

# Perfluoroalkyl and polyfluoroalkyl substances: current and future perspectives

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**Environmental context.** Perfluoroalkyl substances were recognised as global environmental pollutants 10 years ago. Although considerable advancements have been made in our understanding of the environmental distribution, fate and toxicity of perfluoroalkyl substances, several important issues remain to be resolved. This article identifies existing knowledge gaps that deserve further investigations to enable meaningful regulatory decisions.

**Abstract.** It has been over a decade since perfluoroalkyl substances (PFASs) were discovered as global environmental contaminants. Considerable progress has been made in our understanding of the environmental fate and toxic effects of PFASs since then. Government regulations and voluntary emission reduction initiatives by industry have been effective in reducing environmental and human exposure to a major PFAS, perfluorooctane sulfonate (PFOS), in the United States and several other western countries. Although significant advances have been made in our understanding of the environmental chemistry of PFASs, considerable knowledge gaps still exist in several areas of environmental fate and risk assessments. Owing to their complex chemistry, involving existence of multiple precursors with significant numbers of structural isomers and mixtures of homologues, multiple degradation pathways and unique physicochemical properties, challenges remain in elucidating sources and environmental fate. In this overview, some of the knowledge gaps in PFASs' research have been identified and suggestions for future research have been made.

## Introduction

The widespread environmental distribution of perfluoroalkyl substances (PFASs), especially perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), is well known. Since 1950, PFASs and surfactants and polymers made with the aid of PFASs have been widely used in numerous industrial and commercial applications. As a consequence of the extensive production and use of PFASs, a wide range of these compounds have been detected in the environment, wildlife and humans. The global extent of contamination by PFOS and related perfluorinated acids was first demonstrated in wildlife by Giesy and Kannan<sup>[1]</sup> and in humans by Kannan et al.<sup>[2]</sup> Since the first report revealing the widespread global occurrence of PFASs was published a decade ago, the scientific literature on environmental and toxicological aspects has burgeoned rapidly and the rate of publication currently exceeds 400 per year.<sup>[3]</sup> The concern over potential effects on the environment and human health of PFASs has led to the launching of several research programs on PFASs' sources, fate, transport and toxicity. As a consequence, PFOS and related compounds have been phased-out of production by their major manufacturer (3M Co.) in 2001–02. Furthermore, a stewardship agreement between the United States Environmental Protection Agency

(USEPA) and eight leading global manufacturers, to reduce 95 % of emissions of PFOA and related chemicals by 2010, and to work towards elimination by 2015, has been launched. PFOS has been included in the Stockholm Convention on persistent organic pollutants (POPs) as an Annex B substance. There has been a great deal of interest in evaluating toxicities, human exposure pathways (such as by food, food-contact materials, drinking water, house dust) and mode of global transport of PFASs. Several publications have reviewed analytical techniques, environmental distribution, transport, bioaccumulation, fate, toxicity and human exposures of PFASs.<sup>[4–19]</sup> Considerable progress has been made in our understanding of the environmental distribution and fate of several PFASs in the past 10 years. Despite this, several issues pertaining to global transport, human exposures and toxicity of PFASs continue to be a concern. The purpose of this article is to identify the existing knowledge gaps and to provide an overview on future perspectives for PFAS research.

## Global inventory of PFAS family of compounds

There are numerous families of PFASs, each with several homologues and isomers thereof.<sup>[3]</sup> Although the environmental



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fate and toxicities of perfluoroalkylsulfonic acids (PFSA) and perfluoroalkylcarboxylic acids (PFCAs) have been studied extensively, little is known about other families of PFASs including fluorinated polymers and their environmental degradation products. For example, environmental occurrence of perfluoroalkane sulfinic acids and perfluoroalkyl phosphinic and phosphonic acids has been reported.<sup>[20]</sup> Similarly, a wide variety of fluorotelomer-based products, manufactured from perfluoroalkyl iodide, fluorotelomer iodides and fluorotelomer olefins, have been used in diverse commercial products. Perfluoroalkyl iodide and fluorotelomer iodide have recently been detected in air and soil near a fluorotelomer manufacturing facility in China.<sup>[21]</sup> Fluorotelomer alcohols (FTOHs) are key raw materials used in the production of fluorotelomer acrylates, fluorotelomer methacrylates and fluorotelomer phosphoric acid esters. These fluorotelomer-based compounds are used in the manufacture of fluoropolymers, which are used in textiles, leather and paper substrates. FTOHs can degrade to yield PFCAs.<sup>[22,23]</sup> Thus, there exists a wide variety of perfluoroalkylated precursor compounds including fluoropolymers in commerce; the environmental occurrence, distribution and transport of these precursor compounds have not been studied.

The contribution of precursor PFASs to the environmental occurrence, human exposure and global inventories of the metabolic and environmental transformation products (such as PFCAs and PFSA) is still not known. For instance, environmental fate models have shown that current fluorotelomer acrylate use contributed to only <1 % of PFOA present in sea water.<sup>[24]</sup> The environmental fate of other degradation products (other than PFOA) of fluorotelomer acrylate is not known. There is a need for environmental fate models to include all volatile precursor PFASs and degradation products in future modelling endeavours. In general, the families of PFASs are inter-related as industrial, environmental or metabolic precursors, or transformation products of one another.<sup>[3]</sup> The availability of the wide range of complex commercial preparations and the inter-relatedness (several precursors with multiple degradation pathways contributing to direct and indirect sources to the environment) of these families of compounds make an estimate of global inventory a daunting task. Nevertheless, the assessment of global inventories is essential if we are to develop strategies to mitigate environmental and human exposures. Neutral precursor compounds are the predominant PFASs found in abiotic matrices, especially in air, whereas end-stage metabolites are predominant in biota. It is possible that several intermediate compounds of precursor PFAS degradation pathways exist in water and soil matrices. The linkage between the occurrence of PFAS precursor compounds in air and the breakdown products in biota is not well understood. Tracking of the isotope or isomer signatures has been suggested as a means for understanding the link.<sup>[17,19]</sup> Assessment of global inventories of PFASs is also essential for the understanding of global cycling and pathways as well as for multimedia fate modelling of these compounds. Data from systematic and comprehensive global environmental monitoring studies can also be used in the estimation of global inventories.

### Physicochemical properties and modelling

We currently have a limited understanding of the physicochemical properties and partitioning behaviour of PFASs in the environment. An understanding of the environmental fate of PFASs requires quantitative information on their partitioning among various environmental media. The physicochemical

properties and partitioning behaviour of PFASs are poorly understood and widely debated.<sup>[15]</sup> Parameters such as octanol–air ( $K_{OA}$ ) and octanol–water ( $K_{OW}$ ) partition coefficients are used to describe the equilibrium partitioning of the gas phase with a pure organic solvent and the aqueous phase respectively. Accurate measurements of physicochemical properties of precursors and metabolites will increase our credibility in understanding of global transport and fate of PFASs. For instance, such physicochemical parameters can be used in delineating air–water exchange and fluxes and global cycling of PFASs in the oceans. Concurrent collection and analysis of oceanic air and sea water would enable estimation of air–water exchange and global fluxes of PFASs in the oceans.

There has been a disagreement as to the actual  $pK_a$  (acid dissociation constant) value for PFOA. Depending on the  $pK_a$ , perfluorinated alkyl acids will dissociate to their anions in aqueous media, soil and sediments. Because perfluoroalkyl acids are strong acids, the majority of these acids are expected to be present in the ionised (i.e. anionic) form in environmental media. The protonated and anionic forms have different physicochemical properties. For instance, the perfluorooctanoate (PFO;  $C_7F_{15}COO^-$ ) anion is highly water soluble and has negligible vapour pressure whereas perfluorooctanoic acid (PFOA;  $C_7F_{15}COOH$ ) has an appreciable vapour pressure and can be subjected to water–air exchange processes.<sup>[15,25]</sup>  $pK_a$  values of PFOA are reported to range widely from 0 to 3.8. The environmental fate models that have been developed to describe the atmospheric transport potential of PFOA are highly sensitive to the values of  $pK_a$  used. Therefore, for PFCAs, there is an ongoing debate regarding the environmental relevancy of  $pK_a$  and the atmospheric transport potential.

Few studies have reported physicochemical properties of selected PFASs.<sup>[15,26]</sup> Accurate measurements of physicochemical properties of precursors and metabolites of PFASs are needed for the assessment of inter-media partitioning, transport and global fate, which would enable reliable prediction of their environmental fate and sinks. Additional theoretical and experimental work needs to be conducted to better understand why PFCAs have  $pK_a$  values approximately equal to their hydrogenated counterparts, despite the inductively withdrawing character of the perfluoroalkyl chain that would be expected to depress the  $pK_a$  significantly.<sup>[15]</sup> The existence of a wide range of potential PFASs of environmental and toxicological relevance and the difficulty in synthesising authentic standards, preclude complete experimental assessments for the foreseeable future. Nevertheless, this challenge creates an opportunity for the researchers to delve into new research areas.

### Analytical challenges

More than 2500 research articles have been published on PFASs since 2001. Although the analytical methods for PFASs have evolved over time, many challenges, uncertainties and pitfalls still remain.<sup>[19]</sup> Environmental analysis of neutral precursor PFASs and their polymeric forms is a much less developed field, as compared to ionic compounds. Neutral PFASs have so far predominantly been analysed in air. The role of neutral precursors in bioaccumulation and human exposure is a controversial issue that is currently debated.<sup>[19]</sup> Analysis of neutral precursor substances in matrices other than air is thus an upcoming and challenging field. Methods for the analysis of fluorinated polymers are needed. High-quality data are essential for the future progress of our understanding of the fate and toxicity of PFASs. With the understanding of the need for

reliable data coupled with the availability of isotopically labelled standards and sensitive instrumentation, an improvement in the area of analytical chemistry of PFASs is feasible.<sup>[19]</sup>

### Characterisation of PFASs in consumer articles

Humans can be exposed to PFASs from the use of these compounds in a variety of consumer products including personal care products, textiles, carpets, leather, paper and cardboards. Studies that characterise the concentrations and release of PFASs from the consumer products are meager.<sup>[27,28]</sup> The consumer articles are generally treated with the precursor compounds, some of which are dialkylated and polymeric, and contain multiple functional groups. Such complex PFASs, which contain perfluorinated chains, can be precursors of monoalkylated perfluorinated compounds. There have been varying opinions as to whether PFAS-containing consumer articles are a significant contributor to the total exposure.<sup>[29]</sup> Trudel et al.<sup>[30]</sup> reported that product-related exposure can be a source of PFOA in humans. Analytical standards for most of the PFAS precursor compounds (present in consumer articles) are not commercially available. Commercial fluorochemicals are sold as industrial blends, which apart from the mixtures of PFASs, contain impurities.<sup>[28]</sup> Future environmental monitoring studies should include PFAS precursor compounds (e.g. fluorinated olefins, iodides and acrylates). This will enable complete understanding of the sources of human and environmental exposure to PFASs.

### Need for understanding and controlling of sources of environmental release

PFASs are primarily emitted into water and sea water, which represent a major reservoir for these compounds in the environment, as well as an important medium for these chemicals' global transport. Studies have shown that wastewater treatment plants (WWTPs) are important sources of PFASs, especially PFOS and PFOA, to the aquatic ecosystems.<sup>[18,31]</sup> Modelling studies have also shown that WWTPs are the predominant sources of PFASs in the aquatic environment,<sup>[32]</sup> although diffuse non-point sources of pollution exist in urban areas.<sup>[33]</sup> Land application of sewage sludge is another pathway of PFASs to the food chain. Studies have shown that current wastewater treatment processes do not adequately remove PFASs present in the waste stream. Filtration and sorption technologies offer the most promising removal methods for PFASs in aqueous waste streams, although sonochemical approaches hold promise. Several laboratory scale studies have also reported methods to decompose PFASs in water.<sup>[34]</sup> Integration of filtration and sorption techniques into the existing wastewater treatment processes will help reduce environmental release of these compounds. Perhaps one of the most promising research areas would be to exploit the known proteinophilic character of the perfluorinated acids for removal from wastewater streams.<sup>[15]</sup>

Because of the characteristics of high water solubility and persistence, the environmental transport and fate of PFOA and PFOS can be tracked, although their formation from (multiple) precursors complicates the fate assessment. When perfluoroalkyl acids are released into water, they undergo minimal degradation and volatilisation. Their sorption to solids is limited. As a result of these properties, PFOS and PFOA have been suggested as tracers of global oceanic circulation.<sup>[35]</sup> Because the oceans are perceived to be the ultimate sinks for PFASs, future monitoring studies should focus on assessing the fluxes and fate of these compounds in the oceanic environment.

### Temporal trend studies are valuable in elucidating the effectiveness of regulations

Temporal trend studies are valuable for evaluating the effectiveness of restrictions and regulations on global production and emissions and for evaluating environmental clearance rates of pollutants. Temporal trend studies of PFASs, both near point sources and in remote locations in North America, have indicated a decline in PFOS concentrations, in biota and humans sampled after 2001. Nevertheless, temporal trends of PFASs between the Arctic regions (e.g. Canadian Arctic versus European Arctic) are not consistent. Concentrations of PFOS have been reported to decline in ringed seals and beluga whales from the Canadian Arctic<sup>[16,36]</sup> and sea otters from Alaska,<sup>[37]</sup> following the phase-out in the production of POSF-based compounds in 2001. However, PFOS levels in ringed seals<sup>[38]</sup> and polar bears<sup>[39]</sup> from Greenland continued to increase during 1980–2006. The inconsistencies observed between temporal trends point to differences in emission sources. Although some current manufacturers of PFASs in the United States and Europe have voluntarily announced their intentions to reduce future emissions from manufacturing processes, a variety of PFASs are still being produced by several other manufacturers worldwide. For instance, PFOS has been produced in China since 2003 (several hundred tonnes annually), which may influence future global patterns and trends.

Although PFOS concentrations have been declining in wildlife from several locations across the world, the concentrations of PFCAs, particularly perfluoroundecanoic acid (PFUnDA), have been increasing. Between 2001–02 and 2006, the concentrations and contributions of PFCAs, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), PFUnDA and perfluorododecanoic acid (PFDoDA), increased in the livers of meon-headed whales from the Pacific coast of Japan.<sup>[40]</sup> Between 1982–1986 and 2003, ringed seals from two locations in Greenland showed significant increases in PFDA and PFUnDA concentrations.<sup>[38]</sup> The mean concentrations of PFNA and PFDA in livers of seals collected from Lake Baikal (Russia) in 2005 were two-fold greater than in seals collected in 1992.<sup>[41]</sup> Tawny owl eggs collected from Norway between 1986 and 2009 showed significant reduction in the concentrations of PFOS, whereas PFDA, PFUnDA and PFDoDA concentrations increased by 4.2–12 % per year during that period.<sup>[42]</sup> These temporal increases in the concentrations of PFCAs are suggestive of a rise in the production and usage of these compounds or their precursors. In fact, concentrations of several long-chain PFCAs, especially PFUnDA, were similar to those of PFOS in the livers of skipjack tuna collected from the Pacific coast of Japan and the East China Sea.<sup>[43]</sup> Environmental emissions of long-chain PFCAs and their precursors appear to be increasing. Unless adequate emission control strategies are implemented, the levels of PFCAs can supersede those of PFASs in biota in the future. Temporal trend studies of PFCAs (especially, long-chain PFCAs) in the aquatic environments are needed.

In humans, temporal trend studies have shown that PFOS concentrations in blood increased during the 1970s to the 1990s and declined after 2000 in the United States and several western European countries. In the United States, concentrations of PFOS in human blood decreased by two-fold between 2000 and 2008, whereas PFNA concentrations doubled during that period.<sup>[44]</sup> Concentrations of PFOA in human blood from the United States remained unchanged during 2003–08.<sup>[44]</sup> The observed declines in PFOS concentrations after 2000



coincide with the phase-out of perfluorooctylsulfonate fluoride (POSF)-based production in the United States. Besides the phase-out, stringent emission controls in the production processes contributed to the observed declining trends in PFOS levels in humans.

It should be noted that the trends and patterns of PFAS contamination varied among species, location and compound. Systematic trend monitoring studies of PFASs in humans and environmental matrices from several other countries (e.g. China) have not been carried out. As the manufacturing practices and usage patterns of PFASs have been changing (e.g. on-going production of PFHxS and PFBS, and PFOS in other countries), continued trend monitoring studies are needed to assess the effectiveness of regulations and to assess changes in temporal patterns and profiles of PFASs in wildlife and humans.

### Increasing prevalence and bioaccumulation of long-chain PFCAs

It is known that PFASs are more bioaccumulative than PFCAs of the same fluorinated carbon chain length.<sup>[45]</sup> Worldwide biomonitoring studies of wildlife and humans have unequivocally documented that PFOS was the most predominant PFAS species. Nevertheless, recent studies suggest an increase in the prevalence of long-chain PFCAs, such as PFOA, in the livers of seabirds and marine mammals from the Arctic.<sup>[16,37,42]</sup> In the livers of skipjack tuna from the Pacific coast of Japan and the East China Sea, PFOA concentrations rivalled those of PFOS, although PFOA was not detected in seawater samples. The importance of monitoring for long-chain PFCAs is demonstrated in several recent studies by the fact that these compounds typically dominate PFCA profiles.

Although most biomonitoring studies have measured PFASs in blood or liver tissues, the distribution of these compounds in other body tissues is not well understood. Recently, it has been shown that finger and toe nails contain much higher levels of PFOS and PFOA than in serum.<sup>[46]</sup> Finger and toe nails also contained elevated concentrations of long-chain PFCAs such as PFNA, PFDoDA and perfluorotridecanoic acid (PFTrDA), whereas these perfluoroalkyl acids were rarely found in serum. Considering the fact that finger nails contain high levels of PFASs, examination of these compounds in bones and associated health outcomes is needed. The need for monitoring of tissues other than blood and liver can also be exemplified from sex-related differences in PFAS accumulation. PFOS and PFOA can be maternally transferred (from mothers to eggs) in considerable proportions (e.g. birds and fish). Despite the maternal transfer, the sex differences in concentrations of PFOS and PFOA are small; this suggests the existence of additional (other than liver and blood) reservoirs of PFASs in the bodies of animals and humans. Analysis of PFASs in body tissues such as bones, hair, spleen and lungs is needed. This will enable clear understanding of bioaccumulation and biomagnification features and accurate toxicological and risk evaluations.

Because the production methods and usage patterns of PFASs are complex, multiple forms (e.g. polymers, precursors, degradation intermediates and end-stage metabolites) of these compounds are released into the environment. In view of the lack of appropriate analytical standards and methods for all of the potential PFASs (especially precursors) that can occur in the environment and human tissues, a method was developed to measure total organic fluorine in blood samples.<sup>[47]</sup> The results showed that known PFASs accounted for only a fraction of the

total organic fluorine measured in the blood, suggesting the existence of other forms of organofluorine compounds in human blood. Similarly, up to 60–90 % of the organofluorine mass in natural waters remains unidentified, suggesting that most of the fluorinated compounds in aquatic systems are still to be discovered.<sup>[48]</sup> Further monitoring studies should increase the breadth of PFASs being measured in environmental and biological specimens.

### Toxicity mechanisms

Toxicological studies of PFOS and PFOA have been conducted on laboratory animals such as monkeys, rats, mice and rabbits.<sup>[11]</sup> There have been significant advances in descriptive toxicology for a variety of PFASs as well as studies of the potential mode of action for some of the toxicological responses.<sup>[11]</sup> The pharmacokinetics, especially the elimination rates, of PFOS and PFOA appears to vary depending on the species. In some cases (for example, PFOA in rats), sex differences in the elimination rates have been reported. The reasons for the species and sex differences in elimination rates are not well understood. Furthermore, the distributions of PFOS and PFOA in tissues of exposed animals vary depending on the species. The liver to plasma ratio for PFOS in humans is 1 : 1 whereas the ratio in rats is 10 : 1. It is clear that there are vast species differences in the pharmacokinetics of PFASs; this difference precludes the extrapolation of laboratory toxicological studies to human risk evaluation. It is important to explore critical modes of toxicity of PFASs to derive threshold values, for providing a sound basis for health risk assessment of these chemicals.

Whereas the toxicity of PFOS and PFOA has been extensively investigated, there is a paucity of information for many PFASs including the long-chain PFCAs (such as PFOA). Furthermore, studies are needed to characterise potential target organs and to elucidate long-term consequences of prenatal and early life stage exposures. Ecotoxicological studies are needed using model animals such as fish, birds, reptiles, amphibians, and mink to establish a threshold for toxic effects in wildlife.

Studies have reported the occurrence of up to 15 different perfluorinated acids in human specimens. Considerable uncertainties exist in the assessment of risks posed by the mixtures of PFASs found in humans, wildlife and environmental matrices. A few *in vitro* studies have shown that PFASs act through a common mode of action, but with different potencies.<sup>[49]</sup> Based on the mode of toxic action and relative potencies, a PFOS-equivalency approach was suggested for the assessment of risks of PFASs.<sup>[49,50]</sup> However, relative toxicities of several PFASs have still not been investigated. It is also not known if a toxic equivalency approach would be appropriate for the assessment of risks of PFASs because of the differences in bioaccumulation potential (e.g. PFOS versus PFOA). To make collective and comprehensive assessment of the hazard posed by PFASs, collection of additional exposure and toxicity information is required.

### Human exposure pathways and need for epidemiologic studies

The assessment of sources and pathways of human exposure to PFASs is critical, if we are to develop strategies for mitigating human exposure to these compounds. The sources and pathways of exposure appear to vary depending on the type of perfluorinated acid, country and food consumption pattern. In China, fish and seafood accounted for a major proportion of the daily intake of PFOS, whereas meat and meat products

accounted for a major proportion of the intake of PFOA.<sup>[51]</sup> Several studies have also reported that infants, toddlers and children are exposed to greater levels of PFASs than adults. Although studies have determined PFASs in foodstuffs and measured exposure doses of these compounds in people, a reference dose for comparison is not available yet. For instance, provisional short-term health advisory levels for PFOS and PFOA in drinking water set by the USEPA are 200 and 400 ng L<sup>-1</sup> respectively. Such information is not available for daily dietary exposures.

Epidemiologists have begun to focus human developmental outcomes with PFOS and PFOA, as a consequence of developmental toxicological studies that report effects of lowered birthweight, increased postnatal mortality and decreased survival in rats and mice.<sup>[52]</sup> A large cross-sectional study involving the analysis of 293 samples of cord blood from Baltimore, Maryland, USA, compared PFOS and PFOA levels to birth outcomes of gestational age, birthweight, birth length, head circumference and ponderal index and showed negative associations between concentrations of PFOS and PFOA and ponderal index.<sup>[53]</sup> Maternal blood concentrations of PFOA, but not PFOS, were negatively associated with birthweight in newborns from Denmark.<sup>[54]</sup> A further study reported a statistically significant negative correlation between abdominal circumference and maternal PFOA, a statistically significant positive association between ponderal index to maternal PFOA of women who were obese before pregnancy, and a statistically non-significant negative correlation between head circumference and maternal PFOA.<sup>[54]</sup> These findings suggested that PFOS and PFOA may affect the growth of organs and skeleton in infants and can have adverse effects on overall fetal growth and neonatal development. However, the literature results are inconsistent, suggesting the influence of several confounding factors, which need to be carefully controlled for, in epidemiological data analysis and interpretation.

Considering the fact that infants and children are exposed to greater doses of PFASs than adults and that the early life stages are vulnerable to the effects of toxic chemical exposures, more systematic and well-designed epidemiologic studies are needed to understand associations between perfluorochemical exposures and developmental and/or behavioural outcomes in children as well as other health outcomes in adults.

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Manuscript received 21 April 2011, accepted 11 July 2011