluorooctyl phosphonic acid
PFPA	52299-26-0	C10 PFPA	Perfluorodecyl phosphonic acid
Perfluoroalkyl phosphinic acid (PFPiA)	40143-77-9	C6/C6 PFPiA	Bis(tridecafluorohexyl)phosphinic acid
PFPiA	610800-34-5	C6/C8 PFPiA	(Heptadecafluorooctyl)(tridecafluorohexyl) phosphinic acid
PFPiA	40143-79-1	C8/C8 PFPiA	Bis(heptadecafluorooctyl)phosphinic acid
PFPiA	NA	C6/C10 PFPiA	Perfluorohexylperfluorodecyl phosphinic acid

PFPiA	NA	C8/C10 PFPiA	Perfluorooctylperfluorodecylphosphinic acid
PFPiA	NA	C6/C12 PFPiA	Perfluorohexylperfluorododecyl phosphinic acid
Per- and polyfluoroalkyl ether carboxylic acid (PFECA)	958445-44-8	ADONA	Ammonium 4,8-dioxa-3H-perfluorononanoate
PFECA	62037-80-3	GenX	Ammonium, 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoate
PFECA	908020-52-0	EEA-NH4	Ammonium difluoro[1,1,2,2-tetrafluoro-2-(pentafluoroethoxy)ethoxy]acetate
PFECA	13252-13-6	HFPO-DA	Hexafluoropropylene oxide dimer acid
PFECA	39492-90-5	PFO4DA	Perfluoro-3,5,7,9-butaoxadecanoic acid
PFECA	39492-91-6	PFO5DA	Perfluoro-3,5,7,9,11-pentaoxadodecanoic acid
Per- and polyfluoroalkyl ether sulfonic acid (PFESA)	73606-19-6	6:2 Cl-PFESA (F-53B)	6:2 Chlorinated polyfluorinated ether sulfonate
PFESA	763051-92-9	11Cl-PF3OUdS	11-chloroeicosafluoro-3-oxaundecane-1-sulfonic acid
Perfluoroalkane sulfonamide (FASA)	30334-69-1	PBSA	Perfluorobutane sulfonamide
FASA	754-91-6	PFOSA or FOSA	Perfluorooctane sulfonamide
FASA	2806-24-8	FOSAA	Perfluorooctane sulfonamido acetic acid
FASA	31506-32-8	N-MeFOSA	N-methylperfluorooctane sulfonamide
FASA	2355-31-9	N-MeFOSAA	N-methylperfluorooctane sulfonamido acetic acid
FASA	24448-09-7	MeFOSE	N-methyl perfluorooctane sulfonamide ethanol
FASA	4151-50-2	N-EtFOSA	N-ethylperfluorooctane sulfonamide
FASA	2991-50-6	N-EtFOSAA	N-ethylperfluorooctane sulfonamido acetic acid
FASA	2355-31-9	MePFOSA-AcOH	2-(N-methyl-perfluorooctane sulfonamide) acetic acid
FASA	2991-50-6	EtPFOSA-AcOH	2-(N-ethyl-perfluorooctane sulfonamido) acetic acid
FASA	1691-99-2	EtFOSE	N-ethyl perfluorooctane sulfonamido ethanol
n:2 Fluorotelomer alcohol (FTOH)	647-42-7	6:2 FTOH	6:2 Fluorotelomer alcohol
n:2 FTOH	678-39-7	8:2 FTOH	8:2 Fluorotelomer alcohol
n:2 FTOH	865-86-1	10:2 FTOH	10:2 Fluorotelomer alcohol

n:2 FTOH	17527-29-6	6:2 FTAc	6:2 Fluorotelomer acrylate
n:2 Fluorotelomer sulfonic acid (FTSA)	757124-72-4	4:2 FTSA	4:2 Fluorotelomer sulfonic acid
n:2 FTSA	27619-97-2	6:2 FTSA	6:2 Fluorotelomer sulfonic acid
n:2 FTSA	39108-34-4	8:2 FTSA	8:2 Fluorotelomer sulfonic acid
Polyfluoroalkyl phosphate ester (PAP)	57678-01-0	6:2 monoPAP	6:2 Fluorotelomer phosphate monoester
PAP	57678-03-2	8:2 monoPAP	8:2 Fluorotelomer phosphate monoester
PAP	135098-69-0	4:2 diPAP	4:2 Fluorotelomer phosphate diester
PAP	57677-95-9	6:2 diPAP	6:2 Fluorotelomer phosphate diester
PAP	943913-15-3	6:2/8:2 diPAP	6:2/8:2 Fluorotelomer phosphate diester
PAP	678-41-1	8:2 diPAP	8:2 Fluorotelomer phosphate diester
PAP	1895-26-7	10:2 diPAP	10:2 Fluorotelomer phosphate diester
Fluoropolymer	9002-84-0	PTFE	Polytetrafluoroethylene

Abbreviations: NA, not available.

[a] The acronyms for the PFCAs and PFSAs could represent either the acid or anionic forms of the chemicals.

12 Appendix B: Biomonitoring data - tables

Table B-1. Detection frequency (%) of PFAS in human blood from national, regional, or small-scale and birth-cohort studies (part 1)

Substance[a]	Canada[b]	Canada[c]	US[d]	France[e]	Sweden[f]	US[g]	US[h]
PFBA	5.4	0		1.1	67.7	67.7	0
PFHxA	1	0	NR	0	-	98	98
PFHpA	-	-	-	2.8	4.4	43.3	20.2
PFOA	100	99.6	99	100	99.3	98.6	100
PFNA	98.5	96.2	93	99.5	100	92.2	99
PFDA	67.6	60.8	89	89.2	100	65.9	87.9
PFUnDA	36.3	62.4	66	99.5	97.8	58.4	98
PFDoDA	-	-	-	22.3	23	0.3	52.5
PFTrDA	-	-	-	-	-	-	-
PFTeDA	-	-	-	-	-	0	-
PFBS	0.3[16]	0	NR	0	-	10.9	3
PFHxS	99.6	94.3	99	99.6	100	99.7	100
PFHpS	-	-	NR	53.4	-	-	-
PFOS	99.3	98.9	99	100	100	98.3	100
PFDS	-	-	-	0.4	-	59.6	59.6
PFOSA	-	-	-	0.4	-	19.8	3
EtPFOSAA	-	-	-	2.2	-	19.3	3
MePFOSAA	-	-	59	24.6	-	78.8	97
6:2 diPAP	-	-	-	-	-	-	2
6:2 monoPAP	-	-	-	-	-	-	-
PFHxPA	-	-	-	-	-	0	0

[a] Note that other PFAS were measured in the studies listed in this table, but detection frequencies were below 10%. These PFAS include PFPeA, PFOPA, PFHxDA, PFODA, FOSAA, 5:3 FTCA, 6:2 FTCA, 7:3 FTCA, 8:2 FTCA, 6:2 FTUCA, 8:2 FTUCA, ADONA, GenX, 4:2 Cl-PFESA, 8:2 diPAP, 8:2 diPAP, 8:2 monoPAP, 4:2 FtS, 6:2 FtS, 8:2 FtS, 9Cl-PF3ONS, 11Cl-PF3OUdS, HFPO-DA, 7H-PFHpA, 6:6 PFPiA, 6:8 PFPiA, NVHOS, PMPA, PEPA, Nafion by-product 1, PFO2HxA, and PFO3OA. Certain other PFAS precursors detected in studies conducted near industrial sources or contaminated sites were not included in this table as they do not represent general population exposure.
[b] Detection frequencies. Canadian Health Measures Survey (CHMS) cycle 6 2018–2019, Canadian total population (plasma, 3–79 years, n=2354–2514).
[c] % >LOD (limit of detection). Indigenous on-reserve and crown land populations in Canada 2011, Canadian adults (plasma, 20+ years, n=473) (AFN 2013).
[d] Detection frequencies. National Health and Nutrition Examination Survey (NHANES) 2017–2018, US total population (serum, n=1929).
[e] % >LOQ (limit of quantitation). France 2014–2016, Esteban Study (nationwide), adults (serum, 18–74 years, n=744) (Fillol et al. 2021).
[f] % >LOD. Sweden 2010–2011, subgroup of Riksmaten (Swedish national survey of dietary habits among adults), adults (serum, 18–80, n=270) (Bjermo et al. 2013).
[g] Detection frequencies. Biomontoring California (2020). California regional exposure study, Region 2 (CARE-2) adults (serum, 18+ years, n=359) (Biomonitoring California 2020).
[h] Detection frequencies. Biomonitoring California (2020), Asian/Pacific Islander Community exposures (ACE) Project –ACE 2, regional Asian-Pacific islander community adults (serum, 18+ years, n=99) (Biomonitoring California 2020).

Table B-1: Detection frequency (%) of PFAS in human blood from national, regional, or small-scale and birth-cohort studies (part 2)

Substance[a]	S. Korea[b]	Germany[c]	Germany[d]	Norway[e]	Greenland[f]	Faroe Islands[g]	Japan[h]
PFBA	0	-	-	-	-	4	-
PFHxA	-	0	-	0	0	0	38
PFHpA	-	5	-	-	0	18	32.8
PFOA	92	100	100	100	100	100	99.9
PFNA	94	100	56	100	100	100	99.5
PFDA	-	26	1.89	100	100	100	99.1
PFUnDA	-	1	-	95	99	98	99.6
PFDoDA	-	0	0	98	0	0	88.4
PFTrDA	-	0	-	89	0	-	96.6
PFTeDA	-	-	-	97	0	-	13.1
PFBS	-	0	0	51	0	0	-
PFHxS	99	100	98	100	100	100	80.9
PFHpS	-	6	-	100	75	92	-
PFOS	100	100	100	100	100	100	100
PFDS	-	0	-	77	0	33	-
PFOSA	89	0	-	97	0	6	-
EtPFOSAA	-	0	-	-	-	24	-
MePFOSAA	-	2	-	-	-	78	-
6:2 diPAP	-	0	-	49	-	-	-
6:2 monoPAP	-	-	-	41	-	-	-
PFHxPA	-	-	-	62	-	-	-

[a] Note that other PFAS were measured in the studies listed in this table, but detection frequencies were below 10%. These PFAS include PFPeA, PFOPA, PFHxDA, PFODA, FOSAA, 5:3 FTCA, 6:2 FTCA, 7:3 FTCA, 8:2 FTCA, 6:2 FTUCA, 8:2 FTUCA, ADONA, GenX, 4:2 Cl-PFESA, 8:2 diPAP, 8:2 diPAP, 8:2 monoPAP, 4:2 FtS, 6:2 FtS, 8:2 FtS, 9Cl-PF3ONS, 11Cl-PF3OUdS, HFPO-DA, 7H-PFHpA, 6:6 PFPiA, 6:8 PFPiA, NVHOS, PMPA, PEPA, Nafion by-product 1, PFO2HxA, and PFO3OA. Certain other PFAS precursors detected in studies conducted near industrial sources or contaminated sites were not included in this table as they do not represent general population exposure.
[b] Detection frequencies. South Korea 2006–2007, 3 regions (whole blood, 8–82 years, n=319) (Cho et al. 2015).
[c] Detection frequencies. Germany 2019, adults (students of Münster University) (plasma, 20–29 years, n=20) (Göckener et al. 2020).
[d] % >LOQ. Germany 2016, Munich (Site C, control area), adults (plasma, 18–67 years, n=158) (Fromme et al. 2017).
[e] % >MDL (median detection limit). Norway 2013–2014, adults living in Oslo, Norway (serum, 20–66 years, n= 61) (Poothong et al. 2017).
[f] % >DL (detection limit). Denmark (Greenland) 2010–2011, 2013, 2015, ACCEPT (Adapting to Climate Change, Environmental Pollution and Dietary Transition) birth cohort, pregnant Greenlandic Inuit women (serum, 18+ years, n=504) (Hjermitslev et al. 2020).
[g] Detection frequencies. Faroe Islands, 2012, children from birth Cohort 5 study (serum, 5 years old, n=51) (Dassuncao et al. 2018).
[h] % >MDL. Japan, Hokkaido study birth cohort, mother-child pairs (maternal plasma, 31 [mean], n=2206) (Bamai et al. 2020).

Table B-1. Summary of PFAS monitored in the Canadian Health Measures Survey (CHMS)

Cycle	Collection years	Age (years)	Biomarkers in plasma
Cycle 1	2007–2009	20–79	PFCAs: PFOA PFSAs: PFHxS, PFOS
Cycle 2	2009–2011	12–79	PFCAs: PFBA, PFHxA, PFOA, PFNA, PFDA, PFUnDA PFSAs: PFBS, PFHxS, PFOS
Cycle 5	2016–2017	3–79	PFCAs: PFBA, PFHxA, PFOA, PFNA, PFDA, PFUnDA PFSAs: PFBS, PFHxS, PFOS
Cycle 6	2018–2019	3-79	PFCAs: PFBA, PFHxA, PFOA, PFNA, PFDA, PFUnDA PFSAs: PFBS, PFHxS, PFOS

Table B-2. PFAS plasma concentrations (geometric means and 95th percentiles) and detection frequencies in CHMS cycles 1, 2, 5, and 6

Substance/ population	CHMS Cycle[a]	Year	LOD (µg/L)	DF (95% CI) or %>LOD[b]	GM (µg/L) (95% CI)[c]	95th (95% CI)	N
PFOA 3-79 years	Cycle 6	2018–2019	0.066	100	1.2 (1.1–1.3)	2.9 (2.6–3.3)	2513
PFOA 3-79 years	Cycle 5	2016–2017	0.066	100	1.3 (1.2–1.4)	3.1 (2.6–3.6)	2593
PFOA 20-79 years	Cycle 6	2018–2019	0.066	100	1.2 (1.1–1.3)	2.9 (2.6–3.3)	1019
PFOA 20-79 years	Cycle 5	2016–2017	0.066	100	1.3 (1.2–1.5)	3.2 (2.5–3.8)	1055
PFOA 20-79 years	Cycle 2	2009–2011	0.1	100	2.3 (2.1–2.5)	5.3 (3.9–6.7)	1017
PFOA 20-79 years	Cycle 1	2007–2009	0.3	99 (97.7–99.6)	2.5 (2.4–2.7)	5.5 (5.1–5.8)	2880
PFOS 3-79 years	Cycle 6	2018–2019	0.43	99.3 (98.6–99.7)	2.5 (2.3–2.8)	8.3 (7.2–9.4)	2514
PFOS 3-79 years	Cycle 5	2016–2017	0.43	99.9 (99.8–99.9)	3.0 (2.7–3.4)	11 (7.1–15)	2594
PFOS 20-79 years	Cycle 6	2018–2019	0.43	99.3 (98.3–99.7)	2.9 (2.7–3.1)	8.6 (6.9–10)	1020
PFOS 20-79 years	Cycle 5	2016–2017	0.43	99.9 (99.8–100)	3.4 (3.0–3.9)	13 (8.0–17)	1057
PFOS 20-79 years	Cycle 2	2009–2011	0.3	99.8	6.9 (6.2–7.6)	19 (13–25)	1017

				(99.1–99.9)			
PFOS 20-79 years	Cycle 1	2007–2009	0.3	99.9 (99.9–100)	8.9 (8.0–9.8)	27 (22–32)	2880
PFHxS 3-79 years	Cycle 6	2018–2019	0.063	99.6 (99.1–99.9)	0.76 (0.69–0.85)	4.0 (2.9–5.2)	2514
PFHxS 3-79 years	Cycle 5	2016–2017	0.063	99.7 (98.9–99.9)	0.90 (0.78–1.0)	5.3 [d] (1.8–8.7)	2595
PFHxS 20-79 years	Cycle 6	2018–2019	0.063	99.6 (98.9–99.9)	0.83 (0.75–0.93)	4.1 (3.2–5.1)	1020
PFHxS 20-79 years	Cycle 5	2016–2017	0.063	99.6 (98.6–99.9)	0.98 (0.85–1.1)	5.8 [d] (0.39–11)	1057
PFHxS 20-79 years	Cycle 2	2009–2011	0.2	98.4 (96.4–99.3)	1.7 (1.6–2.0)	8.9 [d] (4.6–13)	1015
PFHxS 20-79 years	Cycle 1	2007–2009	0.3	97.8 (96.2–98.8)	2.3 (2.0–2.6)	12 (9.2–15)	2880
PFNA 3-79 years	Cycle 6	2018–2019	0.13	98.5 (97.3–99.1)	0.44 (0.41–0.47)	1.2 (1.1–1.3)	2396
PFNA 3-79 years	Cycle 5	2016–2017	0.13	98.8 (97.1–99.5)	0.51 (0.45–0.57)	1.5 (1.2–1.8)	2442
PFNA 12-79 years	Cycle 6	2018–2019	0.13	98.4 (97.1–99.1)	0.44 (0.41–0.47)	1.2 (1.1–1.3)	1457
PFNA 12-79 years	Cycle 5	2016–2017	0.13	98.8 (96.9–99.6)	0.51 (0.45–0.58)	1.5 (1.2–1.8)	1497
PFNA 12-79 years	Cycle 2	2009–2011	0.2	99.4 (98.6–99.8)	0.82 (0.75–0.90)	1.9 [d] (1.1–2.7)	1524
PFDA 3-79 years	Cycle 6	2018–2019	0.092	67.6 (61.4–73.2)	0.12 (0.11–0.14)	0.51 (0.44–0.57)	2354
PFDA 3-79 years	Cycle 5	2016–2017	0.092	91.4 (86.0–94.8)	0.18 (0.16–0.20)	0.64 (0.47–0.81)	2360
PFDA 12-79 years	Cycle 6	2018–2019	0.092	69.0 (63.1–74.4)	0.12 (0.11–0.14)	0.51 (0.45–0.58)	1427
PFDA 12-79 years	Cycle 5	2016–2017	0.092	91.4 (85.9–94.9)	0.18 (0.16–0.21)	0.65 (0.45–0.84)	1450

PFDA 12-79 years	Cycle 2	2009–2011	0.1	79.3 (72.6–84.7)	0.20 (0.17–0.22)	0.66 (0.45–0.87)	1524
PFUnDA 3-79 years	Cycle 6	2018–2019	0.12	36.3 (29.2–44.0)	-	0.43 (0.34–0.53)	2508
PFUnDA 3-79 years	Cycle 5	2016–2017	0.12	35.8 (26.9–45.8)	-	0.46 (0.30–0.63)	2583
PFUnDA 12-79 years	Cycle 6	2018–2019	0.12	39.0 (31.3–47.2)	-	0.47 (0.35–0.60)	1527
PFUnDA 12-79 years	Cycle 5	2016–2017	0.12	38.5 (29.1–48.9)	-	0.50 (0.34–0.67)	1576
PFUnDA 12-79 years	Cycle 2	2009–2011	0.09	59.3 (47.5–70.0)	0.12 (0.098–0.14)	0.56 [d] (0.30–0.82)	1522
PFBA 3-79 years	Cycle 6	2018–2019	0.075	5.4 [d] (3.3–8.6)	-	0.078 (<LOD–0.091)	2509
PFBA 3-79 years	Cycle 5	2016–2017	0.075	4.2 [d] (2.3–7.7)	-	<LOD	2590
PFBA 12-79 years	Cycle 6	2018–2019	0.075	5.4 [d] (3.3–8.8)	-	<LOD	1525
PFBA 12-79 years	Cycle 5	2016–2017	0.075	3.8 [d] (1.8–7.8)	-	<LOD	1583
PFBA 12-79 years	Cycle 2	2009–2011	0.5	0.40 [d] (0.10–1.6)	-	<LOD	1524
PFHxA 3-79 years	Cycle 6	2018–2019	0.084	1.0 [d] (0.30–2.9)	-	<LOD	2512
PFHxA 3-79 years	Cycle 5	2016–2017	0.084	9.2 [d] (5.0–16.2)	-	0.13 [d] (<LOD–0.18)	2593
PFHxA 12-79 years	Cycle 6	2018–2019	0.084	1.0 [c] (0.30–3.0)	-	<LOD	1526
PFHxA 12-79 years	Cycle 5	2016–2017	0.084	9.2 [d] (4.9–16.4)	-	0.13 [d] (<LOD–0.18)	1583
PFHxA 12-79 years	Cycle 2	2009–2011	0.1	1.6 [d] (0.50–4.9)	-	<LOD	1524
PFBS 3-79 years	Cycle 6	2018–2019	0.066	0.30 [d] (0.10–0.80)	-	<LOD	2514
PFBS 3-79 years	Cycle 5	2016–2017	0.066	0.1 [d] (0.10–0.30)	-	<LOD	2584
PFBS 12-79 years	Cycle 6	2018–2019	0.066	0.20 [d] (0.10–0.70)	-	<LOD	1528

PFBS 12-79 years	Cycle 5	2016–2017	0.066	0.10 [d] (0–0.30)	-	<LOD	1577
PFBS 12-79 years	Cycle 2	2009–2011	0.4	0	-	<LOD	1524

LOD: limit of detection; DF: detection frequency; GM: geometric mean; n: number of samples/participants

[a] For the purpose of total population comparisons between cycles 1, 2, 5, and 6 for PFOA, PFOS, and PFHxS, only data from participants aged 20–79 years were included in the calculation of estimates as participants under the age of 20 years were not included in cycle 1 and participants under the age of 12 years were not included in cycle 2. For total population comparison between cycles 2 ,5, and 6 for PFNA,PFDA, PFUnDA, PFBA, PFHxA, and PFBS, only data from participants aged 12–79 years were included in the calculation of estimates as participants under the age of 12 years were not included in cycle 2.

[b] Cycles 1 and 2 calculated % <LOD to which % >LODs were extracted. Cycles 5 and 6 calculated detection frequencies.

[c] If >40% of samples were below the LOD, the percentile distribution was reported but means were not calculated.

[d] Value must be used with caution due to high variability.

Table B-3. PFAS levels in plasma/serum: females in CHMS (age 18–40), pregnant women from Nunavik (age 16–40), and pregnant women in MIREC (age 18–48)

Substance	Source	Year	Age (years)	LOD (µg/L)	DF or % >LOD*	GM (µg/L)	N
PFHxS	Women: CHMS Cycle 5 (plasma)[a]	2016–2017	18–40	0.063	99	0.44	243
PFHxS	Pregnant women: Nunavik (serum)[a]	2016–2017	16–40	0.04	100	0.27	97
PFHxS	Pregnant women: Nunavik (serum)[a]	2012	16–40	0.2	91.6	0.35	111
PFHxS	Pregnant women: MIREC (plasma)[b]	2008–2011	18–48	0.3	95	1.03	1940
PFOS	Women: CHMS Cycle 5 (plasma)[a]	2016–2017	18–40	0.43	100	1.80	243
PFOS	Pregnant women: Nunavik (serum)[a]	2016–2017	16–40	0.2	100	3.3	97
PFOS	Pregnant women: Nunavik (serum)[a]	2012	16–40	0.3	100	3.8	111
PFOS	Pregnant women: MIREC (plasma)[b]	2008–2011	18–48	0.3	100	4.56	1940
PFOA	Women: CHMS Cycle 5 (plasma)[a]	2016–2017	18–40	0.066	100	0.84	243
PFOA	Pregnant women: Nunavik (serum)[a]	2016–2017	16–40	0.03	100	0.54	97
PFOA	Pregnant women: Nunavik (serum)[a]	2012	16–40	0.07	100	0.67	111
PFOA	Pregnant women: MIREC (plasma)[b]	2008–2011	18–48	0.1	100	1.65	1940
PFNA	Women: CHMS Cycle 5 (plasma)[a]	2016–2017	18–40	0.13	98	0.38	220
PFNA	Pregnant women: Nunavik (serum)[a]	2016–2017	16–40	0.07	100	2.3	97
PFNA	Pregnant women: Nunavik (serum)[a]	2012	16–40	0.24	100	2.0	111
PFDA	Women: CHMS Cycle 5 (plasma)[a]	2016–2017	18–40	0.092	NR	0.16	222
PFDA	Pregnant women: Nunavik (serum)[a]	2016–2017	16–40	0.07	100	0.51	97
PFDA	Pregnant women: Nunavik (serum)[a]	2012	16–40	0.1	98.1	0.45	111
PFUnDA	Women: CHMS Cycle 5 (plasma)[a]	2016–2017	18–40	0.12	NR	NR	241
PFUnDA	Pregnant women: Nunavik (serum)[a]	2016–2017	16–40	0.05	100	0.54	97

PFUnDA	Pregnant women: Nunavik (serum)[a]	2012	16–40	0.1	91.8	0.44	111

LOD: limit of detection; DF: detection frequency; GM: geometric mean; N: number of samples/participants; NR: not reported

[*] % >LODs were presented for the Nunavik study in Caron-Beaudoin et al. (2020) and for the MIREC study in Fisher et al. (2016). DFs were presented from CHMS cycle 5 (HC 2019a; personal communication, email Population Studies Division, HC, to Existing Substance Risk Assessment Bureau, HC, May 2022; unreferenced). These values cannot be directly compared as DFs are weighted to be representative of population level detection.

[a] Caron-Beaudoin et al. 2020

[b] Fisher et al. 2016

Table B-4. PFNA levels in CHMS adults and children, Indigenous on-reserve populations, youth/children from Anishinabe and Innu communities, pregnant women from Nunavik, and adults from two other northern First Nations

Group	Specific Group	Year	Age (years)	LOD (µg/L)	DF or % >LOD [a]	GM (µg/L)	N
Adults	CHMS Cycle 2 (plasma) (HC 2013a; HC 2019a)	2009–2011	12–79	0.2	99.4	0.82	1524
Adults	Indigenous on–reserve (plasma) (AFN 2013)	2011	20+	0.2	96.2	0.72	473
Youth	CHMS Cycle 5 (plasma) (HC 2019a)	2016–2017	12–19	0.13	99.4	0.41	494
Youth	CHMS Cycle 2 (plasma) (HC 2013a; HC 2019)	2009–2011	12–19	0.2	99.1	0.71	507
Youth	Innu and Anishinabe (serum) (Caron-Beaudoin et al. 2019)	2015	12–19	0.07	100	1.18	76
Youth	Anishinabe only (serum) Caron-Beaudoin et al. 2019)	2015	12–19	0.07	100	3.01	38
Children	CHMS Cycle 5 (plasma) (HC 2019a)	2016–2017	6–11	0.13	98.7	0.45	492
Children	Anishinabe only (serum) (Caron-Beaudoin et al. 2019)	2015	6–11	0.07	100	9.44	45
Children	CHMS Cycle 5 (plasma) (HC 2019a)	2016–2017	3–5	0.13	99.3	0.45	453
Children	Anishinabe only (serum) (Caron-Beaudoin et al. 2019)	2015	3–5	0.07	100	3.8	23
Women	CHMS Cycle 5 (plasma) (Caron-Beaudoin et al. 2020)	2016–2017	18–40	0.13	NR	0.38	220
Pregnant women	Nunavik (serum) (Caron-Beaudoin et al. 2020)	2016–2017	16–40	0.07	100	2.3	97
Pregnant women	Nunavik (serum) (Caron-Beaudoin et al. 2020)	2012	16–40	NR	100	2.0	111
Adults	CHMS Cycle 5 (plasma) (HC 2019a)	2016–2017	12–79	0.13	98.8	0.51	1497

Adults	Dehcho, NWT (plasma) (Garcia-Barrios et al. 2021)	2017	20–79	0.01	100	1.42	109
Adults	Old Crow, Yukon (serum) (Garcia-Barrios et al. 2021)	2019	20–79	0.01	100	0.94	54
Adults	Nunavik, Quebec (plasma) (Aker et al. 2021)	2017	18+	0.10	100	3.7	500

LOD: limit of detection; DF: detection frequency; GM: geometric mean; n: number of samples/ participants; NR: not reported

[a] % >LODs were presented for AFN 2013, Caron-Beaudoin et al. (2019), and (2020) studies. DFs were presented for CHMS Cycle 1, 2, and 5, and the Garcia-Barrios et al. (2021) study. These values cannot be directly compared as DFs are weighted to be representative of population level detection.

13 Appendix C: Interpretation of biomonitoring data - tables

This Appendix presents data tables for Figures 7 to 9 presented in the Interpretation of HBM data section.

Table C-1. Geometric mean 25th, 75th, and 95th percentile of the sums of concentrations (in µg/L) of 4 PFAS in the serum/plasma of the general population of CHMS (3–79), women of reproductive age from CHMS, pregnant women and adults in Nunavik, children and youth from Anishinabe and Innu communities (only GM and 95th percentile values), and adults from Dene communities in the Dehcho region and a Gwich'in community

Study	N	GM[a]	P25	P75	P95
CHMS: women 18–40 (2018–2019)[b]	204	3.5	2.4	4.7	8.9[c]
CHMS: all ages (3–79) (2018–2019)	2396	5.4	3.4	8.3	16
Nunavik: pregnant women (2016–2017)[d]	97	6.8	4.4	9.7	20.6
Nunavik: adults (2017)[e]	500	11	6.5	17.1	37.3
Anishinabe/Innu (children/youth) (2015)[f]	186	5.31	-	-	16.77
Dehcho NWT: adults (2017)[g]	125	5.06	2.95	8.03	25.56
Old Crow Yukon: adults (2019)[g]	54	3.64	2.28	5.76	9.02

[a] Estimated from the sum of concentrations of PFOA, PFOS, PFHxS, and PFNA calculated for each participant in the studies (calculations are not shown)

[b] Canadian Health Measures Survey Cycle 6 (2018–2019), plasma, females, 18–40 years (the sum of PFAS concentrations was estimated using individual data from CHMS [personal communication, email Population Health Division, HC, to Existing Substances Risk Assessment Bureau, May 2022; unreferenced])

[c] Value must be used with caution due to high variability

[d] Pregnant women, serum, 16–40 years (Caron-Beaudoin et al. 2020)

[e] Adults, serum (18–80 years) (Aker et al. 2021)

[f] Children/youth (3–19 years) (Caron-Beaudoin et al. 2019)

[g] Adults (20–79 years) (Garcia-Barrios et al. 2021)

Table C-2. Geometric mean and 95th percentile of PFOA and PFOS serum/plasma concentrations (in µg/L) in the CHMS total population (3–79 years), Nunavik pregnant women (Caron-Beaudoin et al. 2020), Indigenous on-reserve and crown populations across Canada (AFN 2013), First Nations populations living in Dehcho (Northwest Territories) and Old Crow, Yukon (Garcia-Barrios et al. 2021), and Inuit adults of Nunavik, Quebec (Aker at al. 2021).

Study	N	PFOA GM (µg/L) (P95 (µg/L))	N	PFOS GM (µg/L) (P95 (µg/L))
CHMS 2018–2019[a]	2513	1.2 (2.9)	2514	2.5 (8.3)
Nunavik 2016–2017 (QC, pregnant women)[b]	97	0.53 (1.1)	97	3.3 (12.3)
FNBI 2011 (adults, 20+ years)[c]	473	1.4 (4.1)	473	3.1 (16)
Dehcho 2017 (NWT, 20–79 years)[d]	109	0.88 (3.1)	109	2 (8.6)
Old Crow 2019 (Yukon, 20–79 years)[e]	54	0.89 (1.85)	54	1.1 (4.1)
Nunavik 2017 (18+ years)[f]	500	1.1 (2.4)	500	5.1 (20.5)

[a] Canadian Health Measures Survey Cycle 6 2018–2019, plasma, total population, 3–79 years, n=2513 for PFOA, and n=2514 for PFOS (HC 2021b)

[b] Pregnant women, Nunavik, serum, 16–40 years, n=97 (Caron-Beaudoin et al. 2020)

[c] Adults, Indigenous on-reserve and crown land populations, plasma, 20+ years, n= 473 (AFN 2013)

[d] Adults, First Nations populations in Dehcho, Northwest Territories, plasma, 20–79 years, n=109 (Garcia-Barrios et al. 2021)

[e] Adults, First Nations populations in Old Crow, Yukon, serum, 20–79 years, n=54 (Garcia-Barrios et al. 2021)

[f] Adults, Inuit of Nunavik from 14 villages (Hudson and Ungava coast) in Quebec, plasma, 18+ years, n=500

14 Appendix D: Biomonitoring data in firefighters – tables

Table D-1. Firefighter serum levels (µg/L) for commonly measured PFAS (geometric means with confidence interval, if available) and comparison population information, including GM and upper CI of GM

Study [a, b]	PFHxA	PFHpA	PFOA	PFNA	PFDA	PFUnDA	PFBS	PFHxS	PFHpS	PFOS
1) Trowbridge et al. 2020 (female; mean age 47.5)	NR	NR	1.13 (1.05–1.25)	0.77 (0.61–0.74)	0.27 (0.23–0.28)	0.23 (0.14–0.22)	0.13 (0.1–0.16)	4.55 (3.24–4.43)	NM	4.33 (3.68–4.59)
Reference population: NHANES 2014–2015; female 20–60 years	-	-	1.2 (1.3)	0.47 (0.53)	0.13 (0.15)	NR	NM	0.71 (0.81)	-	3.1 (3.4)
Ratio of lower CI of GM from FF study / Upper CI of GM in reference population	-	-	0.8	1.2	1.5	NR	-	4.0	-	1.1
2) Shaw et al. 2013 (male; mean age 41.3)	NM	0.3	6	2	1	0.2	NR	1	NM	9
Reference population: NHANES 2009–2010; male 30–55 years	-	-	3.5 (4)	1.4 (1.6)	0.3 (0.33)	0.17 (0.2)	-	2.1 (2.4)	-	12 (14)
Ratio of GM from FF study / Upper CI of GM in reference population	-	-	1.5	1.3	3	1	-	0.4	-	0.6
3) Rotander et al. 2015 (97% male, 3% female; mean age 50)	NR	0.07	4.2	0.69	0.27	0.14	NR	25	NM	66
Reference population: CHMS 2016–2017; male 20–60 years	-	-	1.5 (1.8)	0.53 (0.63)	0.19 (0.24)	NR	-	1.5 (1.9)	-	4.2 (5.1)
Ratio of GM from FF study / Upper CI of GM in reference population	-	-	2.3	1.1	1.1	NR	-	13.2	-	12.9
4) Laitinen et al. 2014 (male; mean age 44.4)	NR	NR	2.94	1.22	NR	NR	NM	2.19	NR	11.1
Reference population: CHMS 2009–2011; male 20–60 years	-	-	2.6 (2.9)	0.81 (0.91)	NR	NR	-	2.3 (2.8)	-	7.9 (9)
Ratio of GM from FF study / Upper CI of GM in reference population	-	-	1.0	1.3	NR	NR	-	0.8	-	1.2
5) Jin et al. 2011 (male; mean age 40)	NR	NR	37.7	1.56	NR	NR	NM	4.77	NM	24.37
Reference population: NHANES 2005–2006; male 20–60 years	-	-	4.8 (5.3)	1.2 (1.5)	NR	NR	-	2.1 (2.5)	-	20 (22)
Ratio of GM from FF study / Upper CI of GM in reference population	-	-	7.1	1	NR	NR	-	1.9	-	1.1
6) Dobraca et al. 2015 (99% male; 2% female; mean age 42.8)	NM	0.13 (0.11–0.15)	3.75 (3.37–4.17)	1.15 (1.06–1.25)	0.9 (0.78–1.03)	0.24 (0.21–0.27)	NR	2.26 (2–2.54)	NM	12.5 (11.3–13.8)
Reference population: NHANES 2011–2012; male 20–60 years	-	-	2.4 (2.6)	1.4 (1.6)	0.21 (0.23)	0.12 (0.14)	-	1.7 (1.9)	-	8 (8.9)
Ratio of lower CI of GM from FF study / Upper CI of GM in reference population	-	-	1.3	0.7	3.4	1.5	-	1.1	-	1.3
7) Graber et al. 2021 (male; mean age 47)	NM	NM	2.07 (1.89–2.26)	0.97 (0.89–1.05)	0.31 (0.29–0.33)	0.11 (0.1–0.12)	NM	1.83 (1.61–2.09)	NM	4.25 (3.76–4.8)
Reference population: NHANES 2017–2018; male 20–60 years	-	-	1.6 (1.7)	0.41 (0.47)	0.18 (0.2)	0.11 (0.12)	-	1.5 (1.7)	-	5.2 (5.8)

Ratio of lower CI of GM from FF study / Upper CI of GM in reference population	-	-	1.1	1.9	1.5	0.9	-	1.1	-	0.7
8) Barton et al. 2020 (gender NR; age >18)	NR	NR	3.1 (2.2–4.3)	0.47 (0.38–0.58)	NM	NR	NR	16 (9.9–25.8)	0.25 (0.17–0.38)	14 (10.4–19)
Reference population: NHANES 2017–2018; male 20–60 years	-	-	1.6 (1.7)	0.41 (0.47)	--	--	-	1 (1.1)	0.25 (0.2-0.33)	5.5 (5.8)
Ratio of lower CI of GM from FF study / Upper CI of GM in reference population	-	-	1.3	1.0	--	--	-	9.0	0.5	1.8
9) Khalil et al. 2020 (male; mean age 51)	NM	NR	3.33 (2.89–3.84)	0.93 (0.81–1.06)	0.25 (0.22–0.29)	0.12 (0.1–0.14)	NR	3.07 (2.66–3.55)	NM	13.36 (11.64–15.34)
Reference population: NHANES 2009–2010; male 30–55 years	-	-	3.5 (4.0)	1.4 (1.6)	0.3 (0.33)	0.17 (0.2)	-	2.1 (2.4)	-	12 (14)
Ratio of lower CI of GM from FF study / Upper CI of GM in reference population	-	-	0.8	0.6	0.8	0.6	-	1.1	-	0.8
10) Leary et al. 2020 (male; mean age 41)	NM	NM	2.17[a]	0.45[a]	NM	NM	NM	6.45[a]	NM	10.69[a]
Reference population: NHANES 2017–2018; male 20–60 years	-	-	1.8 (2)	0.51 (0.56)	--	--	-	2 (2.4)	-	6.2 (6.9)
Ratio of GM from FF study / Upper CI of GM in reference population	-	-	1.1	0.8	--	--	-	2.7	-	1.5
Average of ratios:	**-**	**-**	**1.9**	**1.1**	**1.9**	**1.0**	**-**	**3.5**	0.5	**2.3**

NR: not reported (if a large number of samples is below detection); NM: not monitored (substance not monitored in study); GM: geometric mean; CI: confidence interval

[a] Median

15 Appendix E: References consulted for health effects information in sections 7.2.1 to 7.2.8

Endpoint	Study type	Reports/Reviews	Abstracts
Liver	Epidemiological studies	ATSDR 2021	Salihovic et al. 2018; Seo et al. 2018; Attanasio 2019; Bassler et al. 2019; Donat-Vargas et al. 2019b; Dong et al. 2019; Graber et al. 2019; Jain 2019; Jain et al. 2019d; Lin et al. 2019; Nian et al. 2019; Jin et al. 2020; Yao et al. 2020; Averina et al. 2021; Han et al. 2021
Liver	Animal studies	HC 2006; NTP 2019a; NTP 2019b; EFSA CONTAM Panel 2020; NTP 2020Rice et al. 2020; ATSDR 2021; Rice et al. 2021	Ladics et al. 2008; Loveless et al. 2009; Xie et al. 2009; Gordon 2011; Hirata-Koizumi et al. 2012; Serex et al. 2014; Caverly Rae et al. 2015; Hirata-Koizumi et al. 2015; Mukerji et al. 2015; Beekman 2016; Rushing et al. 2017; Sheng et al. 2017; Wang et al. 2017b; Han et al. 2018a; Han et al. 2018b; Huck et al. 2018; Lai et al. 2018; Li et al. 2018b; Lv et al. 2018; Sheng et al. 2018; Wu et al. 2018; Zhang et al. 2018b; Conley et al. 2019; Guo et al. 2019; Li et al. 2019a; Li et al. 2019b; Liang et al. 2019; Singh and Singh 2019b; Su et al. 2019; Wang et al. 2019c; Han et al. 2020; Huang et al. 2020; Zhou et al. 2020; Chen et al. 2021; Guo et al. 2021a; Guo et al. 2021b; Owumi et al. 2021; Wang et al. 2021
Kidney	Epidemiological studies	Stanifer et al. 2018; Ferrari et al. 2019; ATSDR 2021	Blake et al. 2018; Conway et al. 2018; Wang et al. 2019b; Zeng et al. 2019a; Jain et al. 2019a; Jain et al. 2019b; Jain et al. 2019c; Scinicariello et al. 2020; Yao et al. 2020; Lin et al. 2021; Moon 2021; Shearer et al. 2021
Kidney	Animal studies	HC 2006; Stanifer et al. 2018; Ferrari et al. 2019; NTP 2019a; NTP 2019b; NTP 2020; Rice et al. 2020; ATSDR 2021; Rice et al. 2021	Ladics et al. 2008; Loveless et al. 2009; Gordon 2011; Hirata-Koizumi et al. 2012; Serex et al. 2014; Caverly Rae et al. 2015; Hirata-Koizumi et al. 2015; Kato et al. 2015; Mukerji et al. 2015; Beekman 2016; Han et al. 2020; Rashid et al. 2020; ECHA 2021b; Owumi et al. 2021
Immune system	Epidemiological studies	ATSDR 2021	Averina et al. 2018; Chen et al. 2018b; Impinen et al. 2018; Pilkerton et al. 2018; Beck et al. 2019; Manzano-Salgado et al. 2019; Wen et al. 2019; Zeng et al. 2019b; Abraham et al. 2020; Ait Bamai et al. 2020; Kvalem et al. 2020; Timmermann et al. 2020; Lopez-Espinosa et al. 2021

Immune system	Animal studies	NTP 2019a; NTP 2019b; EFSA CONTAM Panel 2020; Rice et al. 2020; ATSDR 2021; Rice et al. 2021	Ladics et al. 2008; Xie et al. 2009; Gordon 2011; Hirata-Koizumi et al. 2012; Hirata-Koizumi et al. 2015; Kato et al. 2015; Bodin et al. 2016; Rushing et al. 2017; Berntsen et al. 2018; Lee et al. 2018; Wang et al. 2019c; McDonough et al. 2020; Shane et al. 2020; Woodlief et al. 2021
Reproduction	Epidemiological studies	ATSDR 2021	Joensen et al. 2013; Louis et al. 2015; Jaacks et al. 2016; Zhou et al. 2017; Heffernan et al. 2018; Song et al. 2018b; Zhang et al. 2018c; Liu et al. 2020; Mitro et al. 2020; Luo et al. 2021a
Reproduction	Animal studies	HC 2006; Ding et al. 2020; NTP 2019a; NTP 2019b; Rice et al. 2020; ATSDR 2021; Rice et al. 2021	Austin et al. 2003; Miyata 2007; O'Connor et al. 2014; Serex et al. 2014; Kato et al. 2015; Mukerji et al. 2015; Wang et al. 2018a; Zhou et al. 2018; Conley et al. 2019; Blake et al. 2020; Cao et al. 2020; Zhou et al. 2020; Mao et al. 2021; Yan et al. 2021
Development	Epidemiological studies	ATSDR 2021; Erinc et al. 2021	Meng et al. 2018; Sagiv et al. 2018; Ernst et al. 2019; Huang et al. 2019c; Marks et al. 2019; Wikstrom et al. 2019; Xu et al. 2019; Arbuckle et al. 2020; Borghese et al. 2020; Di Nisio et al. 2020; Huo et al. 2020; Jensen et al. 2020; Liew et al. 2020; Rylander et al. 2020; Wikström et al. 2020; Xiao et al. 2020; Birukov et al. 2021; Christensen et al. 2021
Development	Animal studies	HC 2006; Abbott 2015; Ali et al. 2019; Rice et al. 2020; ATSDR 2021; Rice et al. 2021; Tarapore et al. 202**1**	Case et al. 2001; Gordon 2011; Hirata-Koizumi et al. 2012; O'Connor et al. 2014; Hirata-Koizumi et al. 2015; Mukerji et al. 2015; Chang et al. 2018; Ramhøj et al. 2018; Song et al. 2018; Chen et al. 2019; Conley et al. 2019; Du et al. 2019; Singh and Singh 2019a; Zhang et al. 2020; Li et al. 2021c; Li et al. 2021d; Luo et al. 2021b; Zhang et al. 2021
Endocrine function (thyroid)	Epidemiological studies	Boesen et al. 2020; ATSDR 2021; Coperchini et al. 2021	Inoue et al. 2019; Itoh et al. 2019; Reardon et al. 2019; Aimuzi et al. 2020; Kim et al. 2020; Lebeaux et al. 2020; Liang et al. 2020; Liu et al. 2020; Preston et al. 2020; Xiao et al. 2020
Endocrine function (thyroid)	Animal studies	HC 2006; Rice et al. 2020; ATSDR 2021; Rice et al. 2021	Austin et al. 2003; Ladics et al. 2008; Gordon 2011; Hirata-Koizumi et al. 2015; Li et al. 2017; Ramhøj et al. 2018; Conley et al. 2019; Hong et al. 2020
Nervous system	Epidemiological studies	EFSA CONTAM Panel 2020; ATSDR 2021	Gump et al. 2011; Niu et al. 2019; Luo et al. 2020; Shin et al. 2020; Oh et al. 2021a; Oh et al. 2021b
Nervous system	Animal studies	Wang et al. 2019d; EFSA CONTAM Panel 2020; Piekarski et al. 2020; ATSDR 2021	Austin et al. 2003; Miyata 2007; Johansson et al. 2008; Lee and Viberg 2013; Hirata-Koizumi et al. 2015; Hallgren and Viberg 2016; Salgado et al. 2016; Zhang et al. 2016b; Kawabata et al. 2017b; Mshaty et al. 2020

Metabolism and body weight	Epidemiological studies	Qi et al. 2020; ATSDR 2021	Matilla-Santander et al. 2017; Lauritzen et al. 2018; Mancini et al. 2018; Wang et al. 2018b; Alderete et al. 2019; Christensen et al. 2019; Donat-Vargas et al. 2019a; Fassler et al. 2019; Liu et al. 2019; Marks et al. 2019; Rahman et al. 2019; Tian et al. 2019; Valvi et al. 2019; Xu et al. 2019; Chen et al. 2020; Duan et al. 2020; Li et al. 2020c; Mitro et al. 2020; Preston et al. 2020; Ren et al. 2020; Wikström et al. 2020; Xiao et al. 2020; Xu et al. 2020b; Averina et al. 2021; Duan et al. 2021; Geiger et al. 2021; Han et al. 2021; Mitro et al. 2021; Yu et al. 2021; Zeeshan et al. 2021
Metabolism and body weight	Animal studies	HC 2006; NTP 2019a; NTP 2019b; NTP 2020; Rice et al. 2020; ATSDR 2021; Rice et al. 2021	Case et al. 2001; Ladics et al. 2008; Ding et al. 2009; Hines et al. 2009; Xie et al. 2009; Gordon 2011; Fang et al. 2012a; Hirata-Koizumi et al. 2012; Lv et al. 2013; O'Connor et al. 2014; Serex et al. 2014; Wan et al. 2014; Wang et al. 2014b; Caverly Rae et al. 2015; Hirata-Koizumi et al. 2015; Mukerji et al. 2015; Yan et al. 2015; Bodin et al. 2016; Zheng et al. 2017; Du et al. 2018; Huck et al. 2018; Lai et al. 2018; Sheng et al. 2018; Zhang et al. 2018b; Conley et al. 2019; Blake at al. 2020; Zhou et al. 2020; Chen et al. 2021; Conley et al. 2021; Li et al. 2021c; Shao et al. 2021