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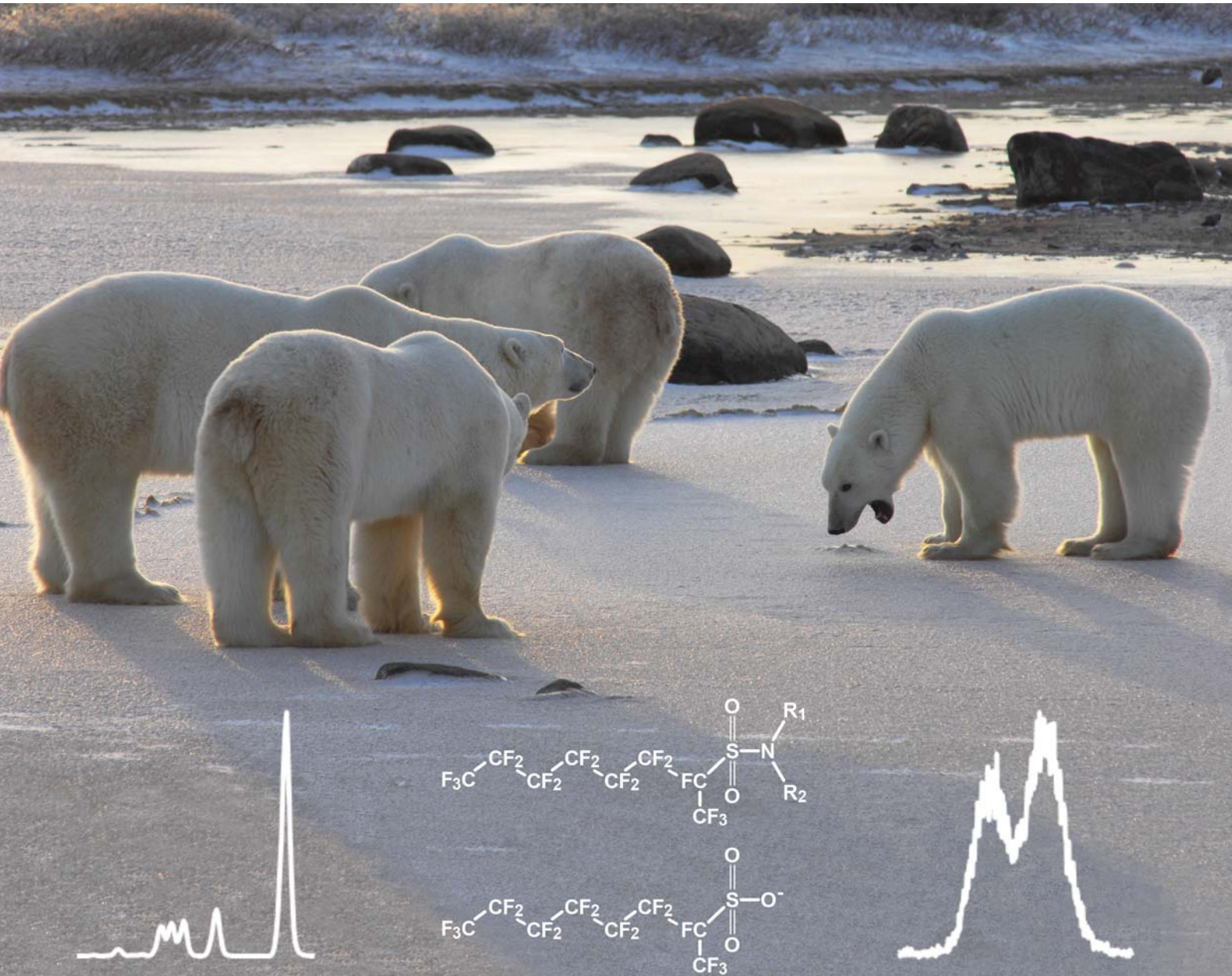

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CRITICAL REVIEW

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PFOS or PreFOS? Are perfluorooctane sulfonate precursors (PreFOS) important determinants of human and environmental perfluorooctane sulfonate (PFOS) exposure?†

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The extent to which perfluorooctanesulfonate precursors (PreFOS) play a role in human or environmental exposure to perfluorooctanesulfonate (PFOS) is not well characterized. The diversity of manufactured PreFOS and its degradation products (*e.g.* $C_8F_{17}SO_2R$ and $C_8F_{17}SO_2NR'R''$, where R is H or F, and R′ and R″ are various) has made it difficult to track their fate. Temporal trends of PFOS in both humans and wildlife are discrepant, thus it is difficult to predict future exposure, and hypotheses about the role of PreFOS have been raised. Although abiotic degradation of commercially important PreFOS materials requires further research, current data suggest that the yield of PFOS is negligible or minor. On the other hand, *in vivo* biotransformation of PreFOS yields PFOS as the major metabolite, and >32% yields have been observed. In Canadians, exposure to PreFOS was equivalent or greater than direct PFOS exposure prior to 2002. In most ocean water, PFOS is dominant to PreFOS, but in the oceans east of Greenland there may be more PreFOS than PFOS, consistent with the fact that whales and humans in this region also show evidence of substantial PreFOS exposure. Quantitative assessments of PFOS body-burdens coming from PreFOS are complicated by the fact that PreFOS partitions to the cellular fraction of blood, thus biomonitoring in serum under predicts PreFOS relative to PFOS. Many unknowns exist that prevent accurate modelling, thus analytical methods that can distinguish directly manufactured PFOS, from PFOS that has been biotransformed from PreFOS, should be applied in future human and environmental monitoring. Two new source tracking principles are presented and applied to human serum.

Introduction and objectives

Perfluorooctane sulfonate (PFOS, $C_8F_{17}SO_3^-$) is among the most prominent organic contaminants in the environment, wildlife, and in human serum. It is persistent, bioaccumulative,[1–4] and it is a developmental toxicant in animal models.[5] Due to its hazardous properties and its wide global distribution, it was phased out of production between 2000 and 2002 by its primary manufacturer, the 3M Co., and many developed countries have since banned or placed strict regulations on the use, import, and manufacturing of PFOS and its higher molecular weight derivatives. Such derivatives are otherwise known "PFOS-precursors", referred to hereafter as PreFOS, because of their potential to degrade to PFOS.

A primary research interest is to what extent the environmental concentrations of PFOS, or the body-burdens of PFOS in humans or wildlife, are due to the degradation of PreFOS. Considering that PFOS has no known routes of environmental degradation, and that environmental burdens of PreFOS will eventually degrade to PFOS over time, this research question has significant implications for accurately predicting future risks to exposed humans and wildlife. The main objective here is to review the state of knowledge on the various forms of PreFOS, historic and contemporary manufacturing and emissions, degradation mechanisms of PreFOS, temporal trends of exposure, environmental monitoring and biomonitoring of PFOS and

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Environmental impact

Perfluorooctane sulfonate (PFOS) is among the most prominent persistent organic pollutant in humans and wildlife, yet its exposure sources are poorly understood. Along with its precursor compounds (PreFOS), PFOS continues to be manufactured and used despite that it is persistent, bioaccumulative, and the long term risks it may present to exposed organisms have not been well characterized. This critical review is intended to integrate knowledge on the exposure and environmental fate of PreFOS, in an effort to determine if, when, or where it contributes to PFOS exposure. It is expected that this information will direct future research, thereby leading to an accurate understanding of sources and enabling effective chemical management in the future.

PreFOS, and predictions from exposure models. Finally, new environmental analytical principles will be discussed with respect to unravelling the relative importance of PFOS and PreFOS in various biological or environmental samples.

What does PreFOS look like?

A great difficulty in attempting to assess the importance of PreFOS under human and environmental exposure scenarios is the vast diversity of PreFOS molecular structures and associated physical properties, which together pose a significant challenge to the analytical chemist. This diversity in PreFOS arises, in part, from its various manufactured forms, but adding to this complexity is that the manufacturing methods resulted in many intermediates, isomers, and impurities in the final commercial products. Small PreFOS molecules (*i.e.* < 1000 daltons) were furthermore incorporated into undefined large oligomers or copolymers through various linkage chemistries. On top of this, the non-fluorinated alkyl portions of PreFOS molecules are generally labile to biotic and abiotic processes, and thus manufactured forms of PreFOS will be modified after entering the environment, or after being absorbed by an organism.

To illustrate the wide variety of PreFOS structures, some of the various forms of PreFOS that are known to have been manufactured by the 3M Co., either as targeted products or as residuals, are shown in Fig. 1. The structures are all identified by acronyms, and each is also assigned a roman numeral and lower case letter for simple identification.

Manufacturing and emission of PFOS and PreFOS

Historic manufacturing

All PFOS and PreFOS is believed to have been manufactured from starting materials produced by the process of electrochemical fluorination. Specifically, electrochemical fluorination of octanesulfonyl chloride yields a mixture of linear and branched perfluorooctanesulfonyl fluoride (POSF, Ia.), with byproducts including short chain homologues.[6] POSF was itself a commercially viable product[7] sold by the 3M Co. in unknown quantities, but its primary use was as the starting material for all subsequent PFOS and PreFOS production. Hydrolysis of POSF yields PFOS and its salts, whereas reaction with methyl or ethyl amines yields the alkyl substituted sulfonamides: N-methyl perfluorooctanesulfonamide (NMeFOSA, Va.) and N-ethyl perfluorooctanesulfonamide (NEtFOSA, Vb.), respectively. Subsequent reaction of these sulfonamides with ethylene carbonate yields the sulfonamide alcohols, N-methyl perfluorooctanesulfonamidoethanol (NMeFOSE, VIa.) and N-ethyl perfluorooctanesulfonamidoethanol (NEtFOSE, VIb.),[7] which have been described as the principal building blocks of the 3M Co.'s fluorochemical product lines. A few of the subsequent products made from these are shown, including acetates (VII),

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Jonathan Martin trained as a toxicologist and environmental analytical chemist at the University of Guelph (PhD) and the University of Toronto (Postdoctoral), and is now an Associate Professor at the University of Alberta. His research program focuses on developing analytical methods in support of hypothesis driven environmental fate studies of emerging persistent contaminants. Current trainees are working on projects relating to detoxification of oil sands process water, or sources of perfluorinated compounds. All co-authors of this review are PhD students in his group.

Brian Asher received his Bachelor of Science degree from the University of Winnipeg in 2004, and is currently working on his PhD in Chemistry at the University of Alberta, under the supervision of Dr Martin and Dr Charles Wong. His current research focuses on the study of chiral environmental contaminants, specifically polychlorinated biphenyls and perfluorinated surfactants. His main focus is on utilizing chiral signatures as a tool for elucidating pollutant sources.

Sanjay Beesoon holds a Diploma in Medical Laboratory Technology from the University of Mauritius, a Bachelor of Science degree in Biochemistry and Microbiology from the University of South Africa, and Master in Public Health in Epidemiology from the University of Alabama at Birmingham. He is presently working on a PhD in Medical Sciences in the Department of Laboratory Medicine and Pathology at the University of Alberta under the supervision of Dr Martin. His current research focuses mainly on tracking human exposure sources to perfluorinated compounds.

Jonathan Benskin received his Bachelor of Science degree in Chemistry from the University of Victoria in 2005 and will complete his PhD in Medical Sciences from the University of Alberta in the Fall of 2010. His research (supervised by Dr Martin) focuses on the development of isomer-specific analytical methodologies for perfluoroalkyl compounds, and application of these to exposure and manufacturing source elucidation experiments.

Matthew Ross received his Bachelor of Science degree in biology from Arizona State University and is currently pursuing his PhD in chemistry under the supervision of Drs Jonathan Martin and Charles Wong. His research centers on understanding the fate of chiral environmental pollutants, and on using enantiomer and isomer signatures to determine routes of exposure to polychlorinated biphenyls and perfluorinated compounds.

phosphate esters (VIII), acrylate esters (IX), and their respective copolymers (*e.g.* X). These synthetic routes did not produce pure products, and final formulations often contained 1–2% unreacted residual material, including but not limited to PFOS, perfluorooctanesulfonamide (PFOSA, Ib.), N-alkyl perfluorooctanesulfonamides (FOSAs, V), perfluorooctanesulfonamidoethanols (FOSEs, VI), and perfluorooctanesulfonamidoacetates (FOSAAs, VII).[7] The structures shown in Fig. 1 are not intended to be comprehensive. For example, not shown are various other derivatives of the sulfonamidoethanols including urethanes, silanes, alkoxylates, adipates, polyesters, and other copolymers. Other PreFOS materials, or their environmental degradation products, are discussed in subsequent sections, and it is likely that others have yet to be discovered. Therefore, in subsequent sections of this review it is important to keep in mind that reports of targeted PreFOS analysis in any sample is unlikely a comprehensive profile of all forms of PreFOS that are present, and in some cases the total PreFOS concentrations may be underestimated.

It is noteworthy to mention that POSF (Ia.) derived products are generally assumed to be a mixture of approximately 70% linear and 30% branched isomers.[8] The relative composition of isomers may be different from manufacturer to manufacturer, but over the span of 10 years and 8 production lots at the 3M Co., whom were responsible for ~80% of global POSF production, PFOS reportedly had a consistent isomer composition of

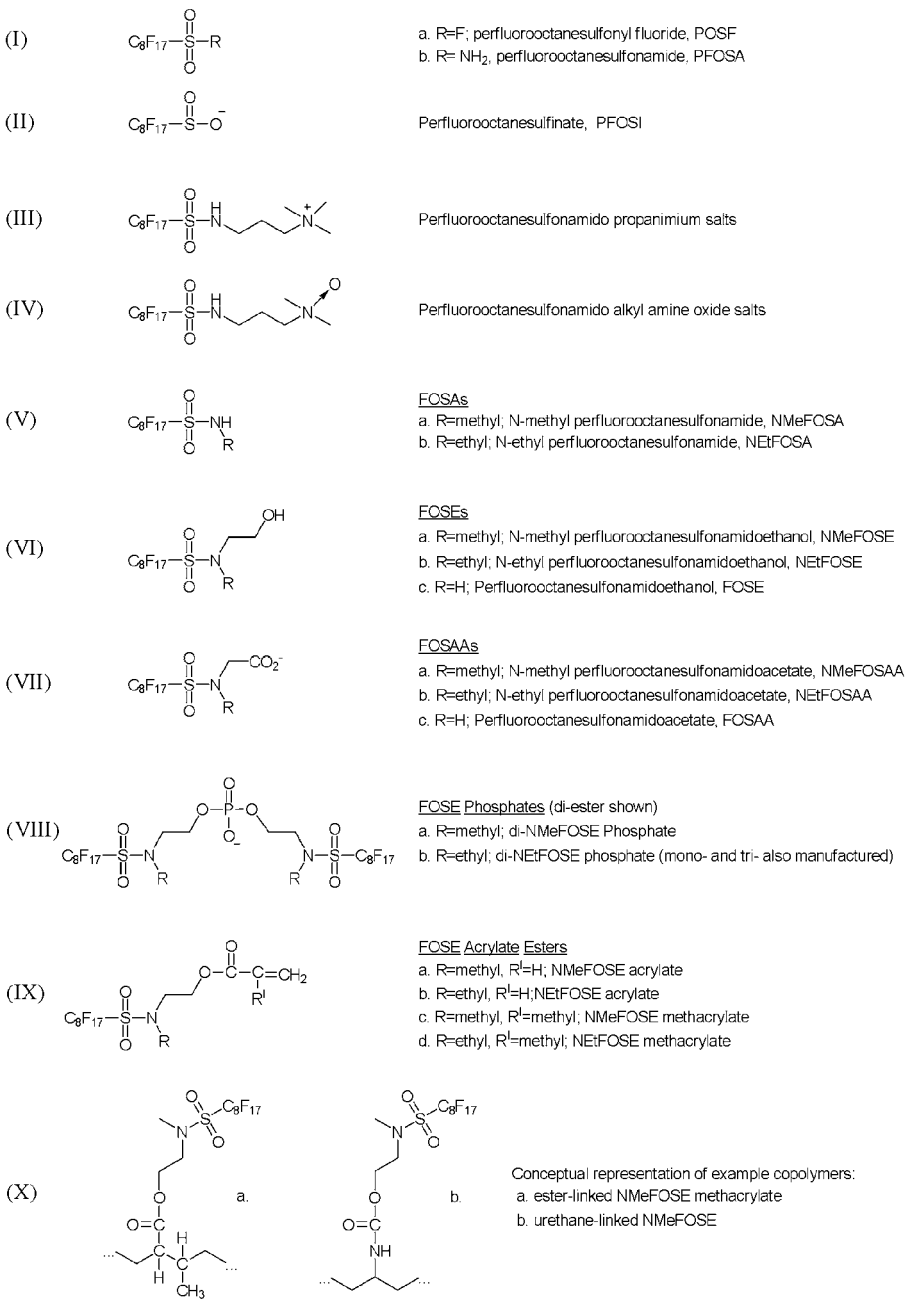

Fig. 1 Various structures of PreFOS known to have been intentionally manufactured, or present as residual in manufactured products.

70% linear (1.1% standard deviation) and 30% branched (0.8% standard deviation), as determined by ^{19}F nuclear magnetic resonance.[9] The isomer composition of 3M Co. PreFOS was also approximately 30% branched, though few samples have been analysed.[10]

The 3M Co. divided fluorochemical production into three different product categories.[7] The first were surface treatments consisting primarily of high molecular weight NMeFOSE acrylates (IXa.) which were polymerized with urethane, acrylate and/or adipate reactants, but the resultant formulations also contained unintentional non-polymeric residuals. These surface treatments were marketed collectively under the ScotchGard™ line of products, including carpet protectors, fabric and upholstery protectors, apparel and leather protectors, and protective products for after market and consumer application.

The second line of the 3M Co.'s fluorochemical products were used for protecting food packaging and paper products, and these were marketed collectively under the Scotchban™ tradename. Two different chemistries were utilized for this application, but it is unclear if these were combined or used independently of one another. The first were phosphate esters consisting of mixtures of mono-, di- and tri-phosphate esters of NEtFOSE alcohol (VIIIb.), in proportions of ~10%, 85% and 5% percent, respectively.[7] The second class of chemicals were NMeFOSE acrylate copolymers, presumably similar or identical to those used in ScotchGard™.

The third class of fluorochemicals manufactured by the 3M Co. were termed performance chemicals, and were marketed under the Fluorad™ tradename. These consisted of low molecular weight substances (including PFOS) for use in fire extinguishing foams, such as PreFOS alkyl amine oxides (IV),[8] mining and oil cationic surfactants, such as PreFOS propanimium salts (III),[8] electroplating and etching bath surfactants, household additives, chemical intermediates, coatings and coating additives, carpet spot cleaners, and insecticide raw materials.

Historic emissions

The bulk (~80%) of historical PFOS and PreFOS production can be attributed to the 3M Co., with other minor production by companies based in Europe and Asia. Up until the year 2002, estimates are that between 65160 t[10] and 96000 t[11] of total PFOS equivalents (*i.e.* PFOS + PreFOS) were manufactured for use in various industrial, commercial and retail applications. Although PFOS and its salts were indeed manufactured and used directly in specialized applications, the historic production volumes and estimated environmental emissions of PFOS are less than those of PreFOS. For example, Paul *et al.*[12] estimated that maximum direct historic emissions of PFOS to the environment were 450–2700 t, compared to 6800–45250 t for PreFOS. Similarly, Armitage *et al.*[11] estimated emissions of 285–2565 t for PFOS, and 735–4005 t for PreFOS. Therefore, on a simple production volume basis there is great potential for PreFOS to contribute to PFOS in the global environment.

Contemporary manufacturing

Since the manufacturing phase out of PFOS and PreFOS by the 3M Co. between 2000 and 2002 (and transition to various perfluorobutyl-based chemistries), minor PFOS production continued in Europe and in China (<42–82 t in Europe and <50 t in China in 2003), but by 2006 China had ramped up its POSF (Ia.) production to 200 t.[13] Approximately half of Chinese production is exported to Europe, Japan, and Brazil,[14,15] the latter of which is dependent on the insecticide Sulfuramid[16] (NEtFOSA, Vb.), for crop protection. No reliable data exist on the proportion of PFOS to PreFOS being manufactured in China, but 50% was assumed by Armitage *et al.*[11] A 2009 presentation to the United Nations Stockholm Convention indicated that 66 PFOS-related products have been registered with the Inventory of Existing Chemical Substances in China,[17] and at the time of this review, one manufacturer's website clearly indicated that PreFOS based phosphates and acrylates were commercially available.[18]

In 2009, PFOS and its precursors were added to Annex B of the International Stockholm Convention Treaty on Persistent Organic Pollutants.[19] While this was indeed a positive step, Annex B only *restricts* the use of chemicals, and many exemptions allow the continued mass production of PFOS and PreFOS. Ironically, the associated list of specific exemptions for PFOS and PreFOS include all of the major historic uses: photoimaging, firefighting foams, insect baits, metal plating, and surface treatment of leather, apparel, textiles, upholstery, paper and packaging.[19] Although scientific review consistently demonstrates PFOS to be hazardous to the environment, the listing of PFOS and PreFOS on Annex B was made in response to diplomatic pressure from developing countries.[20] Therefore, production of PFOS and PreFOS continues today, and the future risks to humans and wildlife in various global environments is difficult to predict.

Future exposure to PFOS is difficult to predict

For humans, temporal trends of PFOS in blood or breast milk have differed by country since the voluntary phaseout of perfluorooctyl chemistries by the 3M Co. between 2000 and 2002. In the United States, both adult blood[21] and newborn blood spots[22] showed declining PFOS after 2000. In Sweden, no clear trend in breast milk PFOS concentrations could be distinguished between 1996 and 2004.[23] Similarly, in young German adults, serum PFOS concentrations have remained stable between 1977 and 2004.[24] On the other hand, PFOS concentrations have increased exponentially since 2000 in human blood from Shenyang China, with concentrations exceeding 100 ng/mL by 2003.[25] Likewise, wildlife temporal exposure trends for PFOS have shown wide variability in different regions since 2000–2002. For example, considering Arctic organisms, completely opposite temporal trends of PFOS in wildlife have been observed. In some areas, PFOS rapidly declined in ringed seals (Canadian Arctic)[26] and sea otters (North Sea)[27] after the phase-out, whereas in Greenland, PFOS concentrations in polar bears have continued to increase.[28] Thus, for human and wildlife alike, trends vary spatially.

To explain the divergent temporal trends for PFOS in wildlife, a hypothesis involving PreFOS has emerged. As first implied by Butt *et al.*,[26] Armitage *et al.*[11] confirmed that the rapid decline of PFOS concentrations in Arctic mammals (*e.g.* references[26,27]) could not be explained if the primary source of exposure to these

particular Arctic foodwebs was direct uptake of PFOS from ocean water. Rather, Armitage *et al.*[11] suggested that certain Arctic foodwebs may have historically received significant proportions of their PFOS exposure from absorption and metabolism of atmospherically transported PreFOS. That is, PreFOS will partition into seawater from the atmosphere to some extent, and could thereby enter foodwebs directly, without first degrading to PFOS in air or water. After the manufacturing phaseout, atmospheric PreFOS emissions and concentrations should have declined quite rapidly. This would have led to a new equilibrium being rapidly established, with water in the Arctic ocean acting as a net source of PreFOS to the remote atmosphere, resulting in lower concentrations of PreFOS in the Arctic ocean, and less PreFOS entering foodwebs. Although there is not enough of a historical record in Arctic air to prove this hypothesis, it is a mechanistically plausible one that highlighted how little is known about the role of PreFOS in the global dissemination of PFOS.

Abiotic environmental degradation of PreFOS to PFOS

Degradation of chemicals in the physical environment may occur by hydrolysis, direct photolysis, or indirect photolysis. To assess the extent to which PreFOS can degrade to PFOS by such mechanisms, the relevant literature was reviewed.

Abiotic hydrolysis of PreFOS

An internal 3M study reported the abiotic hydrolysis rates of NMeFOSE acrylate (IXa.) by monitoring its degradation under various conditions. At 50 °C, half lives were 9.4, 17.8, 9.9, 9.3, and 7.9 days at pH 1.5, 5, 7, 9, and 11, respectively.[29] These experimental data were used to extrapolate half lives of 94, 178, 99, 93, and 79 days at 25 °C, although it is unclear how this extrapolation was made. Another study by the 3M Co. reported abiotic hydrolysis of the related molecule, NEtFOSE acrylate (IXb.), but again, only by monitoring disappearance of the parent compound. Calculated half lives at 25 °C were 42, 35, and 15 days at pHs 4, 7, and 9, respectively.[30] The authors postulated that hydrolysis could occur: i) at the sulfonamide bond, forming PFOS, ii) to the alkene, resulting in the alcohol $C_8F_{17}SO_2N(alkyl)CH_2CH_2OC(O)C_2H_4OH$, or iii) to the ester, yielding NEtFOSE (VIb.). However, in both of the above acrylate monomer experiments, product characterization was not conducted. Furthermore, glass labware was used, thus adsorption of the parent compound to glass may have led to overestimation of hydrolytic rates.

Another 3M Co. study examining base-catalyzed hydrolysis of NEtFOSE (VIb.) in 20% alcoholic KOH at 50 °C, observed 92% degradation of the test substance over 24 h, and PFOS was confirmed as a product by IR and NMR.[31] While this result requires confirmation, it's global relevance is questionable due to the conditions, but it could be relevant under landfill conditions, where pH can range from 4 to 9[32] and temperatures can be up to 57 °C.[33]

Lehmler *et al.*[34] reported a complex mixture of decomposition products resulting from the hydrolysis of NEtFOSE-methyl ester ($C_8F_{17}SO_2N(Et)CH_2CO_2CH_3$) in 2–10% aqueous (or ethanol) KOH solution. It was unclear if PFOS was among the products, but controlled basic hydrolysis yielded N-ethyl perfluorooctanesulfonamidoacetate (NEtFOSAA, VIIb.), which could potentially be an important pathway for release of free PreFOS from copolymeric commercial products. As highlighted by Rayne and Forest,[35] the same study subjected other environmentally relevant sulfonamides to strongly acid or basic conditions, and hydrolysis of the sulfonamide moiety was not observed. Thus, while hydrolysis of certain PreFOS molecules (*e.g.* methyl esters, or acrylate monomers and copolymers) may occur to some extent, it most likely occurs, if at all, *via* hydrolysis of the ester bond to form smaller PreFOS molecules, rather than by hydrolysis of the sulfonamide to form PFOS directly. This is consistent with the modeling results of Rayne and Forest,[35] whereby most perfluoroalkyl sulfonamides were not expected to undergo abiotic hydrolysis at the S–N, C–S, or N–C linkages under environmentally relevant conditions. Nonetheless, Rayne and Forest[35] did present a tentative pathway whereby NMeFOSE (VIa.), NEtFOSE (VIb.), N-methyl perfluorooctanesulfonamidoacetate (NMeFOSAA, VIIa.), or NEtFOSAA (VIIb.) *could* undergo intramolecular acid catalyzed hydrolysis *via* a cyclic transition state to form PFOS.

To date, there is no experimental data on the neutral, acid- or base-catalyzed hydrolysis of the important commercial PreFOS-based phosphate esters (VIII) or various copolymeric materials (*e.g.* X). However, speculation can be made from experiments involving structurally similar compounds. For example, D'eon and Mabury[36] investigated abiotic aqueous hydrolysis of 8 : 2 mono-fluorotelomer phosphate ($(C_8F_{17}C_2H_4OP(O)(OH)_2$) and 8 : 2 di-fluorotelomer phosphate ($((C_8F_{17}C_2H_4O)_2P(O)OH$), at pH 9.0 and 50 °C, but no degradation was observed over 2 weeks. This result is similar to previous data showing the resistance of phosphate mono- and di-esters to hydrolysis,[37] and suggests that the analogous PreFOS mono- and di-phosphates may also be resistant to abiotic hydrolysis, but this requires experimental confirmation. NEtFOSE tri-phosphate esters (VIIIb.) made up 5% of total phosphates in Scotchban™ materials, and these are thought to be more labile to hydrolysis than the corresponding mono- and di-phosphate esters.[38,39] Rayne and Forest[35] predicted hydrolytic half lives of 7,400 and 29,000 years (pH 7, 25 °C), and 2.5 and 19 years (pH 9, 50 °C) for mono- and di-phosphate esters of NEtFOSE, respectively. However, the same study estimated hydrolytic half lives for fluorotelomer-linked phosphates that were up to several orders of magnitude faster than the experimental results of D'eon and Mabury.[36] Given the lack of consistency in the data generated in different studies to date, laboratory experimentation with relevant PreFOS-phosphates is necessary.

Hydrolysis of NMeFOSE acrylate or methacrylate polymers or oligomers (*e.g.* X) can also be considered as potential sources of free (*i.e.* mobile or bioavailable) PreFOS to the environment, but to date little information is available on their degradation. Potential pathways for a perfluorooctylsulfonamide-linked acrylate polymer to be hydrolyzed include cleavage of the carbon backbone to form PreFOS acrylate (IX) or smaller oligomers, hydrolysis of the ester linkage to form FOSEs (VI), or hydrolysis of the sulfonamide linkage to form PFOS; albeit this latter pathway appears less likely to occur based on the above discussion. Rayne and Forest[35] modelled the acid- and base-catalyzed,

and neutral hydrolysis, of several analogous fluorotelomer acrylate polymers and monomers and found a strong temperature and pH dependence. Under landfill conditions (40–50 °C, pH 4–9), the half lives of freely dissolved monomers and polymers were estimated to be 4 days and 1 year, respectively. However, the authors indicated that these estimates, which are based on freely dissolved particles, likely overestimate the true rates of hydrolysis for the polymer particles. As indicated by Washington *et al.*,[40,41] surface area limitations can play a significant role in the hydrolysis of polymers. Certainly, the results of a Dupont study[42] suggest much longer hydrolytic half lives. In that study, abiotic hydrolysis of a fluorotelomer acrylate polymer was examined over 5 days, and no abiotic hydrolysis was observed (pH range 1.2–9.0, temperature range 37–50 °C). Thus, the hydrolysis of PreFOS containing oligomers and copolymers requires further experimentation.

As mentioned briefly by Olsen *et al.*,[21] a potentially important unknown is the emission and hydrolysis of POSF (Ia.). It is predictable that this molecule will convert 100% to PFOS by hydrolysis, although the rate of this reaction is unknown. In 1997, at 3M's Decatur Alabama plant, it was reported that point and fugitive emissions of POSF to air were estimated to be < 34,700 lbs, and in sludge (landfilled) to be 26,000 lbs.[8] POSF, as the common building block for all PFOS and PreFOS manufactured materials, is also noted to have been a residual (typically < 1%) in a variety of manufactured materials, including in aqueous film forming foams. Thus, beyond POSF emissions during manufacturing, it was also likely emitted during various applications due to its presence as a residual. Its relatively high vapour pressure (1.6 torr at 20 °C)[43] and moderate estimated water solubility (1 mg/L)[43] could presumably have led to its emission to the ambient atmosphere, and its subsequent hydrolysis in atmospheric water. A reason for so little information on the fate of POSF is, perhaps, that there are no published analytical methods for the specific detection of it in the open environment. By typical HPLC-MS methods, POSF is indistinguishable from PFOS because, in our experience, it hydrolyses during electrospray ionization to PFOS, and cannot be resolved chromatographically from PFOS. The 3M Co. used air canister sampling with GC-MS or GC-ECD for monitoring of POSF in air in its plants,[8] but details of this method could not be located, and previous attempts at monitoring POSF by GC-MS produced no signal in various ionization modes.[44]

Aqueous photolysis of PreFOS

Photolytic transformation of a substance can occur directly, from molecular absorption of light, or indirectly from reactions with an intermediate molecule that has undergone photolytic transformation/excitation.[39] Several internal studies by the 3M Co. indicate that PFOS is resistant to direct photolysis under simulated environmental conditions. Yamamoto *et al.*[45] did, however, observe direct photolysis of PFOS in water and alkaline 2-propanol following irradiation with a 254 nm UV lamp for up to 10 days, with products including perfluorocarboxylic acids. Photolysis experiments involving PreFOS are comparatively scarce, however one 3M study reported OH radical initiated oxidation by ultraviolet light/hydrogen peroxide (UV/H_2O_2) irradiation of NEtFOSE (VIb).[46] In that work, NEtFOSA (Vb.), PFOSA (Ib.), and perfluorooctanoate were observed as products, but not PFOS, and direct photolysis of NEtFOSE was not observed.[46] Consistent with these results, Plumlee *et al.*[47] also utilized UV/H_2O_2 irradiation to degrade several PreFOS molecules, including NEtFOSE (VIb), NEtFOSAA (VIIb), NEtFOSA (Vb.) and perfluorooctanesulfonamidoacetate (FOSAA, VIIc). The end products of these experiments were perfluorooctanoate and PFOSA (Ib.), which were not observed to undergo further degradation when independently irradiated. Again, PFOS was not observed as a product here.

To our knowledge, photolytic decomposition, whether by direct or indirect processes, has not been investigated in any PreFOS-linked copolymer or phosphate, and there has also been no work on analogous fluorotelomer materials. Further work may therefore be considered to assess photolysis of PreFOS phosphates or copolymers as a potential source of environmental PreFOS.

Atmospheric oxidation of PreFOS

Only two papers have explored the atmospheric oxidation of PreFOS. Martin *et al.*[48] subjected a perfluorobutane analogue of NEtFOSA (Vb.) to gas phase reactions with Cl and OH radicals. It was determined that OH radical reactions would be the dominant removal mechanism in the troposphere, with atmospheric lifetimes ranging from 20–50 days, sufficient for long-range transport to remote global regions. Product studies, conducted with Cl radicals, showed the formation of many N-alkyl oxidized PreFOS intermediates (*i.e.* a ketone and two aldehydes) as well as perfluorinated carboxylates. Martin *et al.*[48] did not detect formation of perfluorobutanesulfonate (analogous to PFOS), however, product studies were conducted in the absence of NO_x, and OH radicals were only used in the kinetic studies, not the product studies. In a follow-up study by D'eon and Mabury,[49] investigating the gas phase OH radical reaction products of the perfluorobutane analogue of NMeFOSE (VIa.), traces of perfluorobutanesulfonate (analogous to PFOS) were reported to be observed. Further work is therefore warranted to elucidate the yield and mechanisms of PFOS formation from PreFOS in smog chambers to determine if these will be significant in the real atmosphere. It is notable that the aldehyde species, $C_4F_9SO_2N(H)CHO$, was common to both studies, thus $C_8F_{17}SO_2N(H)CHO$ may be a good marker of atmospheric oxidation of most PreFOS species. Both studies also tentatively identified perfluorobutanesulfonamide, analogous to PFOSA (Ib.), as a major product, however neither author could confirm that this was not a sampling artefact, or a product of heterogeneous reactions within the experimental smog chamber. This product is noteworthy however, because Saez *et al.*[50] reported that PFOSA was the dominant perfluorinated compound in a Russian Arctic ice core, at concentrations 2–3 orders of magnitude higher than PFOS.

The gas phase-oxidation of PreFOS acrylates (IX) has not been investigated, but some work has been conducted on analogous fluorotelomer-based substances. Butt *et al.*[51] examined the gas-phase Cl and OH radical oxidation of 4 : 2 fluorotelomer acrylate monomer and found it to degrade rapidly by OH radicals (estimated lifetime ~1 day) to $C_4F_9CH_2CH_2OC(O)C(O)H$. Based on this result, it may be speculated that atmospheric

oxidation of NMeFOSE acrylate (IXa.) would yield $C_8F_{17}SO_2N(Me)CH_2CH_2OC(O)C(O)H$ which would likely further degrade to NMeFOSE (VIa.) *via* abiotic or biological degradation. However, PreFOS acrylates have not been detected in ambient air, thus the atmospheric chemistry of these substances may not be an important issue. Shoeib *et al.*[52] monitored for NMeFOSE acrylate (IXa.) in the North Atlantic and Canadian Archipelago, but it was always below detection limits (0.001 pg/m3). Further work is needed to fully characterize the atmospheric oxidation pathways of important PreFOS species known to be present in the atmosphere.

Biodegradation of PreFOS

Although the area has received only little scientific attention, it is generally agreed that PreFOS molecules can degrade to PFOS by biological processes. Even before 3M had voluntarily phased out its production of PFOS and PreFOS, its own internal research indicated that the biotransformation of various PreFOS molecules would yield PFOS as an ultimate metabolite *via* a PFOSA (Ib.) intermediate;[53] and once formed, PFOS was not known to have any subsequent route of biotransformation. Subsequent examples have since appeared in the literature showing similar conclusions for microbes and rodents, these studies and related *in vitro* studies will be reviewed here with an emphasis on the pathways and yield of PFOS.

Aerobic microbial biodegradation

In early studies, the 3M Co. examined the biodegradation of NEtFOSE acrylate (IXb.),[54] NMeFOSE (VIa.),[55] and NEtFOSE (VIb.)[56] in activated sludge, but biodegradation could not be confirmed nor ruled out because only a single measurement of the test substance at the end of the study was made, the solubility of the test substance was not characterized, and potential contamination from the bioreactor was not addressed. A more recent study by Lange,[57] sponsored by the 3M Co., reported that NEtFOSE was 90% biotransformed to seven products after 35 days. Biotransformation followed the following pathway: NEtFOSE → NEtFOSE acetaldehyde ($C_8F_{17}SO_2N(Ethyl)CH_2CHO$) → NEtFOSAA (VIIb. 34.9% yield) → NEtFOSA (Vb. 0.1% yield) → perfluorooctanesulfonamidoethanol (FOSE, VIc.) → NEtFOSA acetaldehyde ($C_8F_{17}SO_2NHCH_2CHO$) → FOSAA (VIIc. 48.9% yield) → PFOSA (Ib. 5.0% yield) → perfluorooctanesulfinate (PFOSI, II, 3.5% yield). PFOSI was then observed to undergo biodegradation to PFOS (7.0% total yield from NEtFOSE) or abiotic degradation to form PFOA (0.6% yield from NEtFOSE). A molar balance indicated that these were the major metabolites. In qualitative agreement with these results, Boulanger *et al.*[58] showed that NEtFOSE biodegraded to PFOSI (5.3% yield) either directly or indirectly *via* formation of the major metabolite NEtFOSAA (VIIb. 23% yield) following 96 h of aerobic biotransformation. However, FOSAA (VIIc.), PFOSA (Ib.), and PFOS were not observed as products here, and only 68% of the transformed parent material could be accounted for in the products. No anaerobic transformation of NEtFOSE was observed, confirming that the observed products were strictly from aerobic biotransformation. The much shorter length of this study, relative to Lange,[57] likely accounts for no observation of PFOS by Boulanger *et al.*

More recently, Rhoads *et al.*[59] conducted separate incubations of NEtFOSE (VIb.), NEtFOSAA (VIIb), NEtFOSA (Vb.), PFOSA (Ib.), and PFOSI (II) with activated sludge to refine the biotransformation pathways suggested by Lange[57] and Boulanger *et al.*[60] For NEtFOSE, only 0.3% of the starting material remained after day 10, and degradation followed the order: NEtFOSE → NEtFOSAA (VIIb. 75.7% yield) → NEtFOSA (Vb. 1.6% yield) → PFOSA (Ib., 20% yield, possibly *via* FOSAA (VIIc. 8% yield) → PFOSI (II, 0.7% yield) → PFOS (7.9% yield). The molar balance of products was ~114%, demonstrating reasonable mass balance. These results are largely consistent with the results of Lange,[57] with the main exception being observation of PFOA, which was detected by Lange[57] but not here by Rhoads *et al.*[59] The metabolic activity of various microbial cultures used and/or the differences in incubation time used in these studies may have played a role in the observed biotransformation pathways. Common to all three studies, however, was the observation of NEtFOSAA (VIIb.) as the major metabolite, and PFOSI (II) as a minor metabolite. PFOSI detection in the environment, or in wastewater treatment plants (WWTPs), is challenging because it is known to hydrolyze abiotically to PFOS.[61] NEtFOSAA, which has been observed in waste water and various surface waters[58,60,62] may therefore represent the best biomarker of PreFOS biotransformation, although as noted it was also a commercial material and a residual material. Overall, both Boulanger *et al.*[60] and Rhoads *et al.*[59] concluded that precursor biotransformation to PFOS in waste water treatment will occur microbially, and Boulanger *et al.*[58] postulated that the elevated concentrations of PFOS in WWTP effluent are likely due to the presence of PreFOS in various consumer and commercial materials. However, both studies also note that formation of PFOS is not the major fate of PreFOS in WWTPs. For example, Rhoads *et al.*[59] suggested that 76% of NEtFOSE entering a WWTP could enter the atmosphere by air stripping. Thus, while microorganisms in WWTPs can clearly oxidize PreFOS to PFOS to some extent, the more important point may be that WWTPs play an important role in emitting neutral PreFOS molecules (*i.e.* those having some measurable vapour pressure) to air. As previously discussed, the atmospheric chemistry of PreFOS needs more attention, but the yield of PFOS in the atmosphere appears minimal, relative to biodegradation of PreFOS.

It is currently unclear if PreFOS-containing copolymeric materials can undergo biodegradation to yield free PreFOS, nor is it clear if this has been considered as a potential source of PreFOS (and ultimately PFOS) in inventory and modeling publications.[7,12] The biodegradation stability of analogous fluorotelomer acrylate monomers and polymers has been a debated issue, on account of the impact this source could potentially have on future PFOA concentrations. Russell *et al.*[63] investigated the aerobic biodegradation of a fluorotelomer acrylate containing polymer (*e.g.* $F(CF_2)_8C_2H_4OC(O)CHRCH_2R$) in four soils over 2 years and found only a slight potential for biodegradation, with calculated half lives of 1200–1700 years. In stark contrast to this result, Washington *et al.*[40] conducted biodegradation studies on a similar material, and calculated half lives as low as 10–17 years. However, concerns about both studies have been made,[41,64]

Table 1 Concentrations of PFOS and PreFOS measured in the same human samples of blood, serum, or plasma. Due to their divergent partitioning properties in blood, note that when comparing across studies that whole blood PFOS concentrations will be lower than if serum or plasma were used, whereas PreFOS whole blood concentrations will likely be higher than if serum or plasma were used.[a]

Study details	Country and year of blood collection	PFOS (ng/ml or ng/g)	PreFOS (ng/ml or ng/g)
Olsen *et al.*[160] 645 serum samples from blood donors in 6 American cities – (*Medians*)	USA – Six Cities – 2003	35.8	NEtFOSAA < 2.8 NMeFOSAA < 1.3
Olsen *et al.*[99] 600 plasma samples (301 M, 299 F) from blood donors in 6 American cities – (*Geometric Means*)	USA – Six Cities – 2006	34.3	NMeFOSAA = 1.6 NEtFOSAA = 2.5
	2000–2001	14.5	NMeFOSAA =0.5 NEtFOSAA = 0.5
Olsen *et al.*[89] Serum samples from 238 elderly people in Seattle – (*Medians*)	USA – Seattle – 1996	30.2	EtFOSAA = 1.6 MeFOSAA = 1.8
Spliethoff *et al.*[22] Newborn blood spots between 1997 and 2007. (*Medians*)	USA – New York State 1999–2000	2.29	PFOSA = 1.59
	2003–2004	1.74	PFOSA = 0.33
Haug *et al.*[100] pooled serum, pooled by year of collection, age, and sex (select data for men, age 40–50, are shown)	Norway – 1977	3.8	PFOSA < 0.05
	1982	11	PFOSA = 0.095
	1988	18	PFOSA = 0.6
	1993	33	PFOSA = 0.57
	1999	29	PFOSA = 0.32
	2003	27	PFOSA = 0.081
	2006	12	PFOSA < 0.05
Kannan *et al.*[91] 473 human blood[b], serum, or plasma samples from different countries - (*Medians*)	USA – Michigan – 2000 (75 Sera)	28.9 (F) & 32.9 (M)	PFOSA = 2.2 (F) & 3.0 (M)
	USA – Kentucky – 2002 (30 Whole Blood[b])	81.0 (F) & 72.0 (M)	PFOSA = 3.1 (F) & 4.0 (M)
	Colombia – 2003 (56 Whole Blood[b])	7.3 (F) & 8.1 (M)	PFOSA = 0.9 (F) & 1,4 (M)
	Brazil – 2003 (29 Whole Blood[b])	8.4 (F) & 12.7 (M)	PFOSA = 0.7 (F) & 1.7 (M)
	Italy – 2001 (50 Sera)	3.5 (F) & 4.2 (M)	PFOSA = 1.7 (F) & 1.6 (M)
	Poland – 2003 (25 Whole Blood[b])	33.8 (F) & 40.9 (M)	PFOSA = 1.6 (F) & 1.0 (M)
	Belgium – 1998/2003 (20 Plasma)	10.4 (F) & 17.6 (M)	PFOSA = < 3 (F) & < 3 (M)
	India – 2000 (45 Sera)	2.5 (F) & 1.3 (M)	PFOSA = < 3 (F) & <3 (M)
	Malaysia – 2004 (23 Whole Blood[b])	11.7 (F) & 13.1 (M)	PFOSA = 4.1 (F) & 3.9 (M)
	Japan – 2002 (38 Sera)	18.3 (F) & 12.4 (M)	PFOSA = 5.8 (F) & 5.8 (M)
	Korea – 2003 (50 Whole Blood[b])	11.3 (F) & 21.7 (M)	PFOSA = 1.1 (F) & 1.3 (M)
Kuklenyik *et al.*[161] 20 human serum samples from 10 females and 10 males – (*Medians*)	USA – Georgia – 2003	31.6 (F) & 63.7 (M)	PFOSA = 0.25 (F) 0.25 (M)
Calafat *et al.*[162] 23 pooled serum samples in the United States and 44 individual Peruvians– (*90th centiles*)	USA – 1990–2002	51.0	NEtFOSAA 0.80 (F) 0.80 (M) NMeFOSAA 1.35 (F) 1.40 (M)
	Peru – 2003	0.7	PFOSA = 0.6 NEtFOSAA = 2.5 NMeFOSAA = 1.0 PFOSA < 0.2 NEtFOSAA < 0.4 NMeFOSAA < 0.6
Inoue *et al.*[163] 21 plasma samples from 10 female and 11 male volunteers (*Medians*)	Japan – 2003	12.1 (F) & 17.5 (M)	PFOSA < 1.0 (M &F)
Yeung *et al.*[94] 85 samples of whole blood[b] from healthy volunteers. (*Means*).	China (8 different provinces) – 2004	52.7	PFOSA = 1.82[b]
Yeung *et al.*[93] 30 samples of whole blood (range of means for 5 cities shown)	China (5 cities)	1.4–56.3	PFOSA = 0.112–1.65
Karrman *et al.*[164] 40 pools of serum from 3802 individuals, stratified by age, gender and rural(R) /urban(U) living. (*Medians*)	Australia – 2002/2003	17.9 (F-R) & 22.3 (M-R) 20.8 (F-U) & 22.8 (M-U)	PFOSA 0.56 (F-R) & 0.87 (M-R) 0.65 (F-U) & 0.74 (M-U)
Karrman *et al.*[95] whole blood from 26 females and 40 males- *Study A* -(*Medians*)	Sweden – 1997 to 2000	28.9 (F) & 32.9 (M)	PFOSA 2.7 (F) 2.7 (M)
Plasma and whole blood from 3 females and 2 males –*Study B – Individual Values for plasma* (*whole blood*) *are given*	Sweden – 2004	F-17.3(14.2), 17.3(15.0), 14.8(11.3)	PFOSA F 0.11 (0.86), <0.1(0.37), 0.10(0.37)
		M –18.9(15.2),34.1(27.8)	PFOSA M <0.1 (0.27), 0.22(1.3)
Ericson *et al.*[96] whole blood from 24 females and 24 males - (*Medians*)	Spain (Catalonia) – 2006	7.22 (F) & 8.31 (M)	PFOSA = 0.38 (F) & 0.33 (M)
Weihe *et al.*[112] paired serum of 103 children at ages 7 and 14 and	Faroe Islands – 7 yr olds (1993–1994)	26.3	PFOSA = 1.3 NMeFOSAA = 0.4

Table 1 (*Contd.*)

Study details	Country and year of blood collection	PFOS (ng/ml or ng/g)	PreFOS (ng/ml or ng/g)
from 12 pregnant women and their children 5 years later (*Medians*)	14 yr olds (2000–2001)	31.2	NEtFOSAA = 1.4 PFOSA = 0.3 NMeFOSAA = 0.4
	Pregnant Women (2000)	23.7	NEtFOSAA = 1.0 PFOSA = 0.6 NMeFOSAA = 0.9
	their children 5 years later	16.3	NEtFOSAA <LOD PFOSA = <LOD NMeFOSAA = 0.3 NEtFOSAA = <LOD
Rylander *et al.*[165] Plasma from 91 delivering women -(*Medians for PFOS*)	Vietnam – 2005	3.2 (F)	PFOSA 2% > LOD (0.04) *Range* <0.04–0.13 (F)
Rylander *et al.*[166] Plasma from 326 women -(*Medians*)	Norway – 2004	20 (F)	PFOSA 0.02 (F)
Rylander *et al.*[167] Plasma from 44 women and 16 men in coastal area (*Medians*)	Norway – 2005	24 (F) & 43 (M)	PFOSA 0.08 (F) & 0.11 (M)
Toms *et al.*[168] 84 pools of human serum stratified by age and gender (*Medians*)	Australia – 2006 & 2007	14.8	PFOSA 24% > LOD (0.1) *Range* <0.1–0.5 NEtFOSAA 1% > LOD (0.2) *Range* <0.2–0.2 NMeFOSAA = 0.6
Von Ehrenstein *et al.*[169] 34 and 30 Serum Samples from women at 2–7 weeks and 3–4 months post partum respectively (*Medians*)	USA – 2004 & 2005	Visit 1: 20.0 (F) Visit 2: 16.9 (F)	PFOSA Visit 1: < 0.05 (F) Visit 2: 0.1 (F) NEtFOSAA Visit 1: < 0.05 in all Visit 2: < 0.05 in all NMeFOSAA Visit 1: 0.20 (F) Visit 2: < 0.05 (F)

[a] (M) = male, (F) = female. When gender is not indicated, it refers to the overall (M & F combined) median or mean. [b] The authors multiplied all whole blood data by a factor of two, to equate with serum concentrations, however as discussed this may be inappropriate for PFOSA and other PreFOS based on partitioning results of Karmaan *et al.*[95]

including the extraction methods and the high concentration of residuals present in the study of Russell *et al.*;[63] which would preclude observation of important degradation products.[63] Criticisms of Washington *et al.*[40] related to the few data points used in half life calculations. Washington *et al.*[40] postulated that the fluorotelomer acrylate polymer degraded through attack on the carbon backbone, and/or the ester linkage connecting the polymer backbone to the fluoroalkyl side chains, both of which are linkages used for PreFOS acrylate containing copolymers. Most recently, Russell *et al.*[65] investigated degradation of a fluorotelomer urethane polymer and observed an average half life of 102 years (range 28–241 yrs). PreFOS based urethanes (*e.g.* Xb.) are also known to have been incorporated into 3M's ScotchGard™ line of products, and thus it is reasonable to speculate that these also may yield free PreFOS, and ultimately PFOS, *via* similar pathways. The important unknowns are the overall emission of such copolymers to the environment, and the rate of degradation, which needs to be assessed experimentally.

NEtFOSE phosphates (VIII) also likely contribute to smaller PreFOS intermediates and PFOS concentrations in the environment *via* microbial biodegradation pathways, but this has only been demonstrated *in vitro* for mammals (next section). Further data is needed on emission of PreFOS phosphate esters to the environment, and studies on their microbial biodegradation potential (products and rates) are also needed.

In vitro biotransformation

Early work by the 3M Co. characterized the metabolites formed from the human and rat hepatocyte incubation of NEtFOSE (VIb.) and NEtFOSE mono-phosphate (VIII). After 6 h, NEtFOSE phosphate was dephosphorylated to yield free NEtFOSE, and both compounds were metabolized to various products including NEtFOSAA (VIIb.), FOSE (VIc.), PFOSA (Ib.) and PFOS;[53,66] the product yields were not quantified in this study. Interestingly, a four-fold increase in the concentrations of NEtFOSAA in human blood between 1974 and 1989 coincides with the commercialization of perfluoroalky sulfonamide-based phosphates for food contact applications in 1974.[67] The recent decrease in the concentration of PFOS in human blood, since 2002 (discussed later), may primarily reflect the phase-out of these products.

Xu *et al.*[68] recently further elucidated the pathways of NEtFOSE (VIb.) metabolism in human and rat liver slices, microsomes, and isolated cytochrome P450 (CYP450) enzymes. The dominant initial pathway was deethylation to form FOSE (VIc.), a reaction catalyzed by CYP450 3A2 and 2B1 in rats, and 2C19, 3A5 and 3A4 in humans. Subsequent metabolism of FOSE yielded PFOSA (Ib.). This reaction occurred quickly, and was catalyzed by rat CYP450 2C11 or human 2C19. The initial deethylation of NEtFOSE to FOSE is likely the rate-limiting step in the metabolic pathway to PFOSA.[68] Both the alcohols,

NEtFOSE and FOSE, can alternatively be oxidized to the corresponding carboxylic acids, NEtFOSAA (VIIb.) and FOSAA (VIIc.).[68] This pathway, however, was only observed in cytosol or whole liver slices, implying that enzymes other than CYP450 must be responsible for this step. NEtFOSAA and FOSAA did not undergo any further transformation, which may explain why FOSAAs (VII) have been commonly detected in humans.

It has also been hypothesized that dealkylation of NEtFOSE (VIb.) could occur, yielding NEtFOSA (Vb.). NEtFOSA was not detected in either microsomes or liver slices by Xu *et al.*,[68] although it was detected in hepatocytes in earlier studies.[53,66] It has been suggested that the lack of NEtFOSA detection in some studies may be due to its rapid conversion to PFOSA.[68,69]

PFOS has been found as a metabolite of NEtFOSE (VIb.), NEtFOSA (Vb.), and NEtFOSE mono-phosphate (VIIIb.) in rat and human hepatocytes.[53,66] Interestingly, Xu *et al.*[68] were only able to detect the formation of PFOS from PFOSA (Ib.) in rat liver slices (*i.e.* no PFOS was formed in hepatocytes or microsomes), but even in liver slices the biotransformation rate was very slow. Benskin *et al.*[69] were also unable to detected PFOS in their microsomal studies of NEtFOSA. Tomy *et al.*[70] is the only report on the formation of PFOS from PreFOS in microsomal preparations (20% of NEtFOSA was converted to PFOS), although trout liver microsomes were used in this work. Thus, certain fish species may have an increased capacity for transformation of PreFOS to PFOS, relative to humans and rats.

PreFOS can also undergo phase II metabolism *in vitro*. NEtFOSE (VIb.) and FOSE (VIc.) undergo *O*-glucuronidation, and PFOSA is *N*-glucuronidated in liver slices and microsomes.[68,71] V_{max} for the *N*-glucuronidation of PFOSA by human UDP-glucuronosyltransferase (UDPGT) enzymes, was 2–4 times higher than those observed for rat, dog, or monkey UDPGTs, indicating that species specific differences can be expected in the glucuronidation of PFOSA,[71] although how these results translate to *in vivo* metabolism is unclear. PFOSA is commonly detected in human blood, but to our knowledge the glucuronide conjugate has never been examined in biomonitoring studies, despite that it may enter into enterohepatic recirculation and be pseudo-persistent. As discussed below, the mechanism by which PFOSA yields PFOS may involve the intermediate glucuronide, thus species specific activities of UDPGT could affect PFOS yields from PreFOS.

In vivo mammalian biotransformation

The metabolic pathways of PFOS precursors described *in vitro* have been confirmed through several *in vivo* studies. The greatest difference from *in vitro* studies, however, is that the dominant metabolite detected *in vivo* is PFOS.

Of the few *in vivo* pharmacokinetic studies on PreFOS, only two have measured the bioavailability of PreFOS, and both of these were conducted with NEtFOSA (Vb.). It was found that NEtFOSA had limited bioavailability, with between 19.5% (for a 100 mg/kg dose) and 28.6% (for a 500 mg/kg dose) of an intraruminal dose being absorbed in sheep.[72] In rats, NEtFOSA is slowly absorbed, with maximum concentrations in whole blood being reached 4–6 h after oral dosing, and 25% of NEtFOSA may be excreted unchanged.[73] However, like with other hydrophobic contaminants,[74] the role of diet appears to be a factor in the bioavailability of NEtFOSA. NEtFOSA administered in an oil vehicle showed much higher bioavailability, measured by higher blood concentrations, longer elimination half-lives, and larger areas under the plasma concentration-time curves.[73]

Once in the body, PreFOS tends to partition into protein-rich compartments. In rats administered ^{14}C-NEtFOSA (Vb., radiolabel on the ethyl group), the largest proportion of radiation was found in the kidney, liver, and adrenal gland.[73] Likewise, PFOSA (Ib.) was present at the highest concentration in liver and lung of rats dosed with NEtFOSA in food, and in the liver, lung and kidneys of sheep administered a single intraruminal dose of NEtFOSA.[72,75] Similar results have been found in studies examining the tissue distribution of PFOSA in wildlife,[76,77] however higher concentrations of PFOSA were detected in stomach and intestine of sturgeon than in other tissues;[78] albeit these two tissues were not analyzed in the above studies for comparison.

No studies to date have investigated the *in vivo* metabolism of PreFOS-phosphates (VII). Recently, however, it was found that 8 : 2 fluorotelomer mono- and di-phosphates were dephosphorylated *in vivo* to the 8 : 2 fluorotelomer alcohol.[36] Given that perfluorooctane sulfonamidoethanol mono-phosphate is dephosphorylated *in vitro*,[53,66] it likely occurs *in vivo* as well (*e.g.* to yield NEtFOSE, VIb.), as it did for the analogous fluorotelomer material, but this will also depend on the extent of bioavailability through gastrointestinal absorption.

Several studies have investigated the *in vivo* metabolism of NEtFOSE (VIb.). After receiving a dose of 5 mg/kg for 21 days by gastric intubation, rats metabolized approximately 9.5% of the total dose to PFOS, with all the other metabolites, including NEtFOSAA (VIIb), FOSE (VIc.) and PFOSA (Ib.) accounting for only 1.1%.[79] This resulted in concentrations of PFOS in liver and serum that were an order of magnitude higher than NEtFOSAA or PFOSA, which is a common relative profile of perfluorinated compounds in human biomonitoring studies (discussed later). In a separate study, Seacat *et al.* reported that 20% of an oral dose of NEtFOSE was converted to PFOS in rats,[80] however the dose and the conditions of this exposure were not discussed. No pharmacokinetic information was presented in either of these studies, but these percentage yields have been used in exposure models[81,82] to estimate the importance of PreFOS to PFOS body burdens. However, it is important to consider that the *in vivo* yield can be affected by the dose. At low environmentally relevant doses, the yield of PFOS may be higher, due to better bioavailability and little or no saturation of enzymatic pathways, or may be lower, due to increased importance of phase II conjugation and excretion (*i.e.* if phase II enzymes become saturated at higher doses of PreFOS).

The most detailed pharmacokinetic studies of PreFOS are for NEtFOSA (Vb.), owing to its use as an insecticide (*i.e.* Sulfluramid). These studies have found that NEtFOSA is rapidly dealkylated in rats and sheep to PFOSA (Ib.), with elimination half-lives of 15 to 20 h.[72,2,75] In fact, in rats fed chow spiked with NEtFOSA for 56 days, no NEtFOSA was detected in whole blood or tissues at any time point.[75] This likely explains why NEtFOSA could not be detected in the *in vitro* metabolism of NEtFOSE (VIb.), as described above, and why NEtFOSA is rarely detected in samples of humans or wildlife. The efficiency

with which NEtFOSA is metabolized *in vivo* indicates that it is subject to extensive first past metabolism, resulting in a high yield conversion to PFOSA. In rats, large quantities (56%) of ^{14}C radiolabel was recovered in respired air 72 h after receiving a 50 mg/kg dose of ^{14}C-NEtFOSA by gavage,[73] indicating that NEtFOSA is deethylated very easily. In rats receiving a lower (2 mg/kg) interarterial bolus injection of NEtFOSA, the metabolism of NEtFOSA to PFOSA was approximately 100%.[83] Administration of NEtFOSA in food, or by intraruminal injection, yielded PFOSA:NEtFOSA ratios in whole blood of 450 : 1 and 25 : 1, respectively.[72,73] Unfortunately, these NEtFOSA studies did not monitor for PFOS as a product.

The pharmacokinetics of PFOSA (Ib.) indicate that it is slowly metabolized or excreted, with elimination half-lives ranging from 2 days in sheep, to 5 to 10.6 days in rats, depending on the route of administration.[72,75,84] Although considerably shorter than the elimination half-life for PFOS (30–103 days in male rats, depending on the isomer[85]), the relatively long half-life of PFOSA may be the result of the resistance of the sulfonamide group to metabolism, the binding of PFOSA to red blood cells, or through the enterohepatic recirculation of the *N*-glucuronide. *N*-glucuronide conjugates have been recovered in the bile from rats administered an interarterial dose of PFOSA, accounting for 3% of the dose, while only 0.3% of the dose was excreted as unchanged PFOSA.[83]

Despite inconsistent findings *in vitro*, the metabolism of PFOSA (Ib.) to PFOS has been confirmed *in vivo*, and the extent of biotransformation was quite high. In rats given an oral dose (5 mg/kg by gavage) of PFOSA, 32% of the dose was recovered as PFOS in the serum and liver 4 days after dosing.[84] Other body compartments were not analyzed, thus the total yield of PFOS must have been considerably higher than 32%.

The mechanism by which PFOSA (Ib.) is metabolized to PFOS is not clear. The sulfonamide group is generally considered resistant to biotransformation,[86] and the *in vivo* hydrolysis of any other sulfonamide has only been reported in one study to our knowledge.[87] Similar to the intramolecular rearrangement that was hypothesized as an abiotic degradation pathway for NEtFOSAA (VIIb.) and NEtFOSE (VIb.),[35] an analogous pathway could be constructed for the glucuronide of PFOSA. Xu *et al.*[71] proposed that the formation of PFOS could proceed through the enzyme catalyzed hydrolysis of the *N*-glucuronide intermediate by protonation of the amide, followed by opening of the glucuronide ring, and subsequent S_N2 hydrolysis at the sulfur-nitrogen bond. While plausible, such a mechanism has not been reported *in vivo*.

The elucidation of the mechanism by which PFOSA is biotransformed to PFOS is important. If the metabolism of PFOSA to PFOS does indeed proceed through the glucuronide intermediate, those animals with low or no UDGPT activity may have a reduced capacity to biotransform PFOSA to PFOS. Conversely, for those organisms with more efficient UDPGT activity for glucuronidation of PFOSA (*i.e.* as was shown with humans[71]), the relative contribution of PreFOS to PFOS may be greater.

Based on the *in vitro* and *in vivo* evidence, it is clear that PFOS precursor compounds are efficiently metabolized to PFOS in some species. However, it is also clear that more work must be done to elucidate the pharmacokinetics of PFOS precursors at low doses in order to clarify the role that PreFOS plays in contributing to PFOS exposure, and to facilitate accurate modeling and exposure assessments. The limited information available indicates that anywhere from 9 to >32% of PreFOS may be metabolized to PFOS. However, these figures may underestimate the percent contribution of PreFOS due to the high doses used. Additionally, *in vivo* studies on PreFOS have thus far looked only at mammalian models. Foodweb modeling studies would benefit greatly from pharmacokinetic studies on PreFOS in other environmentally relevant species, including aquatic invertebrates and fish. Furthermore, a wider variety of relevant PreFOS compounds should be studied.

PFOS and PreFOS in human samples

Comparison of PFOS and PreFOS in serum, plasma, and whole blood

In 2001, the first reports on the compound specific identification of perfluorinated chemicals in human serum[88] included the identification of PFOSA (Ib.) in addition to PFOS. NEtFOSAA (VIIb.) and NMeFOSAA (VIIa.) were later detected in a geriatric population by Olsen *et al.*[89] These were described as oxidation products of NEtFOSE (VIb.)[68] and NMeFOSE (VIa.), respectively, by Olsen *et al.*[89] who noted that these could be good markers of consumer related exposure. However, there is some uncertainty in whether detection of NEtFOSAA in humans can necessarily be considered as a marker of exposure to NEtFOSE because NEtFOSAA was also a common residual in commercial products,[67] as well as a commercial product itself (<100 000 lbs in 1997).[90] Its was documented to have been used as a surfactant (<1%, 50–100 ppm) in water-based cleaning products, floor polishes, and personal care consumer denture cleaners.[90] The latter case could certainly explain its detection in senior citizens, as shown by Olsen *et al.*[88] With respect to NMeFOSAA, although Olsen *et al.*[89] described this as an oxidation product of NMeFOSE, we are not aware that this has been shown as a metabolite experimentally; albeit we agree it is most likely a primary metabolite of CYP450 metabolism of NMeFOSE.

Human biomonitoring of PFOS and PreFOS has largely been conducted in samples of serum, plasma, and to a lesser extent in whole blood. By and large, when efforts are made to measure PreFOS and PFOS in the same samples, the measured concentrations of targeted PreFOS molecules (usually PFOSA, Ib.) are detectable but much lower than PFOS (Table 1). For example, Kannan *et al.*[91] examined human serum samples from various countries, and generally found PFOSA to be an order of magnitude lower than PFOS. However, in Japan, Malaysia, and Italy, serum PFOSA concentrations were approximately one third that of PFOS. In the U.S. it appears that children were more highly exposed to PFOS and PreFOS than adults, as Kato *et al.*[92] showed the highest concentrations of PFOSA (Ib.), NMeFOSAA (VIIa.), and NEtFOSAA (VIIb.) in children aged 3–11, compared to all other ages (12–60+ years). Extrapolating from the figures presented in Kato *et al.*,[92] PFOS was approximately 2-fold higher in children than adults, whereas NMeFOSAA and NEtFOSAA were up to an order of magnitude higher.

Several other studies have looked simultaneously at PFOS and PFOSA (Ib.) in human samples from different parts of the world

and whenever PFOSA is monitored it is often detected, particularly prior to 2002, or when the sample was whole blood,[91,93–96] including infant blood spots.[22] In fact, infant blood spots[22] had the highest proportion of PFOSA, relative to PFOS, suggesting that PreFOS may cross the placenta to a greater extent than PFOS. Furthermore, if PreFOS (including PFOSA) is biotransformed to PFOS in the fetus, then previous estimates of the placental transfer of PFOS will be biased to some extent.

It is possible that simple comparison of PFOS and PreFOS in serum or plasma substantially underestimates the relative extent of PreFOS exposure due to significantly different partitioning behavior of PreFOS in whole blood. For example, Karrman *et al.*[95] found high whole-blood-to-plasma ratios for PFOSA (Ib.) in a small survey of 5 individuals (mean ratio = 5.3), suggesting that the bulk of PFOSA resides in the cellular fraction of blood, not the serum or plasma. This is the only blood partitioning data we are aware of for humans, but similar behavior has been found for PreFOS in blood of sheep exposed to NEtFOSA.[72] The whole-blood-to-plasma concentration ratios for NEtFOSA and PFOSA were 1.43 and 26.7, respectively. In rats, the whole-blood-to-plasma ratio of PFOSA was 33.[83] Thus, the higher affinity of PreFOS for the blood cell fraction appears to be a consistent finding, and therefore the biomonitoring of human populations in serum should be viewed as an underestimate of PreFOS, relative to PFOS. Clearly, more human biomonitoring of PreFOS in whole blood is required to confirm this, and to better understand the partitioning of various PreFOS compounds in humans. The possibility that other PreFOS molecules may be eluding detection in human blood is raised by the data of Yeung *et al.*[93] who noted that analysis of a dozen perfluorinated compounds in human whole blood (including PFOS and PFOSA) only accounted for >70% of total extractable organic fluorine in human serum from Beijing, Shenyang, and Guiyang, and only 30% of total organic fluorine in Jintan.

It is also notable that an isotopically labeled PFOSA internal standard only came available in December 2009 (from Wellington Laboratories, Guelph, ON), thus the accuracy of future PFOSA monitoring will improve in all samples, including human samples.

Temporal trends

As mentioned, recent temporal trend studies of PFOS in human samples show a range of results, depending on the country. PFOS in Americans has been reported to be declining,[21] in Swedes and Germans no clear trend could be distinguished up to 2004, in serum or breast milk, respectively,[23,24] while in Shenyang, China, serum PFOS concentrations began increasing in 2000.[25] Declining trends in the US, and increasing trends in China, likely has much to do with the phase out of perfluorooctane sulfonyl-based products by 3M Co. in the US, and recent increasing PFOS and PreFOS manufacturing in Asia, respectively. These studies, however, did not report the concurrent temporal trends for PreFOS.

To our knowledge the most comprehensive longitudinal cross-sectional study reporting on levels of PFOS and PreFOS in human samples is the U.S. National Health and Nutrition Examination Survey (NHANES). The large sample size of the three NHANES surveys (n = 1591 in 1999–2000, n = 2368 in 2003–2004, and n = 2323 in 2005–2006) makes the data very representative of the general American population. Since the first PFOS and PreFOS data were presented for 1999–2000, a time corresponding to before the 3M Co.'s phase out of PFOS and PreFOS, there is evidence for declining serum concentrations of all these compounds. Calafat *et al.* compared NHANES data between 1999–2000 and 2003–2004 for PFOS,[97] but the trends for PFOSA (Ib.), NMeFOSAA (VIIa.) and NEtFOSAA (VIIb.) were not clear at the time due to low frequencies of detection. Although we have not tested the statistical significance of the results, we examined the most recent NHANES data for 2005–2006[98] and compared it to previous years at the level of median, 90th centile, and maximum serum concentrations (Fig. 2). In general, PFOS, PFOSA, NMeFOSAA and NEtFOSAA all showed net declines. As noted previously, NEtFOSAA increased in American human blood between 1974 and 1989 after PreFOS-phosphates were introduced for food contact applications in 1974,[67] thus it is possible that a large extent of these declines could be the removal of these phosphates from the market place in the U.S.

Other human temporal trend studies have been conducted that monitored both PFOS and PreFOS. Trends in adult American blood donors, reported by Olsen *et al.*,[99] showed declining trends for PFOS, NMeFOSAA (VIIa.), and NEtFOSAA(VIIb.) (Table 1), and in American newborn blood spots, PFOS and PFOSA were declining.[22] These two studies are consistent with the NHANES data discussed above, and all three studies generally demonstrated that PreFOS disappeared at a faster rate than PFOS, presumably owing to their metabolic transformation. For example, in newborns[22] the disappearance half life for PFOS was 4.4 yrs, and for PFOSA it was 1.7 years. In one temporal trend study from outside the US that reported PFOS and PreFOS trends together for the same samples, Haug *et al.*[100] reported declining trends for both PFOS and PFOSA in serum of Norwegian residents. For males between 40 and 50 years of age, PFOS began to decline in 2000, but PFOSA peaked between 1985 and 1993 and may have slowly declined prior to 2000, although it is clear that PFOSA disappeared precipitously after 2000.

PFOS and PreFOS in the human environment

In general, humans may be exposed to PFCs by ingestion, inhalation, or dermal absorption. Dermal absorption studies are rare, but in one study sponsored by 3M it was clear that PFOS could be absorbed across the skin of rats exposed to authentic commercial materials.[101] This study was not detailed enough to rule out the absorption of PreFOS from these materials, but this appeared to be less significant than absorption of PFOS. Overall, the relative importance of dermal exposure to commercial products is not clear and more difficult to quantify than other routes. We reviewed the results of human exposure models, and also the comparative levels of PFOS and PreFOS in indoor air, house dust, drinking water, and food items consumed by the general population (Table 2).

Models

Fromme *et al.*[81] reviewed the literature on human exposure to PFOS and PreFOS and reported that daily intakes were slightly

Table 2 Concentrations of PFOS and PreFOS in indoor air, indoor dust, food items, and drinking water. Food items are from studies which sampled food from retail markets, farmed seafood or diet portions

	Study details	PFOS	PreFOS
Indoor Air (pg/m^3)	Barber *et al.*[103] (Norway-2005)	<47.4	∑(FOSEs + FOSAs): 14 909 (Geo. Mean)
	Shoeib *et al.*[104] Canada – 2001/2003)	—	NMeFOSE = 2589 NEtFOSE = 772 (Means) NMeFOSE Acrylate = <0.1–283 (range)
	Shoeib *et al.*[105] (Canada – 2002/2003)	—	NMeFOSE = 1970 NEtFOSE = 100 NEtFOSA = 59 NMeFOSE Acrylate = 35 (Means)
Indoor Dust (ng/g)	Moriwaki *et al.*[170] (Japan –prior to 2003)	Median = 2500	—
	Kubwabo *et al.*[171] (Canada – 2002/2003)	Median = 38	—
	Strynar *et al.*[172] (USA – 2000/2001)	Mean = 760	—
	Shoeib *et al.*[105] (Canada – 2002/ 2003	—	NMeFOSE = 412 NEtFOSE = 2200 (Means) NEtFOSA <2 NMeFOSE Acrylate = 14 (Means)
	Kato *et al.*[106] (USA – 2004)	Median = 479	PFOSA <2.0 NMeFOSA < 2.0 NEtFOSA = 201 NMeFOSAA < 2.0 NEtFOSAA = 243.5 NMeFOSE = 218.6 NEtFOSE = 176.8 (Medians)
	Bjorklund *et al.*[173] (Sweden – 2006/ 2007) in various microenvironments	12 (Car), 31 (Daycare Centers) 39 (Houses) 85 (Apartments), 110 (offices) (Medians)	—
Food Items (ng/g wet weight)	3M Company[174] – Six cities in US (2003) 180 food items analysed in duplicate	Mean <0.5, Range <0.5–0.85	—
	Clarke *et al.*[111] – 75 Food Items (2007 Samples from UK)	Median = 2, Range <1–59	Median <1, Range <1–27
	Fromme *et al.*[110] – 214 duplicate food samples from 31 adults (Germany – 2005.)	Median = 0.025 Range = 0.025–1.03	PFOSA undetected in all 214 samples at a detection limit of 0.2 ng/g
	Ericson *et al.*[175] (Spain – 2006)	Range <0.014–0.654	—
	Van Leeuwen *et al.*[176] (Farmed fish purchased in the Netherlands in 2007/2008)	Range = 0.2–0.5	PFOSA undetected in all 33 samples
	Tittlemier *et al.*[107] (1992 – 2004 food samples from Canada)	—	∑ FOSAs range from 3.8 (fish Burgers) to 27.3(pizza) (NMeFOSA + $NNMe_2$FOSA + NEtFOSA + $NNEt_2$FOSA + PFOSA)
	Tittlemier *et al.*[108](Samples from 1992–2004 food samples from Canada)	Range <0.6–2.7	—
Drinking Water (ng/L)	Skutlarek *et al.*[177] (Germany 2006)	Mean = 10	—
	Ericson *et al.*[178] (4 samples of tap water from Spain 2007)	0.39, 0.44. 0.73, 0.87	PFOSA undetected in all 4 samples at a detection limit of 0.19 ng/L
	Quinones *et al.*[179] (USA 2008)	Range = 13–24	—
	Jin *et al.*[180] 29 samples of tap water (China 2003)	Range <0.1–14.8	—
	Tagaki *et al.*[181] (Japan 2006)	Range = 0.16–22	—
	Loos *et al.*[113](Italy 2007)	Range = 6.2–9.7	—
	Quinette *et al.*[145](Brazil 2008)	Range = 0.58–6.70	—
	Mak *et al.*[114] (China, Japan, USA, India, Canada)	Means:China- 3.9 Japan: 1.09 India: 8.29 for one sample, 3 other samples <0.04 USA: 1.39 Canada: 2.20 (1 sample each)	PFOSA detected in 4 sites in China and 2 sites in Japan NEtFOSAA detected in 6 sites in China and 2 sites in Japan Highest PFOSA (0.445) and NEtFOSAA (0.35) in Tokyo, Japan.

higher for PreFOS: 1.6–8.8 ng/kg body weight for PFOS, and 1.7–11 ng/kg body weight for PreFOS (range represents mean and a "high" exposure category). For PFOS, exposure was dominated by diet, and for PreFOS, indoor air, house dust, and diet were all important contributors to the mean daily intake. Fromme *et al.* concluded, however, that PreFOS only contributes 10% of PFOS to the body burden, based on a presumed 20% metabolic conversion rate of PreFOS to PFOS. Another modeling study with respect to human exposure to PFOS and PreFOS was conducted by Vestergren *et al.*,[82] and similar findings were made. Based on estimated consumer PFOS exposure,[102] it was concluded that the general population in North America and Europe may only receive 2–5% of PFOS from PreFOS, but that PreFOS could account for up to 60–80% of the total body burden of PFOS in a human subpopulation with "high exposure". Both studies[81,82] identified food as an important source of exposure, but, as discussed below in the food section, there is significant temporal variation of PreFOS concentrations in food due to the voluntary phase-out by 3M Co., thus exposure scenarios may be much different today.

Both studies[81,82] also noted that a large contributor to their uncertainty was the biotransformation yield of PFOS from various precursors, and valid reasons for this uncertainty were discussed in the prior section of this review. Under real world chronic exposure to PreFOS, however, there is another important source of error that was not discussed in these studies. For example, it is feasible that neutral and hydrophobic forms of PreFOS may be more rapidly absorbed, or more slowly excreted, than PFOS. If true, then the predictions of Fromme *et al.*[81] and Vestergren *et al.*[82] are underestimates of the importance of PreFOS, and a more sophisticated model is needed that considers the overall pharmacokinetics of PreFOS, not just the biotransformation yield of PFOS from PreFOS.

Indoor air

Indoor air concentrations have rarely been measured for PFOS or PreFOS and, in fact, PFOS has never been detected above detection limits in indoor air. Barber *et al.*[103] attempted to measure both PFOS and PreFOS in indoor air in Norway, but PFOS concentrations were below limits of detection (<47.4 pg/m^3) despite very high PreFOS concentrations in the same samples. Nearly equivalent geometric mean concentrations of NEtFOSE (VIb.), NMeFOSE (VIa.), NEtFOSA (Vb.) and NMeFOSA (Va.) were detected.[103] Two Canadian studies by Shoeib *et al.*[104,105] are the only other data for indoor PreFOS concentrations, and PFOS was not analyzed in the same samples. Here, NMeFOSE was the most prominent PreFOS molecule, with concentrations being an order of magnitude higher than concentrations of NEtFOSE and NEtFOSA. These relative concentrations were much different from those in Norway. Shoeib *et al.* also monitored for the NMeFOSE acrylate (IXa.) in indoor air and detected it occasionally, with an arithmetic mean concentration of 35 pg/m^3 in one study,[105] 1.5 orders of magnitude lower than NMeFOSE, and up to 283 pg/m^3 in another study,[104] with higher concentrations detected when NMeFOSE was also high. It is clear that indoor air is dominated by PreFOS, which is not surprising given the negligible vapour pressure of PFOS.

Indoor dust

Unlike indoor air, both PFOS and PreFOS can be easily detected in indoor dust. Unfortunately, it is difficult to determine whether PFOS, or PreFOS, is predominant in this matrix because only one study, by Kato *et al.*[106] for US house dust, has reported both PFOS and PreFOS concentrations for the same dust samples. On the whole, PFOS and measured total PreFOS concentrations were similar in these samples, but the sum of median NEtFOSAA (VIIb.), NMeFOSE (VIa.), and NEtFOSE (VIb.) concentrations did exceed the median PFOS concentration on a mass basis. The only other study[105] that quantified PreFOS concentrations in house dust found relatively higher concentrations of NMeFOSE (geometric mean = 0.412 μg/g) and NEtFOSE (geometric mean = 2.2 μg/g) in house dust from Canada, and NMeFOSE acrylate was also detected at lower concentrations. PFOS concentrations in dust can vary widely from country to country, for example median PFOS was 2.5 μg/g in Japanese homes, 0.038 μg/g in Canadian homes, 0.016 μg/g PFOS in German homes, 0.030 μg/g in Swedish homes, and the mean was 0.76 μg/g in American homes (Table 2). Although it is difficult to summarize, in general it appears that PreFOS concentrations in house dust are similar to, or greater than, PFOS.

Food

To our knowledge, the most comprehensive monitoring survey for PreFOS in food was conducted by Tittlemier *et al.*[107] for composite samples collected as part of the Canadian Total Diet Study between 1992 and 2004. A lack of authentic standards prevented monitoring of FOSE phosphates, which were known to have been applied to paper and paperboard food packaging for oil repellence. Instead, Tittlemier *et al.* analyzed for PFOSA (Ib.), NEtFOSA (Vb.), NMeFOSA (Va.), and some related FOSAs (V, see Table 2), and many were detected between 1992 and 2002, with an immediate subsequent disappearance that was presumably related to the phase-out by the 3M Co. Food items with the highest concentrations of PreFOS included chicken burgers, chicken nuggets, french fries, wieners, and pizza. NEtFOSA (*i.e.* the insecticide Sulfluramid) was the most commonly detected PreFOS molecule, with a maximum concentration of 23 ng/g in pizza. It is important to note that NEtFOSA would only have been a minor residual (<1%) in food contact formulation of FOSE-phosphates, thus it is possible that these same food items contained 100-fold higher concentrations of total PreFOS. NEtFOSA was not detected in the same types of composite samples in 2003 or 2004, but was still detectable in freshwater fish and in shrimp after the phase out. Tittlemier *et al.*[107] reported that the estimated median daily dietary intake of total PreFOS for male and female Canadians (12 years and older) amounted to 90 and 55 ng, respectively. Tittlemier *et al.*[108] later reported that PFOS was the most prominent perfluorinated acid in composite Canadian food samples, with PFOS ranging up to 2.7 ng/g in beef steak. Based on 2004 samples, the daily dietary exposure to PFOS was estimated as 110 ng, which is in the same range that these authors estimated for PreFOS.

Del Gobbo *et al.*[109] tested raw, boiled, fried and baked fish regularly consumed in Canada and found PFOS to be the most commonly detected compound (24% of the samples), among 17

perfluorinated compounds, with wet weight concentrations ranging from 0.21 to 1.68 ng/g. PFOSA (Ib.), the only PreFOS monitored in this study, was only detected in scallops with concentrations between 0.20 to 0.76 ng/g. The other interesting finding was that cooking reduced both PFOSA and PFOS concentrations, particularly baking.

In a study by Fromme *et al.*,[110] involving 31 healthy Germans (15 females and 16 males), daily duplicate food portions were collected over a period of 6 months in 2005 (n = 214). Contrary to the findings of Tittlemier *et al.*,[107] PFOSA was below detection limits in all the food samples and PFOS was the second most frequently detected analyte, after perfluorooctanoate. Clarke *et al.*[111] recently published on a study funded by the British Food Standards Agency on the presence of PFOS and PreFOS in 75 retail food items from the UK. Among the eleven PFCs monitored in that study, the most commonly detected was PFOS (68 out of 75) followed by PFOSA (Ib.) (20 out of 75) the highest concentrations of PFOS and PFOSA being in fish with high fat content such as whitebait, eels and sprats. The highest concentrations of PFOS were in smoked eel (59 ng/g) and Whitebait (40 ng/g), and highest PFOSA concentrations recorded were in 2 samples of Whitebait (27 and 14 ng/g).

One unique study was conducted in the Faroe Islands, an island group located in the North Atlantic Ocean between Norway and Iceland. The human population maintains a level of self-sufficiency by consuming traditional foods, including pilot whale meat and blubber. Here, Weihe *et al.*[112] studied serum levels of PFOS and PreFOS in pregnant women and children (Table 1). The dominant compound detected was PFOS, with lower concentrations of PFOSA (Ib.), NMeFOSAA (VIIa.), and NEtFOSAA (VIIb.). For the 14 year old children, PFOS was significantly associated with the frequency of consuming pilot whale, and PFOS concentrations correlated well with the combined concentrations of PreFOS for 7 year old and 14 year old children. Furthermore, all 4 of the 12 pregnant mothers who indicated that they did not consume any pilot whale had undetectable concentrations of NMeFOSAA, while 3 out of 4 of these women had undetectable NEtFOSAA concentrations. All together, this is strong evidence that the Faroese population received significant exposure to NMeFOSAA and NEtFOSAA through pilot whale consumption. These findings also provide indirect evidence that pilot whales are exposed to significant PreFOS in the oceans, possibly NEtFOSAA and NMeFOSAA, or possibly higher molecular weight PreFOS derivatives through their prey.

Overall, food studies suggest that there is wide variability in the relative exposure of different populations to PFOS and PreFOS in food, but considering that PreFOS was purposely used in food contact applications there is surprisingly little data available, possibly because no authentic standards for PreFOS phosphates are available. Overall it appears that European foods do not contain significant PreFOS today (compared to in Canada before the phase-out), but additional data on food items consumed in Asian populations are needed.

Drinking water

In drinking water, PFOS is usually the first or second most commonly detected perfluorinated compound, and PreFOS is rarely analyzed in this matrix. This is evident from water quality monitoring surveys done in the United States, Japan, Italy, Germany, Spain, Brazil, and China where the PFOS concentrations are similar (Table 2). Only Loos *et al.*[113] (Spain) and Mak *et al.*[114] (China, India, Canada, USA and Japan) tested for PreFOS. In Spanish drinking water, only PFOSA was analyzed, and it was undetected. Mak *et al.* found that in Chinese drinking water samples, PFOS ranged from 0.39–11 ng/L among several cities. In the same samples, PFOSA and NEtFOSAA were detectable in 4 of 10 (max concentration = 0.058 ng/L) and 6 out of 10 sites (max concentration = 0.26 ng/L), respectively. The same general pattern of contamination was evident in all other countries (India, Canada, USA, Japan) and the highest PreFOS concentrations recorded were in Tokyo tap water for PFOSA (0.445 ng/L) and NEtFOSAA (0.35 ng/L, personal communication from Mak *et al.*). These results suggest that drinking water exposure is usually dominated by PFOS, but that PreFOS is not always insignificant and water soluble forms like PFOSA and NEtFOSAA should be monitored more often.

PFOS and PreFOS in the environment

PFOS and PreFOS have been detected worldwide in seawater, river water, air, soil, sediment, and precipitation. In order to elucidate sources of PFOS in the open environment, analysis of the relative concentrations of PFOS and its precursors may provide some insight. To evaluate the importance of PFOS *versus* PreFOS concentrations, a summary of concentrations of PFOS, PFOSA (Ib.), and other PreFOS molecules (if measured and detected) in abiotic samples from select studies are presented in Table 3.

Oceans

Concentrations of PFOS in open ocean seawater samples are, as expected, far lower (by 2–3 orders of magnitude) than those of water bodies near urban and industrial regions. However, most urban, industrial, and open-ocean sampling locations had similar relative concentrations of PFOS and PFOSA (Ib.), with PFOS concentrations exceeding those of PFOSA by 1–3 orders of magnitude. Reasons for this overall trend are likely due to several factors, including greater emissions of PFOS than PFOSA, and significantly different environmental disposition; PFOSA is far more likely to volatilize or adsorb to sediments than sulfonates.[115] There are, however, notable exceptions whereby PFOSA exceeded PFOS in ocean water. Ahrens *et al.*[116] detected PFCs along a latitudinal gradient in the Atlantic Ocean and observed detectable concentrations for PFOSA, but no PFOS (and no other perfluorinated compounds), south of the equator, including latitudes as far south as 4°S. The authors suggested that atmospheric transport and deposition of PFOSA may have been important determinants of its detection at this south polar region. Similarly, Busch *et al.* observed higher concentrations of PFOSA than PFOS in the Arctic Ocean near Eastern Greenland.[117] One out of nine field blanks had PFOSA concentrations higher than most samples (251 pg/L), while the remaining eight were below the method quantification limit, thus it is not clear if some contamination may have occurred during sampling or transport. The authors discussed that both oceanic and

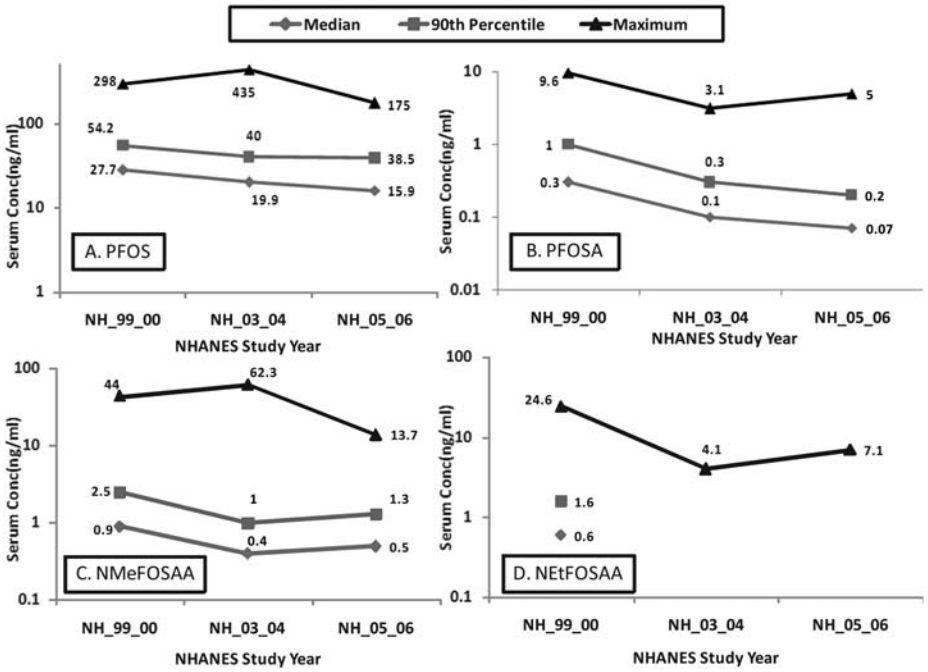

Fig. 2 Decline of (A) PFOS, (B) PFOSA, (C) NMeFOSAA, and (D) NEtFOSAA in the blood of the general U.S. population from recent NHANES data. Median, 90th centile, and maximum concentrations are shown, except for NEtFOSAA in 03–04 and 05–06 because 90th centile and median was below limit of detection. Plots generated from SAS data files on the National Center for Health Statistics webpage of the CDC.[98]

atmospheric mechanisms could be involved in transporting PFOSA to this location, but it is not clear which pathway was dominant, nor is it clear why PFOSA concentrations are only dominant to PFOS in some areas of the globe. Curiously, as discussed in greater detail later, polar bear samples from Eastern Greenland show increasing concentrations of PFOS and PFOSA since the phase out, despite opposite trends in other remote areas, thus the ocean and foodwebs of Eastern Greenland show distinct behaviour that is worthy of additional study.

Air

The prevalence of PFOS and PreFOS in air has become a subject of considerable importance after detection of PFOS in remote regions such as the Arctic, and the need for a thorough understanding of its long-range transport mechanism(s). Early air monitoring campaigns detected NEtFOSE (VIb.), NMeFOSE (VIa.), and NEtFOSA (Vb.) at pg/m^3 concentrations in air of Southern Ontario,[44,118] and these findings were later replicated in other areas of the world including Europe,[103] and the remote Arctic.[52] Shoeib *et al.*[52] found average gas-phase concentrations of 8.30 and 1.87 pg/m^3 for NMeFOSE and NEtFOSE, respectively, for cruise samples in the Canadian Archipelago and North Atlantic Ocean, with similar gas-phase concentrations observed in Toronto, Canada, a heavily urbanized centre.

Most studies of perfluorinated compounds in air did not report detection of PFOS in the gas phase, presumably owing to its negligible volatility, although Kim *et al.*[119] detected measurable concentrations in both the gas and particulate phase of air from Albany, NY. In ambient air, PFOS is primarily detected in the particulate fraction, and when detected it is present at similar concentrations to PreFOS. For example, Barber *et al.*[103] found average concentrations of 46 pg/m^3 in particulate phase samples from Manchester, UK, higher than the sum of PFOSA (Ib.) + FOSEs (VI) (30 pg/m^3). Detectable but significantly lower PFOS and PFOSA concentrations in airborne particulate matter have been detected at remote locations such as the Canadian Arctic,[120] with average PFOS concentrations of 5.9 pg/m^3. Detection of both PFOS and PreFOS on particulate matter in this and other studies[52,104,120,121] suggests that airborne transport of particulate matter may be another means of regional and long range transport that warrants further consideration for both PFOS and PreFOS.

Wildlife

In contrast to abiotic samples, the relative concentrations of PFOS and PreFOS in biological samples are far more variable. Houde *et al.*[122] summarized concentrations of PFOS and PFOSA (Ib.) in biota for studies up to 2006. Numerous studies showed concentrations of PFOS exceeding PFOSA by at least one order of magnitude, similar to the abiotic samples discussed above, including in mink samples from the United States,[123] polar bears from the Hudson Bay[124] and Greenland,[125] numerous bird species from Japan,[126] and harbor seals from the northwest Atlantic.[127] There are, however, several studies that have detected concentrations of PreFOS at approximately equal or greater concentrations than PFOS. Martin *et al.*[3] observed higher concentrations of PFOSA than PFOS in benthic feeding diporeia and slimy sculpin in a Lake Ontario foodweb. This may have indicated a contribution of sediment-associated PreFOS to PFOSA in these organisms.[3] Higher or similar concentrations of

Table 3 PFOS and precursor concentrations in abiotic samples from select studies.[a]

Location	Sampling Year(s)	PFOS concentration	PFOSA	Other related precursors	Ref
Ocean water and remote lakes – Concentrations in pg/L					
Northern Europe, Atlantic, Southern Ocean	2008	(<11–232)	<3–67 (Majority ND)	PFOSI: <3–22 (majority ND)	182
Indian Ocean (Asia/Antarctica)	Not reported	<5–71.7	All ND		183
North Atlantic ocean	2007	<10–291	<17–307	NMeFOSA,NEtFOSA,	116
Middle		<10-60	<17–60	NMeFOSE, NEtFOSE, PFOSI	
South		<10	<17–53	all ND	
Mid Atlantic ocean	2002	38-73	2.7–3.7		184
Eastern Pacific ocean	2002	54–78	2.2–2.8		
Central to Western Pacific ocean	2003	1.1–4.6	Majority ND		
Water bodies near urban areas and industrial sites – Concentrations in ng/L					
German Bight	2007	0.69–3.95	0.004–0.20 (Majority ND)		185
China and Hong Kong coast	2003–4	0.02–12	<0.005–0.07		186
North Sea Canal, Amsterdam	2007	(34.4)	(3.5)		187
Conasauga River, near Dalton, GA	2006	(1–318)	(74.9–282.5)		188
Lake Erie	2003	11–39	0.5–1.3	NEtFOSAA: (Erie: 7.5)	58
Lake Ontario		15–121	<0.3–2.3	(Ontario: 5.7)	
				PFOSAA, NEtFOSE, NEtFOSA: Majority below DL for both lakes	
Pearl R.	2004–5	<0.9–99	0.073–0.34		189
Yangtzee R., china		<0.01–14	<0.005–0.053		
Streams, Shihwa, South Korea	2004	(89.11)	(1.05)		190
Several lakes, Albany, NY	2006	(2.88)	ND–0.47		119
Various rivers, Japan	2003–5	<5.2–10	All ND		191
Wastewater treatment plant (WWTP) influent (IFF) or effluent (EFF) – Concentrations in ng/L					
WWTPs, River Elbe, Germany	2007	<0.06–82.2	0.3–1.1		192
WWTPs, Japan	2006–7	INF: 14–336	INF: Majority ND		129
		EFF: 42–635	EFF: All ND		
WWTPs, New York	2004–5	EFF: 3–68	Below DL		130
WWTPs, Denmark		INF: <1.5–10.1	INF: <0.2–1.0		131
		EFF: <1.5–18.1	EFF: <0.2–2.1		
WWTP, California, (reclaimed wastewater)	2007	20–190	2.1–4.8	NEtFOSAA: 5.5–23	62
WWTPs, various locations USA		INF: 1.4–400	INF: Majority ND		193
		EFF: 1.1–130	EFF: Majority ND		
Outdoor air and precipitation – water concentrations in ng/L, air concentrations in pg/m^3					
Rainwater, Tsukuba and Kawaguchi city	2007	.132–1.02	0.064–0.17	NEtFOSAA: 0.039–0.326	194
Albany, NY					119
Air (gas)	2006	(1.70)	(0.67)		
Air (part.)	2006	(0.64)	(0.29)		
Rain	2006	<LOQ–1.51	ND to <LOQ		
Snow	2007	(0.62)	ND–0.57		
L. Erie and L. Ontario				Gas: (NEtFOSE: ND–1.0, NEtFOSA: ND–2.2)	195
Air (gas)	2003	ND	ND		
Air (part.)	2003	ND–8.1	ND	PFOSI and PFOSA: ND in air and particulate	
Europe, Air	2005–6	Particulate: (<1.8–46)	n/a	Gas + Part.: NMeFOSA: 5–8 NEtFOSA: 5–10 NMeFOSE: 36–54 NEtFOSE: 16–33	103
Air (gas), Toronto, ON, Canada	2001	n/a	n/a	NMeFOSE (101) NEtFOSE (205) NEtFOSA (14)	44
Air (gas *via* passive air sampling), Ottawa, ON, Canada	2002–3	n/a	n/a	NMeFOSE 75–83 NEtFOSE 79–88 NEtFOSA (ND) NMeFOSE Acrylate <0.05	105
Air, Hamburg, Germany	2006	n/a	n/a	NMeFOSA (part.): 1.1–2.6 NEtFOSA (part.): 0.5–1.1 NMeFOSE (gas + part): 6.9–14.1 NEtFOSE (gas + part): ND–4.1	196
Ice Core, Russian Arctic	2007	0.0053	0.824		50
Air, Canadian Archipeligo, North Atlantic	2005	n/a	n/a	NMeFOSE (gas): (8.30) NEtFOSE (gas): (1.87) NMeFOSE (part.): 3.53 NEtFOSE (part.): 1.05 NMeFOSE Acrylate (part, gas): ND	52

Table 3 (*Contd.*)

Location	Sampling Year(s)	PFOS concentration	PFOSA	Other related precursors	Ref
Sediment – concentrations in ng/g dry weight					
River sediment, Japan	2003–5	ND–11	ND–6.5		191
Sediment, Ariake sea, Japan	2004	0.09–0.14	ND		197
Sediment, various locations, USA	2002, 2004	(ND–3.07)	n/a	FOSAA: ND–0.289 NMeFOSAA: ND–1.04 NEtFOSAA: ND–1.43	198

[a] ND = measurements below the detection limit. Values reported as <value are below the authors' detection limit. <LOQ refers to values that are below the authors' limit of quantitation. n/a = compound not analyzed. Most values are reported as ranges. Values in parentheses are means, ranges in parentheses are ranges of reported means, usually based on grouped data.

PFOSA, compared to PFOS, have also been found in Minke whales and long-finned pilot whales from Greenland,[125] bottlenose dolphins from the Adriatic sea,[128] and in northern sea otters from Alaska.[27] These are interesting findings, given that PFOS is dominant to PFOSA in most open ocean water. This might be explained by a higher bioaccumulation potential of PFOSA than PFOS (as discussed later), higher PFOSA than PFOS in ocean water as shown by Ahrens *et al.*[116] and Busch *et al.*,[117] or other PreFOS molecules in ocean water that are not routinely monitored.

Wastewater treatment plants (WWTPs)

Within urban and industrial environments, WWTPs represent an important pathway for anthropogenic contaminants to enter aquatic ecosystems, and as noted earlier for PreFOS, for stripping relatively volatile contaminants to the atmosphere. Concentrations of PFOS and PreFOS in WWTP influent/effluent are included in Table 3. PFOS is easily detected in both the influent and effluent, with concentrations as high as 635 ng/L (Japanese WWTPs[129]), generally much higher than lake, river, and coastal water concentrations near urban areas. Thus, WWTPs are likely the major source of PFOS to waterbodies in populated regions. As with background natural water samples, PFOS concentrations in WWTPs exceed those of measured PreFOS, usually by one or more orders of magnitude. Among studies of WWTPs, PFOSA (Ib.) has been the most frequently analyzed precursor, but interestingly was often found below detection limits. This is consistent with our earlier discussion of the aerobic microbial biotransformation of PreFOS, which showed that PFOSA was not a major product of higher molecular weight PreFOS.

Despite the paucity of analytical evidence for PreFOS in WWTPs, studies suggest that precursors play a significant role in the overall concentrations of PFOS in WWTP effluent. Sinclair and Kannan[130] observed increases in the mass flow of PFOS after secondary treatment (*via* activated sludge) at a WWTP in New York, suggesting that the biodegradation PreFOS was responsible, but the concomitant decreased mass flow of any PreFOS molecule was not evaluated. Similar behavior was observed for PFOS at WWTPs in Denmark,[131] Kentucky and Georgia, USA,[132] and Japan.[129] Laboratory experiments, as discussed earlier, showed that aerobic microbial biodegradation of PreFOS can indeed produce significant quantities of PFOS,[57,59] consistent with these WWTP studies. Thus far, however, the importance of PreFOS, particularly the contribution and fate of PreFOS-containing copolymers or phosphates, in WWTPs remains poorly understood.

Correlations between PFOS and PFOSA

Numerous studies have attempted to correlate concentrations of PFOS and PFOSA (Ib.) on an individual sample basis to infer the importance of PFOSA, or PreFOS in general, to the body burdens of PFOS. A list of these correlations, with the type of biological sample (as well as correlations involving abiotic samples) is shown in Table 4. In most cases, the existence of a correlation between PFOS and PFOSA has been used to imply that atmospheric deposition of precursors plays an important role in the levels of PFOS. Strictly speaking, correlations between PFOS and PFOSA do not necessarily mean that PFOS concentrations are due to biodegradation of PFOSA and/or other precursors. Rather, such correlations may only imply a similar emission or exposure source for the two compounds. The same rationale has been used previously to suggest that the sources of PFOS are similar to the sources of perfluorooctanoate and perfluorononanoate in specific locations, such as in cormorants from Sardinia Island in the Mediterranean Sea,[128] and in fur seals from Antarctica.[133] Caution is thus advised against over interpreting such correlations.

Wang *et al.* found correlations with PFOS and PFOSA (Ib.), respectively, and several other organohalogen contaminants such as PCB congeners in waterbird eggs from South China.[134] This may be indicative of a commonality of contaminant sources in general, driven by proximity to pollution sources such as urbanized centres. Correlations may therefore be most useful when likely sources of PFOS are remote, such as studies of biological samples in the Canadian Arctic. For example, temporal trends that were suggestive of a PreFOS source in ringed seals from the Canadian Arctic[26] and northern sea otters from Alaska[27] (discussed further in next section) were also supported by observed correlations between PFOS and PFOSA in those same sample sets. However, as evident in Table 4, the outcomes of these correlations are often difficult to interpret, further complicated by a multitude of contaminant sources and various capacities for biotransformation of precursors within different foodwebs.

Temporal trends

Analysis of PFOS and PreFOS temporal trends in the environment have provided some clues as to the relative importance of

PFOS and PreFOS, and it appears that the relative contribution of PreFOS is changing over time. Much of this evidence has come from studies of both biotic and abiotic samples in the Arctic. Butt *et al.*[26] observed significant increases in PFOS and PFOSA (Ib.) concentrations in liver samples from ringed seals at two sites in the Canadian arctic, Resolute Bay (1972–2000) and Arviat (1992–1998). This was followed by a rapid decrease in both PFOS and PFOSA concentrations in the following years up until 2005, corresponding to the phase-out of POSF (Ia.) production by 3M between 2000 and 2002. Such a rapid decline (half lives of 3.2 ± 0.9 and 4.6 ± 9.2 years for PFOS in Arviat and Resolute Bay, respectively) after the phase-out is suggestive of a strong atmospheric source contribution (*i.e.* volatile PreFOS) to body burdens of PFOS in local ringed seal. Similarly, northern sea otters in Alaska showed a decrease in PFOS and PFOSA concentrations in the years following the phase-out. PFOSA concentrations were similar to, or higher, than PFOS concentrations in the mid to late 90s, but dropped below detection limits in 2004–2007, while PFOS concentrations fell by an order of magnitude relative to the peak in 2001.[27] This data suggests a cutoff of precursor sources, and elimination of PFOSA *via* metabolism to PFOS. However, there is no strong evidence yet for a rapid decline in atmospheric PreFOS in the Arctic. Furthermore, the model of Armitage *et al.*[11] could not account for all the PreFOS that is currently detectable in Arctic air,[52] suggesting that sources of PreFOS, including total historic emissions of PreFOS, could be underestimated.

As previously discussed, other studies of biological samples in the Arctic and elsewhere have observed temporal trends that do not indicate a rapid decrease in PFOS or PreFOS concentrations after 2001. PFOS concentrations in Arctic seabirds[135] and peregrine falcon eggs in Sweden[12] showed increasing concentrations in the 1970s and 1980s, corresponding to increases in PFOS and PreFOS production during that time, but no significant post-2000 decrease in concentration of these contaminants was observed. Meanwhile, Bossi *et al.*[136] found concentrations of PFOS in ringed seal livers in East Greenland continued to increase after the phase-out. Also in East Greenland, Dietz *et al.*[28] observed increases in polar bears after the phase-out by 19.7% and 9.2% for PFOS and PFOSA concentrations, respectively. The observed increase in PFOS concentrations was explained by a growing importance of slowly transported oceanic PFOS to this region of the Arctic, and this agrees with model predictions of Armitage *et al.*[11] It is unclear if PFOSA was also slowly transported in ocean water, but PFOSA concentrations in ocean water off Eastern Greenland have been reported to be unusually high,[117] relative to ocean water in other areas of the world.

Recent changes in PFOS and PreFOS concentrations have been observed in non-polar regions as well. Ahrens *et al.*[137] observed decreasing concentrations of PFOS, and both PFOSA and PFOSI, in harbor seals from the German Bight, with similar elimination half-lives (5.6 ± 18.9 and 2.8 ± 0.9 years for PFOS and PFOSA, respectively) to those observed by Butt *et al.*[26] Furdui *et al.*[138] observed an increase in PFOS and PFOSA concentrations from 1979 to 1993 in Lake Ontario lake trout, followed by lower concentrations in samples from 1998 and 2004. A similar trend was observed by Martin *et al.*,[3] who suggested changes in foodweb structure by invasive zebra mussels in the lake may also play a role, although stable nitrogen isotope analysis by Furdui *et al.* indicated that no trophic changes in lake trout were observed over this time period.

The use of temporal trends from these highly populated regions, however, for assessing the role of PreFOS cannot be widely extrapolated because changes in contaminant levels are primarily affected by local changes in their usage and disposal. Furthermore, the phase out by the 3M Co. was accompanied by a concomitant increase in manufacturing of PFOS and PreFOS in other regions of the globe, thus even in remote regions the trends are difficult to interpret. Finally, because the phase out by 3M was so recent, the majority of existing temporal trend studies have a limited number of time points after 2002, thus the uncertainty of any trend is high. Continuing data collection from biomonitoring, and better manufacturing data from Asia, will provide improved temporal resolution, and a clearer assessment of the relative importance of PFOS and PreFOS in the future.

Bioaccumulation of PreFOS

Although abiotic environmental concentrations of PFOS and PreFOS are an important clue regarding their relative importance to biota, the relative bioaccumulation potential of PFOS and PreFOS must also be considered.

Bioconcentration and bioaccumulation factors

Few studies to date have investigated the magnitude to which PreFOS can bioconcentrate. Bioaccumulation factors (BAFs) are normally calculated in the field by dividing the concentration in an organism by the concentration in the respiratory medium (*i.e.* air or water). Lake trout in the Great Lakes had log BAFs for PFOSA (Ib.) ranging from 3.4 to 4.0, depending on the lake.[139] These log BAFs were similar to those determined in the same study for PFOS (log BAF = 3.8 to 4.3). Keeping in mind that PFOSA can be metabolized to PFOS, the field BAFs for PFOS are likely an over-prediction of the true accumulation potential for PFOS. Certainly, these field BAFs for PFOS are higher than bioconcentration factors (BCFs; concentration in organism by the concentration in the respiratory medium, determined in the lab under controlled conditions) determined for PFOS in laboratory tests with rainbow trout (log BCF = 3.0).[2]

Computational modeling has found that log BCFs for FOSAs (V), FOSAAs (VII), and FOSEs (VI) all range from 2 to 6, indicating that they may potentially accumulate in organisms.[140] NEtFOSE (VIb.) was reported to accumulate in fish,[141] but this study did not report water concentrations of NEtFOSE or calculate a BCF. The potential for other PFOS precursors to bioconcentrate is unclear, and many additional studies would be valuable. For example, NEtFOSAA (VIIb.) has been found in high concentrations in WWTP effluent (Table 3), and no studies have investigated the bioconcentration of this in fish despite its presence in fish samples.[78]

Sediment accumulation

The steady-state biota-sediment accumulation factor (BSAF) has been determined in aquatic oligochaetes (*Lumbriculus variegates*) for NEtFOSAA (VIIb.) to be 0.12 ± 0.03.[142] This was an order of magnitude lower than the BSAF for PFOS, indicating that

NEtFOSAA will not accumulate in this species. The low BSAF was, in part, a result of the rapid metabolism of NEtFOSAA to PFOSA (Ib.) and PFOS, as demonstrated in the study. Although the authors did not determine the percentage of NEtFOSAA biotransformed to PFOS, the maximal tissue concentrations suggests that approximately 10% of the total body burden was biotransformed to PFOS and PFOSA. Furthermore, direct exposure to PFOS produced higher tissue concentrations of PFOS than the exposure to NEtFOSAA. After 56 days, worms exposed to PFOS spiked sediment (11.4 ng/g d.w.) had PFOS tissue concentrations of approximately 100 ng/g w.w., whereas worms exposed to NEtFOSAA spiked sediment (51.9 ng/g d.w.) had PFOS tissue concentrations of approximately 20 ng/g w.w. Among the most significant finding in this work was that PreFOS can be bioavailable in sediment to benthic organisms, and that even low trophic level organisms may have the capacity to biotransform PreFOS to PFOS. While PreFOS itself may not accumulate within lower trophic level organisms, the metabolism of PreFOS to PFOS in these organisms is possible and may contribute to the abiotic burden of PFOS (*i.e. via* excretion of PFOS into sediments or the water column) or up the food chain when predators consume the oligochaetes. This may have significant implications in foodweb modeling studies of PFOS and PreFOS, as lower trophic level organisms are generally thought to have reduced capability for biotransforming other persistent organic pollutants.[143]

Dietary accumulation

The biomagnification factor (BMF), defined as the concentration of a compound in a predator relative to its prey, is used to describe the potential of a xenobiotic to increase in food chains. For PreFOS, wet weight BMFs have been determined for NEtFOSA (Vb.) and PFOSA (Ib.) for several feeding relationships. Martin *et al.*[3] reported BMFs for PFOSA in lake trout to be 4.0, 0.22, and 0.11 assuming 100% consumption of alewife, smelt, or sculpin, respectively. However, since lake trout are known to consume various proportions of these fish, Martin *et al.*[3] also calculated a weighted PFOSA BMF (weighted to the average percentage of each prey species consumed) to be 1.4. This weighted BMF is similar to the calculated weighted BMF for PFOS of 2.9, and indicates the potential for PFOSA to biomagnify in this top predator fish; despite that PFOSA is likely being metabolized and that the BMF for PFOS is overpredicted for this very reason.

Trophic level BMFs (BMF_{TL}; BMFs corrected for trophic level, determined by stable isotope analysis) of PFOSA (Ib.) and NEtFOSA (Vb.) have also been calculated for a series of feeding relationships in an Eastern Arctic foodweb. For PFOSA, the BMF_{TL} for cod to narwal was 347, while for cod to beluga and redfish to beluga BMF_{TL}s were 889 and 860, respectively.[4] These BMF_{TL}s are, remarkably, over two orders of magnitude higher than those observed for PFOS in this study. While it is clear that PFOSA is accumulating within narwal and beluga, these results should be interpreted with caution, as no detectable levels of PFOSA were found in cod or redfish, and concentrations in these organisms were estimated by one half of the detection limit for purposes of BMF calculation. Furthermore, the use of liver concentrations in beluga and narwal, but whole body concentrations of the fish, likely lead to an overestimate of the BMF_{TL}.[144] Nonetheless these factors would also affect the BMF_{TL} for PFOS to a similar extent, and thus the higher value for PFOSA, compared to PFOS, is perhaps reflective of a true difference in their respective accumulation behaviours.

Table 4 Statistical correlations between PFOS and PFOSA in select studies

Sample medium	Location	Trend direction & significance	Ref.
Mink, Fox	Canada – various upper latitude locations	Positive, $p < 0.05$[a]	199
River otter	Oregon	Positive, $p < 0.05$[a]	200
Alewife, smelt, sculpin	Lake Ontario	Positive, $p < 0.05$	3
Coastal water samples	China, Hong Kong	Positive, $p < 0.05$	186
Harbour seal	Northwest Atlantic	Positive, $p < 0.05$	127
Minke whales	Korea	Positive, $p < 0.001$	201
Yangtzee and Pearl River water	China	Positive, $p < 0.001$	189
Herring Gull eggs	Great Lakes	Positive, $p < 0.0001$	202
Northern Sea Otters	Alaska	Positive, $p < 0.01$	27
Melon-headed whales	Japan	Positive, $p < 0.01$	203
Ringed seals	Arviat, Nunavut, Canada	Positive, $p < 0.05$[a]	26
Bottlenose dolphins	Gulf of Mexico, Atlantic Ocean	Positive, $p < 0.005$ at three sites, Not significant ($p > 0.05$) at one	204
Polar bear, loon, ringed seal	Canada – var. Upper latitude locations	Not significant, $p > 0.05$[a]	199
Mink, river otter	USA, var. locations	Not significant, $p > 0.05$[a]	200
Seawater	German bight	Not significant, $p > 0.05$	185
Trout, *Mysis relicta*	Lake Ontario	Not significant, $p > 0.05$	3
Adélie penguin eggs	Antarctica	Not significant $p > 0.05$	133
Common dolphins	Korea	Not significant, $p > 0.05$	201
Cormorant eggs	Japan, Korea	Not significant, $p > 0.05$	205
Polar bears	Greenland	Not significant, $p > 0.05$	206
Grise Fjord ringed seal, various fish	Canada – var. upper latitude locations	Negative, $p < 0.05$[a]	199

[a] Denotes that statistical significance, or lack thereof, was reported, but the p-value was not. Therefore, $\alpha = 0.05$ is assumed.

Because PFOSA can also be a metabolite of larger PreFOS molecules, it is possible that PFOSA (Ib.) BMFs are also over predicted. For example, in contrast to PFOSA, very low BMF_{TL}s were found for NEtFOSA (Vb.), with BMF_{TL}s of 0.1 and 0.04 for narwal-cod, and beluga-cod, respectively, albeit BMF_{TL}s of 9.6 for beluga-redfish, and 238 for cod-zooplankton were reported. The low BMF_{TL}s of NEtFOSA for beluga-cod, and the high BMF_{TL} of NEtFOSA for cod-zooplankton may indicate that cod are accumulating NEtFOSA due to an inability to metabolize NEtFOSA, while beluga may be able to rapidly excrete NEtFOSA, or to form PFOSA, which is then not extensively metabolized. This efficient metabolism of NEtFOSA to PFOSA by beluga may have lead to the high PFOSA BMF_{TL}s observed in beluga.

The BMF_{TL}s found for NEtFOSA (Vb.) between the beluga-redfish and cod-zooplankton pairs were 2.4 and 595 fold greater, respectively, than the BMF_{TL}s of PFOS for these same pairs. The finding of NEtFOSA in wildlife is interesting, because NEtFOSA was found to be rapidly metabolized to PFOSA (Ib.) *in vivo* (see above discussion on biotransformation). Nonetheless, the presence of NEtFOSA in these species indicates that exposure to PreFOS compounds, other than PFOSA, was occurring in this foodweb. It is unclear whether this exposure was to NEtFOSA itself, or to some larger PreFOS compound which was subsequently metabolized to NEtFOSA. Further biomonitoring of NEtFOSA in wildlife is warranted to discern whether exposure to NEtFOSA is a widespread phenomenon, or just specific to this foodweb. Although it was only indirect evidence, NEtFOSAA and NMeFOSAA in serum of children and pregnant women from the Faroe Islands was associated with consumption of pilot whale,[112] thus some marine mammals may contain even higher molecular weight PreFOS molecules than NEtFOSA.

Tomy *et al.*[144] also investigated the trophodynamics of PFOSA (Ib.) in a western Canadian Arctic foodweb, and found, in general, lower BMF_{TL}s than those observed in the eastern Canadian Arctic. Ringed seal-cod had the lowest PFOSA BMF_{TL} (0.1), while BMF_{TL}s for beluga-cod, beluga-herring, and beluga-cisco were 31, 52, and 26, respectively. The finding of $BMF_{TL}<1$ for ringed seal-cod, and a $BMF_{TL}>1$ for beluga-cod was interesting, as these two species feed at approximately the same trophic level. These differences may indicate species differences in biotransformation capability towards PFOSA, or differences in diet source and exposure between the two species.[144] In addition, in contrast to the eastern Canadian Arctic foodweb, PFOS BMF_{TL}s were consistently higher than those of PFOSA, with the exception of cod-calanus and cod-thermisto pairs, in which the PFOSA BMF_{TL}s were higher than for PFOS.

PFOSA (Ib.) BMFs have also been calculated between tucuxi dolphins (*Sotalia guianensis*) and several fish species, ranging from 5.6 to 35.[145] Similar PFOSA BMFs were found in two bottlenose dolphin foodwebs from the eastern US. BMFs ranged from 1.0 (seatrout:stripped mullet and seatrout:sheephead) to 30 (dolphin:pinfish), although for most species pairs BMFs were between 1 and 5.2.[146] Interestingly, PFOS BMFs were consistently lower than those of PFOSA in the bottlenose dolphin foodweb from Charleston, SC, yet generally higher than those of PFOSA in the Sarasota Bay, FL foodweb.[146]

Another metric for quantifying biomagnification of xenobiotics in food chains is the trophic magnification factor (TMF). TMFs can be used to quantify the average extent to which a chemical biomagnifies across longer food chains or more complex foodwebs, and TMFs greater than 1, like a BMF, indicate that a compound is being magnified in the foodweb. In general, examination of larger food chains support the findings from BMF studies that PFOSA (Ib.), the only PFOS precursor for which TMFs are available, can biomagnify. In a zooplankton to bottlenose dolphin food chain (2.1 trophic levels) from the eastern US, Houde *et al.*[146] found a TMF of 5.9 for PFOSA when using dolphin plasma concentrations to calculate TMFs, and a TMF of 5.0 when plasma concentrations were extrapolated to total-body burden concentrations. Similarly, Kelly *et al.* calculated the lipid-normalized TMFs of PFOSA for piscivorous and marine mammal foodwebs (~5.5 trophic levels) from the Canadian Arctic to be 4.53 and 4.46, respectively.[147] A slightly lower TMF of 1.9 was calculated for PFOSA in the calanus to beluga food chain (1.6 trophic levels) from the western Canadian Arctic.[144] Conversely, however, Martin *et al.*[3] found PFOSA not to biomagnify in a Lake Ontario food chain (~1.7 trophic levels), as the calculated TMF of PFOSA was 0.51. The degree to which PFOSA biomagnifies through food chains, relative to PFOS, is unclear. With the exception of the bottlenose dolphin food chain, TMFs of PFOS were generally greater than those of PFOSA, ranging from 2–3 fold higher[144,147] to 11.5 fold higher.[3] Whole dolphin TMFs were 2.8 fold higher for PFOSA than PFOS, but the difference was reduced to 1.2 fold when only plasma was used,[146] likely due to an underestimate of the PFOSA concentrations in the blood to its known binding to blood cells.

The differences observed amongst these TMF studies may be related to the location of the respective foodwebs, or the length of the foodwebs investigated and the number of species included in the analysis.[147] There appear to be some foodweb specific differences in the biomagnification of PFOSA, particularly in relation to PFOS. This could be, in part, due to differences in exposure to PreFOS, because exposure to PreFOS and subsequent metabolism to PFOS may affect the observed BMFs and TMFs in these food chains. Additionally, there appears to be inconsistency amongst researchers in the way in which BMFs and TMFs are calculated, as some studies used wet weight, while others used lipid or trophic level normalized values. The role that tissue lipid and/or protein concentrations play in bioaccumulation and biomagnification of PFOS or PreFOS is unclear. Unlike classic persistent organic pollutants, such as PCBs, perfluorinated compounds (including precursors) appear to partition to protein rich tissue rather than lipids. A further understanding of tissue distribution and behaviour of PreFOS, and their impacts on bioaccumulation, would help greatly in removing some variability and inconsistency amongst studies.

Despite the inconsistencies between studies in regards to how BMFs and TMFs were calculated, the weight of the evidence would suggest that PFOSA is bioaccumulating through food chains, despite being amenable to biotransformation. BMFs for PFOSA were generally greater than 1, indicating continual exposure to PFOSA at a rate that outpaces the rate at which it is metabolized and excreted. All studies on PreFOS accumulation to date have centred on aquatic organisms; the trophodynamics of any PreFOS molecule in a terrestrial food chain has yet to be examined.

New analytical principles in source tracking of PreFOS

From the current review it is apparent that PreFOS has significant potential to contribute to PFOS in humans, wildlife, and the environment, primarily through biodegradation and metabolism mechanisms, and to a much lesser extent through abiotic mechanisms. Thus, new analytical principles that would enable environmental chemists to distinguish directly emitted PFOS from PFOS that had been biologically degraded from PreFOS would be powerful tools for investigating the contributions of PreFOS to PFOS in the global ambient and human environment. Until recently there have been no tools that could differentiate between PFOS that was released directly to the environment, *versus* PFOS that originated from biodegradation or metabolism of PreFOS. However, two recently published studies[69,148] offer new source tracking principles for PFOS which might assist in differentiating PFOS from these two possible sources. The two principles are discussed here, and an application is demonstrated.

PFOS isomer patterns

The first new principle is based on the fact that CYP450 enzymes and human microsomes tend to biodegrade the branched isomers of PreFOS more rapidly than the linear isomer of PreFOS *in vitro*.[69] Furthermore, in rodents exposed sub-chronically to PFOSA (Ib.), this is borne out by significantly enhanced proportions of PFOS isomers in blood and tissues.[149] Thus, for biological or environmental samples that are enhanced in the relative content of branched PFOS isomers; this could be a biomarker of significant exposure to PreFOS. As mentioned, 3M Co.'s PFOS was always approximately 70% linear and 30% branched. Therefore it is curious that certain human samples have up to 50% branched isomers[10] (*e.g.* Fig. 3, compare A and B) when we know that branched PFOS isomers are excreted more rapidly in mammals than linear PFOS.[69,85] In other words, known pharmacokinetics of PFOS exclude a PFOS signature with more than 30% branched isomers, assuming exposure is to historical 3M Co. PFOS.

It is anticipated, however, that this isomer biomarker will be mainly applicable to abiotic environmental samples (*e.g.* water, soil, or sediment) and to humans exposed to PreFOS in the household environment. In aquatic or marine foodwebs, the biomarker will likely be of no utility because the excretion half-lives of all branched isomers are expected to be quite short compared to the linear isomer in aquatic organisms such as fish.[150] For example, several studies have recently been published showing highly linear PFOS signatures in freshwater and marine organisms.[151–153] We suspect these examples largely reflect isomer-specific biomagnification,[150] rather than any source biomarker.

Isomer profiling of PFOS is accessible to any researcher already analyzing PFOS by LC-MS/MS. Simple substitution of the reversed phase C8 or C18 column with a perfluorinated stationary phase allows most PFOS isomers to be distinguished by retention time and distinct MS/MS fragmentation pattern,[154,155] and a GC method is also available.[152] Our lab demonstrated a method that also separates the isomers of PreFOS molecules in the same analytical run,[154] opening the possibility to simultaneously profile the isomers of PFOS and various PreFOS molecules. An enhanced linear signature of PreFOS, combined with an enhanced branched signature of PFOS in the same sample, would be the best validation of this biomarker in environmental or human samples, but this has only been demonstrated in laboratory tests with rodents to date.[149]

PFOS enantiomers

The second analytical principle is based on *in vitro* evidence that human microsomes can degrade certain chiral PreFOS molecules (specifically α-branched) enantioselectively.[148] Therefore, non-racemic PFOS body burdens of 1*m*-PFOS (*i.e.* $C_6F_{13}CF(CF_3)SO_3^-$) could also be a biomarker of significant exposure to PreFOS. In rodents exposed sub-chronically to PFOSA (Ib.), strongly non-racemic proportions of 1*m*-PFOS were detected in blood.[156] It is anticipated that this biomarker will be applicable to any organism in any environment, and also to abiotic samples such as water or sediment. The same principle is well established for other chiral POPs, such as PCBs.[157]

The preferred metric for quantifying relative enantiomer concentrations in a sample is the enantiomer fraction (EF),[158] defined as EF = A/(A + B); where A and B are the concentrations of the 1st and 2nd eluting enantiomers. In human serum it is evident that non-racemic proportions can indeed be detected (Fig. 3C and 3D), highly suggestive evidence that PreFOS made a significant contribution to PFOS in these pooled populations. These non-racemic enantiomer fractions were not due to a matrix effect, but one caveat that still must be investigated before this biomarker can be interpreted is to what extent, if any, 1*m*-PFOS excretion may be enantioselective. This phenomenon is rare, but it has been demonstrated for other chiral drugs.[159]

The results presented in Fig. 3 for pooled human serum should, therefore, not be over-interpreted at this stage, but they are discussed briefly here. The serum shown in Fig. 3A and 3C (NIST SRM 1589a) was collected in 1996 from 50 donors who consumed fish caught around the Great Lakes. These samples showed a slight deficiency in branched content (28% branched

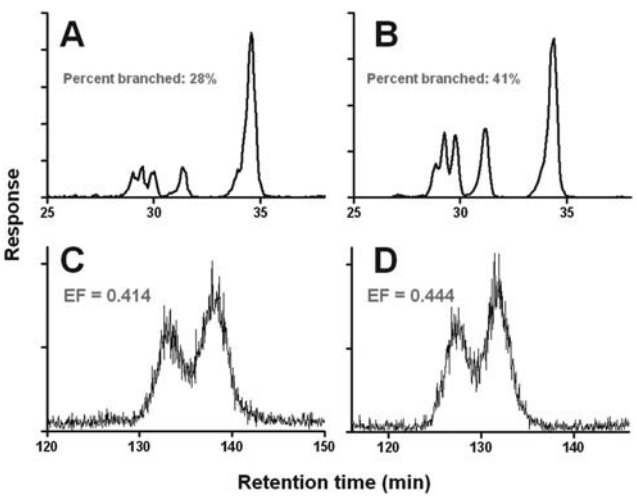

Fig. 3 PFOS isomer profiles (A, B) and enantiomers of 1*m*-PFOS (C, D) in NIST SRM 1589a (A, C), collected in 1996 from 50 pooled blood samples from donors who consumed fish caught around the Great Lakes, and in NIST SRM 1957 (B, D), collected in 2004 and pooled from serum of individuals across the United States.

content) and a non-racemic chiral signature (EF = 0.414). Serum shown in Fig. 3B and 3D (NIST SRM 1957) was collected in 2004 from individuals across the United States. This sample was enriched in branched content (41% branched) and also had a non-racemic chiral signature (EF = 0.444). The chiral signatures suggest that the PFOS measured in both samples was, to some extent, originally from PreFOS, but interpreting this in conjunction with isomer profile data is more difficult. One possibility is that the branched isomer enrichment, and non-racemic EF, in NIST SRM 1957 is representative of direct human exposure to precursors (*e.g.* NEtFOSE in house dust or NEtFOSE-phosphates in packaged foods), while the slight deficiency of branched isomers in NIST SRM 1589a, despite a non-racemic EF, may be due to PreFOS exposed sport fish in the Great Lakes which is then consumed as PFOS by humans. Even if the consumed fish had received a significant portion of their PFOS body burden from PreFOS, the faster excretion of branched isomers[150] could lead to a deficient branched isomer signature (as has been show for fish in the Great Lakes[153]), while the non-racemic 1*m*-PFOS EF would have been transferred to humans ingesting these fish.

Clearly many unknowns still exist with respect to exposure of PFOS or PreFOS in the past, today, and in the future. Many lab studies and (bio-)monitoring campaigns are needed before clear answers will be available, and new analytical tools should continue to be developed with such questions in mind.

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