Critical Review

Biological Monitoring of Polyfluoroalkyl Substances: A Review

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Polyfluoroalkyl substances (PFSs) are used in industrial and commercial products and can degrade to persistent perfluorocarboxylates (PFCAs) and perfluoroalkyl sulfonates (PFSAs). Temporal trend studies using human, fish, bird, and marine mammal samples indicate that exposure to PFSs has increased significantly over the past 15−25 years. This review summarizes the biological monitoring of PFCAs, PFSAs, and related PFSs in wildlife and humans, compares concentrations and contamination profiles among species and locations, evaluates the bioaccumulation/biomagnification in the environment, discusses possible sources, and identifies knowledge gaps. PFSs can reach elevated concentrations in humans and wildlife inhabiting industrialized areas of North America, Europe, and Asia (2−30 000 ng/mL or ng/g of wet weight (ww)). PFSs have also been detected in organisms from the Arctic and mid-ocean islands (≤3000 ng/g ww). In humans, PFSAs and PFCAs have been shown to vary among ethnic groups and PFCA/PFSA profiles differ from those in wildlife with high proportions of perfluorooctanoic acid and perfluorooctane sulfonate. The pattern of contamination in wildlife varied among species and locations suggesting multiple emission sources. Food web analyses have shown that PFCAs and PFSAs can bioaccumulate and biomagnify in marine and freshwater ecosystems. Knowledge gaps with respect to the transport, accumulation, biodegradation, temporal/spatial trends and PFS precursors have been identified. Continuous monitoring with key sentinel species and standardization of analytical methods are recommended.

Introduction

The chemical and thermal stabilities of polyfluoroalkyl substances (PFSs) have led to their integration, mainly as polymers, in a myriad of products such as lubricants, adhesives, stain and soil repellents, and paper coatings, as well as pharmaceuticals, insecticides, and fire-fighting foams (*1*). Two main manufacturing processes are used to synthesize PFSs: electrochemical fluorination and telomerization. Electrochemical fluorination involves the replacement of all hydrogen atoms of a hydrocarbon by fluorine in the presence of an electric current (*2*). Electrochemical fluorination was used to make perfluorooctane-sulfonyl fluoride based products, which were used to create perfluoroalkyl sulfonamido alcohols (e.g., *N*-ethyl perfluorooctanesulfonamidoethanol (*N*-EtFOSE)). These products were phased out in 2001 and replaced by analogous butyl-based substances (*3*). The electrochemical technology yields a mixture of branched and linear isomers as well as shorter chain-length impurities. Perfluoroalkyl sulfonamido alcohols are known to degrade to perfluoroalkyl sulfonate acids (PFSAs) via biotransformation processes (*4*) and through abiotic oxidation (*5*). For example, perfluorooctane sulfonate acid, (PFOS; all definitions of acronyms and molecular structures are available in Table 1 in the Supporting Information), may arise from environmental release of perfluorooctylsulfonamides, such as *N*-EtFOSE.

The second important manufacturing process for PFSs is telomerization which involves reacting pentafluoroiodoethane with tetrafluoroethylene oligomers to yield a mixture of perfluoroalkyl iodides. These straight, even-chained, fluorotelomer iodides are then used to make a variety of telomer products, including the fluorotelomer alcohols (FTOHs) (*6*). FTOHs have been shown to be transformed in the atmosphere, and metabolically in animals and microorganisms, to fluorotelomer carboxylic acids (FTCAs) and perfluorocarboxylates (PFCAs; e.g., perfluorooctanoic acid, PFOA) (*7*−*10*). The biotransformation of 8:2 FTOH to fluorotelomer carboxylic acids and PFOA in rodents (*7*) and to FTCAs, PFOA, and perfluorononanoic acid (PFNA) in rat hepatocytes has been confirmed (*10*, *11*).

PFSs have been measured in water, fish, birds, mammals, and humans worldwide (*12*−*14*). It is widely recognized that PFSAs and PFCAs are persistent in the environment; to date there is no evidence for biodegradation of these chemicals. Accumulation and environmental fate of neutral organohalogen compounds can be predicted using physical properties such as the octanol−water partition coefficients (K_{ow} values) (*15*). However, because perfluoroalkyl chains are both oleophobic and hydrophobic, K_{ow} based models are not suitable for the evaluation of the fate of PFSAs and PFCAs. It remains uncertain if K_{ow} is a suitable physical property for

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the evaluation of PFS precursor accumulation or fate, but because these neutral compounds are more easily transformed in the environment, such modeling may be of limited utility. Furthermore, where physicochemical property data for PFSs do exist, there is generally a lack of agreement for measurements made by different methods, and in different laboratories, therefore confidence in existing data is low. These problems underline the importance of current biomonitoring for understanding the fate and behavior of PFSs in the environment. If results are carefully and accurately interpreted, analysis of biological samples can provide information on sources of wildlife and human exposure, transport mechanisms, bioaccumulation potential, global distribution, and temporal trends.

This review summarizes the biological monitoring data for PFSs across species as well as spatially and temporally. Data were obtained primarily from peer-reviewed articles published up to January 2006. The literature research was conducted with integrated web-based software (e.g., ISI Web of Knowledge). The available data consisted mainly of arithmetic or geometric mean concentrations or data ranges. We have used the midpoint where only ranges were given. Because of lack of information on the statistical distribution of the data in most studies, we did not weight the means for sample size or variance. We have analyzed the patterns of PFS contamination among species and considered if congener identification and profiles could be used to infer sources. Finally, we characterized the bioaccumulation potential of PFSs through food webs. The entire results of our review are compiled in tables available in the Supporting Information (SI) section.

Analytical Considerations and Data Quality

A recent international study has demonstrated significant interlaboratory variations in analytical results for PFSs (*16*). Comparisons of analytical results for PFOA, PFOS, and perfluorooctanesulfonamide (PFOSA) have shown good reproducibility for standards, fish extracts, and blood/plasma samples. However, poor reproducibility among laboratories was observed for the same compounds for water samples and the fish tissue analyses (*16*). As a conclusion, the development of certified standard materials for different matrices was highly recommended. Quality assurance issues for PFS analyses are discussed in detail by Martin et al. (*17*). We have not excluded studies based on quality assurance criteria from this review because information on this is usually quite limited. At the same time, the majority of biomonitoring data has been generated by a small number of laboratories and there is some overlap among the species and locations analyzed which shows good agreement among studies. Data produced by individual laboratories for temporal trend analyses were considered acceptable because of consistent intra-laboratory analytical bias over time. Most studies have used similar ion-pairing liquid extraction methods. A minority of studies were conducted using a solid-phase extraction, liquid extraction (without an ion-pairing agent), or direct LC-MS injection (*18*−*22*). Contamination during sample handling, storage, laboratory processing, and sample analysis are potential problems that must be monitored closely, especially for PFOA and PFNA, due to their use as processing aids in the manufacture of fluoropolymers such as poly(tetrafluoroethylene) (PTFE) and polyvinylidene fluoride (PVDF) (*23*) which may be in contact with samples during workup and PFS determination. Challenges to PFS analyses, such as matrix effects on ionization enhancement/suppression in the LC-MS, are also factors that can significantly affect results and may be addressed by use of isotope labeled standards and standard addition techniques. The stability of PFSAs and PFCAs gives confidence that sample storage conditions are not a major factor that would influence data quality, and lends justification and confidence to the use of archived samples. It has been recognized that consideration must be given to possible degradation of precursors to PFCAs/PFSAs in archived tissues or storage of extracts (*17*) but there is currently no evidence to suggest that this would be significant under any reasonable sample storage conditions. Virtually all results in this review are from studies that used non-isotope-labeled internal standards because, with the exception of ^{13}C-PFOA, these have only become available since mid-2004. The use of ^{13}C-labeled and ^{18}O-labeled PFSs is likely to improve the accuracy of future PFS analyses. Thus, we are still at an early stage of comprehensively evaluating and understanding the data quality concerns among the various PFS classes and congeners.

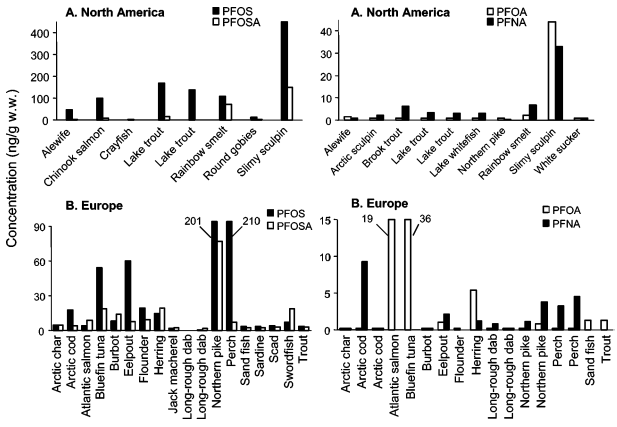

FIGURE 1. (A) Pattern of PFSA and PFCA contamination in liver or whole homogenates of fish collected in North America. (B) Pattern of PFSA and PFCA contamination in fish liver collected in Europe (refs *14, 26, 31, 34, 40, 41*).

Overview of PFSs in Biota and Humans

Invertebrates. PFSs have been reported in organisms at all levels within aquatic food webs. Starting at the bottom of the food chain, PFSs were measured in benthic algae (*22*) as well as invertebrates from different regions of North America, Asia, and Europe (SI Table 2). Low concentrations of PFOS and PFOA (<2 ng/g ww) were reported for zooplankton (all species Latin names are available in the SI tables), mollusks, and shrimp from the Eastern Canadian Arctic and Asia (*24*, *25*). High concentrations of PFCAs and PFSAs (2−280 ng/g ww) were observed in an invertebrate, *Diporeia hoyi*, from the Great Lakes (*26*). Elevated concentrations of PFOS (9−877 ng/g ww) were also detected in oyster from the United States (*27*), mussels from Portugal (*28*), and shrimp, starfish, and crabs from the Belgian and Dutch coasts (*29*). It was suggested that sediment could be a major source of PFSs to the Lake Ontario food web and that this may be mediated through accumulation of PFS precursors in the sediment (*26*).

Fish, Amphibians, and Reptiles. PFOS was the predominant compound detected in freshwater and saltwater fish samples (Figure 1 A and B; SI Table 3). The highest PFOS concentration (3250 ng/g ww) was reported in the liver of the carnivorous and near-bottom feeder ornate jobfish from Okinawa, Japan (*12*). The authors of this latter study noted the presence of an electric power plant and a military base in Okinawa and suggested that fire-fighting operations on the army base may be the source of PFOS in this area. Elevated PFOS concentrations (>100 ng/g ww) were also found in liver, muscle, and egg samples of numerous species of fish from different locations (*12*, *30*−*34*). The lowest PFOS concentrations were reported in samples of fish collected in the Eastern Canadian Arctic and from the Faroe Islands (*24*, *31*). Several sources, such as discharge of industrial and

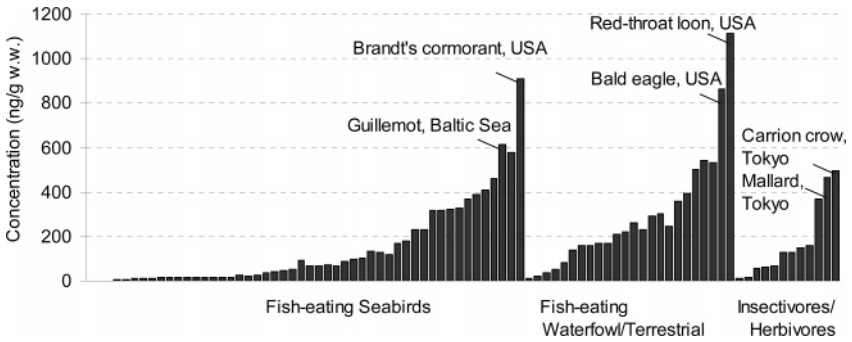

FIGURE 2. PFOS concentrations (ng/g ww) in eggs, liver, kidney, serum, and plasma of marine and terrestrial birds (1990−2004) (order of references (left to right) follows SI Table 4: *12, 14, 24, 30, 31, 42−47*).

municipal wastewater, fire-fighting operations at military bases and airports, and landfill leachate may all be responsible for the elevated exposure to PFSs in urban areas (*12*, *35*). Laboratory studies suggest that in fish uptake from water via gills and diet are both important routes of exposure (*36*, *37*).

In addition to PFOS, PFCAs and other PFSAs have been measured in fish samples (Figure 1). The highest PFOSA concentrations were found in liver of Norway Pike (91 ± 37 ng/g ww) (*31*) and whole slimy sculpin homogenates from Lake Ontario (150 ± 17 ng/g ww) (*26*, *31*); both species also had high PFOS concentrations. In fish from North America, PFNA exceeded PFOA concentrations in a variety of species. PFSAs and PFOA were predominant in fish sampled in Europe and Asia with PFNA predominating in a few species. Considering the limited number of samples and species represented by these measurements, results may not be entirely representative of fish populations but are appropriate for preliminary assessments.

Overall, no clear inter-species or geographical trends could be observed in the profile of PFS contamination in fish. In addition to fish tissues, PFSAs and PFCAs have been reported in eggs (*22*) inferring significant oviparous transfer to offspring, possibly by binding to eggs proteins (*22*). PFOS is known, from laboratory studies, to accumulate in gonads (*36*, *38*) and the subsequent thresholds for effects on fish development have been investigated (*38*).

A few studies report PFS in plasma and liver of frogs and turtles from areas in the United States (SI Table 3). PFS concentrations measured in these animals fall in the same range as concentrations detected in fish, with PFOS being the predominant compound in all organisms; the greatest PFOS concentrations were measured in liver of green frogs from Michigan (PFOS <285 ng/g ww) and yellow-bloched map turtles from Mississippi (190 ng/g ww) (*30*). Generally, PFOS concentrations were followed in order by PFOA, perfluorohexane sulfonate (PFHxS), and PFOSA. PFCAs (9−12 carbons) are also reported in sea turtles (*39*). Smaller PFOSA concentrations were measured in amphibians and reptiles compared to *Mysis* and *Diporeia* from Lake Ontario, suggesting that these neutral precursor molecules may be a source of PFSs in the aquatic food web and that these are quickly metabolized to PFSAs or PFCAs.

Birds. PFSs have been detected worldwide in seabirds and in terrestrial birds and waterfowl (Figure 2; SI Table 4). The highest PFOS concentrations were found in birds from industrialized areas. Bird samples from Antarctica and (*14*, *30*, *42*) Nunavut, Canada, in addition to oceanic birds such as albatrosses, had the lowest PFOS concentrations (*14*, *30*, *42*).

Waterfowl are mainly herbivores and/or insectivores and therefore feed at a lower trophic level than fish-eating terrestrial or seabirds which may explain the lowest PFOS values measured in some of these animals. PFS concentrations in fish-eating birds are usually lower than concentrations measured in fish-eating mammals, an observation that could be linked to the trophic positions of prey and predators in their respective foodwebs or to a rather short elimination half-life in birds (14 and 21 days in mallards and quail, respectively) (*48*), which is similar to the elimination half-life measured in juvenile fish (*36*). Environmental and dietary exposure may vary between resident and migratory birds. Migratory birds are exposed to a multitude of temporary food sources and environments that may affect the concentration and pattern of PFS contamination. Only a few studies in birds (mainly for seabirds) have assessed a wide range of PFSs in tissue rather than just PFOS and PFOA. Two studies have analyzed for the homologous series of PFCAs, with a chain-length up to 15 carbons, in Arctic birds from Norway and Canada. Environmental/dietary exposures and unique metabolic activities (biotransformation, sequestration, and elimination) could explain this PFS profile of seabirds. In addition to PFCAs, 8:2 and 10:2 fluorotelomer unsaturated carboxylic acids (FTUCAs) also have been measured in some species of Arctic seabirds (*49*). Finally, as observed in fish (*22*), PFSs have been detected in bird eggs (*42*, *46*, *47*) indicating oviparous transfer to offspring.

Mammals. Few biomonitoring studies have been conducted for terrestrial mammals (Figure 3; SI Table 5). Wood mice inhabiting the area around a fluorochemical plant in Belgium had the highest PFOS concentration encountered in generating this review for any organism, with a maximum of ~180 000 ng/g ww (*50*). The results of this site-specific study imply that PFSs can be highly bioavailable in the terrestrial ecosystem. In mink, elevated PFOS burdens were found in the midwestern and northwestern United States (≤ 2630 ng/g ww) (*30*). Despite their remote habitat, Arctic fox had unexpectedly high concentrations of PFOS in liver (250 ng/g ww) (*14*), which may be explained by their opportunistic and scavenging diet that includes small terrestrial mammals and marine mammal carcasses. Surprisingly, PFOS and PFCAs were also detected in liver of the herbivorous northern caribou (*51*). Overall, terrestrial mammals (with the exception of mink from the United States and wood mice from Belgium) showed concentrations in the same range as those measured in marine mammals.

A much greater number of studies have been conducted on marine mammals compared to terrestrial animals (Figure 3; SI Table 5). Except for studies on live-captured bottlenose dolphins, all PFS assessments have been conducted on hunted, by-catch, or stranded marine mammals. Concentrations of persistent contaminants in dead animals may not be entirely representative of the free-ranging population (*52*); dead animals may have been stressed, starved, and/or sick before death. Due to the resistance of PFSA/PFCAs to biodegradation and their nonvolatility, these factors may not be as important for PFSs but should be kept in mind especially since neutral precursors, if present, can degrade to PFCAs or PFSAs.

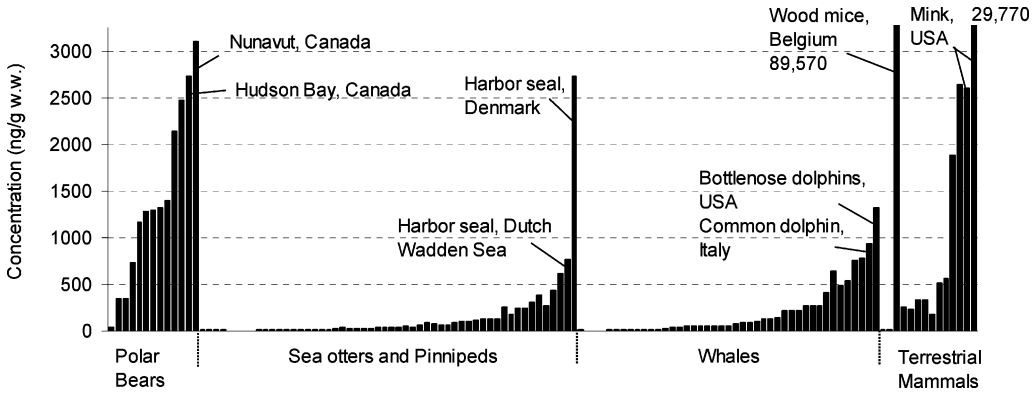

FIGURE 3. PFOS concentrations in liver, kidney, and plasma of terrestrial and marine mammals (1990−2003) (reference order follows SI Table 5: *14, 24, 30, 31, 41, 43, 45, 50, 51, 54−62*).

PFS concentrations measured in baleen whales were lower than concentrations found in toothed whales. This is most likely explained by the different trophic levels at which these two cetacean classes feed: baleen-filtering versus fish-eating, respectively (*53*). Observations, such as the detection of PFOS in livers and kidneys of North Sea sperm whales (*54*), a deep-water feeder, imply its presence in the deep sea food web. The actual pathway of PFOS transport to deep oceans is not clear, but may be through sedimentation on sinking particles. There is limited information on PFS concentrations in prey species of toothed whales such as squid and specific species of fish.

The highest PFS concentrations were found in plasma and liver of bottlenose dolphins from the United States and in polar bears. Bottlenose dolphins from the eastern U.S. coast and the Gulf of Mexico have a coastal habitat and many are year-round residents in areas surrounded by human activity, which could explain the high PFS concentrations measured in these animals. Polar bears are food chain apex predators in the Arctic food web and feed largely on seals (*14*, *57*), and mainly on ringed seal blubber and skin. One study reported PFOS in blubber samples of harbor seals (mean PFOS concentration 100 ng/g ww) (*59*). Considering the elevated concentrations of PFOS in polar bears, seal blubber and skin may be a significant source for polar bears. However, analysis of PFSs, particularly the anionic species, in fatty tissue is challenging and improved analytical methods are needed. It is unclear how PFSs are transported to remote regions such as the Arctic and the mid-Pacific. The leading hypotheses are atmospheric and oceanic transport (*9*, *23*).

In harbor seals from the Dutch Wadden Sea, tissue distribution of PFOS followed the rank order kidney > spleen > liver > blubber and skeletal muscle (*59*) and was similar to the tissue distribution determined in rainbow trout with liver and kidney being among the most contaminated tissues (*36*). Measurements of PFCAs and PFSAs in bottlenose dolphin tissues have shown that plasma, liver, and lungs are among the most contaminated organs; the compounds were also detected in thyroid, thymus, and heart (*63*). PFOS has been measured in the brain of two sea otters from the western U.S. (*62*), suggesting that it can cross the blood/brain barrier as observed in rats (*64*). Bottlenose dolphin calves have been shown to have higher PFS concentrations in plasma compared to their mothers (*65*). PFSs were found in milk of bottlenose dolphins, suggesting that maternal transfer occurs during lactation (*65*). Similarly, concentrations of PFOS found in the liver of a North Sea harbor porpoise fetus were more than 2-fold greater than in its mother (*61*) suggesting the placental transfer and fetal accumulation of PFOS in cetaceans.

The general lack of correlation between concentrations and age in bottlenose dolphins implies that the elimination of PFSs via urine and feces may be important and that PFS half-lives may be relatively short in certain marine mammals compared to organochlorine compounds. The half-life for PFOS in dolphins was estimated at 21 weeks based on the known diets and feeding rates and assuming no precursor sources. PFCAs and PFSAs have been measured in urine of dolphins which indicates that urine may be an important depuration pathway (*65*). This depuration also implies that concentrations are sustained by continuous exposure and uptake of PFSs. FTUCAs (8:2 and 10:2) have been measured in plasma of dolphins from the United States (*60*) and in Arctic seals (*49*). The highest concentrations of FTUCAs were found in open-ocean dolphins compared to the coastal animals, a result that is strongly suggestive of an atmospheric transport route for PFCAs (*9*). The detection of FTUCAs, which are primary biotransformation products of FTOHs, also suggests that FTOHs may bioaccumulate in the marine food web but this has not been confirmed.

Humans. PFSs have been detected globally in human blood/serum, with PFOS being the most prevalent compound followed by PFOA (Figure 4; SI Table 6). In addition to PFOS and PFOA, PFHxS and the precursor PFOSA were the most commonly studied PFSs in humans. PFOS and PFOA concentrations measured in humans are shown in Figure 4 according to geographic locations.

Higher PFOS concentrations were measured in blood and serum from North Americans (Canada and United States) compared to people from Asia, Europe, and the Southern Hemisphere (*12*, *13*, *18−21*, *66−74*). Overall, the highest concentrations of PFOS in human serum were measured in Kentucky (<73 ng/mL; blood concentrations have been adjusted to serum concentrations by multiplying by 2) (*13*), males from Poland (54 ng/mL) (*13*), and people from China (53 ng/mL) (*71*). The lowest PFOS concentrations were measured in workers from two rural Sri Lanka locations (<6 ng/mL), Italy (<5 ng/mL), and India (<2.5 ng/mL) (*13*, *73*). PFOS concentrations measured in serum of 10 persons from urban Sri Lanka (*73*) were similar to those in people from Colombia, Brazil, Malaysia, and Japan (*12*, *13*). Concentrations measured in maternal blood from northern Canada fell in the range of concentrations measured in females from southern urban Canadian regions (*70*). These results indicate that some residents of developing countries and remote regions are exposed to PFSs in a manner similar to people inhabiting industrialized and urban areas. An assessment of fish, caribou, and ringed seal livers has shown that PFCAs and PFSAs are present in traditional food items of northern indigenous populations in Canada (*51*). Fish have also been found to be a source of PFS contamination in people inhabiting the Baltic coast (*75*). Overall, patterns of PFS contamination between human and wildlife are different, indicating that fish and mammals may not be the major

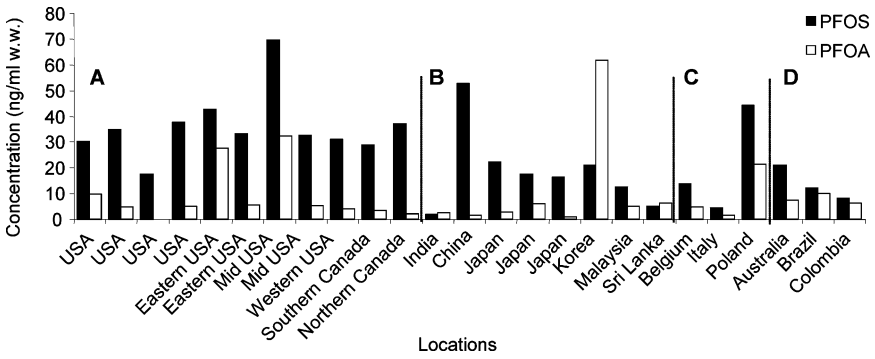

FIGURE 4. Mean concentrations of PFOS and PFOA (ng/mL ww) in human serum collected after 1988, in (A) North America, (B) Asia, (C) Europe, and (D) other countries (*12, 13, 18−21, 66−74*). Blood concentrations have been adjusted to serum concentrations by multiplying by 2.

source of PFS contamination in humans. Personal care and cleaning products, in addition to indoor dust, may constitute additional exposure routes (*1*, *76−78*). A potential source for PFOS-related precursors (e.g., PFOSA) (*79*) and PFOA is migration from food-packaging. Additionally, PFOA could have an indirect source through metabolism of fluorotelomer-based precursors, also used in food-packaging such as microwave popcorn bags (*80*). PFOA is also used in the manufacturing of fluoropolymers incorporated in treated cookware. However, studies of PFOA release from anti-adhesive cookware did not show detectable amounts of PFOA (*81*).

In humans, PFOA concentrations were usually lower than those of PFOS except for a report from Korea (*13*). The serum elimination half-life elimination for PFOA has been reported to be 4.4 years (*82*), indicating a substantial persistence in humans. The absence of active excretion in human kidneys has been suggested by Harada et al. (*83*). This study also suggested that menstrual bleeding could be a route of PFS excretion in women (*83*).

The effects of ethnicity and sex on PFS concentrations have been evaluated in pooled serum samples from the United States (2001−2002). Results indicated that concentrations of PFOS, PFOA, and PFHxS in ethnic groups significantly ranked as followed: non-Hispanic whites > non-Hispanic blacks > Mexican Americans (*84*). Also males had significantly higher concentrations of PFOS, PFOA, and PFNA than females. The genetic variability, diet, lifestyle, or a combination of all these factors may influence the pattern of contamination in human populations (*84*). In addition, higher PFHxS serum concentrations have been found in American children compared to adults (*67*). The authors suggest that the different activity (e.g., playing on carpeted floors) and exposure pattern of children may explain these differences. The large concentrations of PFHxS detected in house dust (357 μg/g dust; *78*) support these hypotheses.

In addition to serum and blood, PFSA and PFCAs were reported in maternal and cord blood of pregnant Canadian and Japanese women, indicating the exposure of human fetuses (*18*, *70*). Moreover, PFSs were reported in human breast milk from China (*85*) suggesting some lactational transfer to infants. PFSs were also measured in seminal plasma (mean of individual PFS ≤0.6 ng/mL), indicating the presence of these chemicals in the human reproductive system (*73*).

Variations in PFS Profiles. Different profiles of PFSs have been reported in the tissues, mainly liver, of various species (Figure 5), and a detailed examination may assist in identifying different sources of exposure and degradative capacity. Overall, it is clear that PFOS is the predominant PFS in biotic samples. Long-chain PFCAs (>8 carbons) have also been detected, as well as PFSAs with 4 to 10 carbons. Humans have much greater concentrations of PFOA than wildlife which results in different ratios of PFOS/PFOA. The isomer profile in human blood samples also shows a dominance of linear PFCAs (*86*). Linear PFCAs have also been observed to be predominant in polar bear livers (*87*). These results imply that these organisms are (1) more exposed to linear PFCAs, (2) linear PFCAs are preferentially adsorbed and/or, (3) branched PFCA isomers are more readily eliminated (*86*). The large proportion of linear PFCAs, in addition to the odd- and even-chain-length pattern observed in humans and wildlife (*14*, *60*, *73*, *88*), is consistent with the hypothesis that FTOHs are a major source of environmental PFCAs. For example, the atmospheric oxidation of 8:2 FTOH produces equal amounts of PFOA and PFNA (*9*), but because PFNA is more bioaccumulative, this odd-chain length acid would be expected to predominate in biota samples. Similarly, atmospheric oxidation of 10:2 FTOH to perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUA) may lead to the predominance of PFUA in biota. However, for biota living near sources such as wastewater effluents, this pattern could be obscured by direct sources of the PFCAs.

The PFCA profile determined in invertebrates and reptiles, for which adequate data were available, are similar among species, showing decreasing concentrations with increasing chain length (Figure 5). Long-chain PFCAs were also measured in several species of fish from Lake Ontario, Canada, although the main observation in fish was the large proportion of PFOSA. This distinct presence of PFOSA in fish indicates limited biotransformation capacities for this compound in certain species of fish and strongly suggests that PFOSA and sulfonamide derivatives are important source chemicals. PFOS concentrations are usually much higher than PFCAs in wildlife; however, in Northern fulmars, concentrations of PFNA and PFDoA exceeded PFOS (*43*). The proportions of some PFCAs were also very similar to, or exceeded, PFOS in beluga and dolphins.

Elevated ratios of PFOS to ΣPFSs were found in polar bears, slightly varying from the proportion observed in ringed seals (Figure 5). Contamination profiles and spatial trends in polar bears and ringed seals, a major prey item, were quite similar. A marked presence of PFOSA was detected in Arctic belugas compared to bottlenose dolphins from the western Atlantic. Since both species are members of the same superfamily, similar profiles might be expected. Arctic belugas have lower exposures to environmental contaminants that are known to induce xenobiotic-metabolizing enzyme systems (*89*). As a consequence, Arctic beluga whales generally have a lower biotransformation potential toward organohalogens such as polychlorinated biphenyls and flame retardants (*90*). This may explain the greater accumulation and higher concentrations of precursor PFS compounds such as PFOSA. PFNA/PFOS and PFNA/PFOA ratios in polar bears were higher in the western North American arctic and lower in bears from Greenland and Svalbard (*88*). The western North

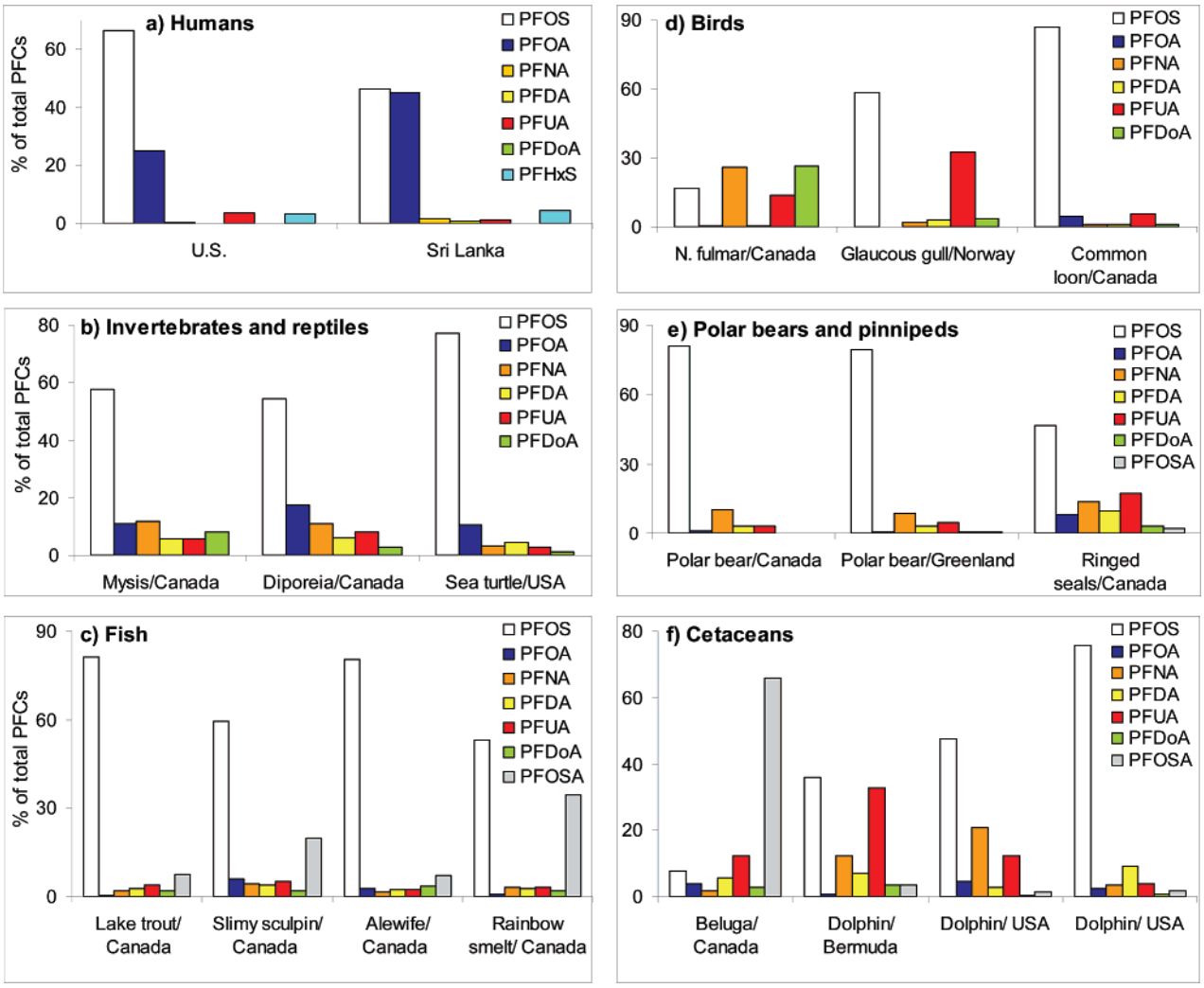

FIGURE 5. Proportion (%) of individual PFS/ΣPFSs for (a) humans (*21, 73*), (b) invertebrates and reptiles (*26, 39*), (c) fish (*26*), (d) seabirds (*46, 49*), (e) polar bears and pinnipeds (*14, 45, 55, 88*), and (f) cetaceans (*43, 60*). Samples were selected based on data availability (1990−2004).

American arctic is known to be influenced by east Asian sources of semivolatile organics such as hexachlorocyclohexane (*91*). Interestingly, Prevedouros et al. (*23*) report that PFNA production is primarily in Japan and that 14 of the world's 33 fluoropolymer production sites are in east Asia. Yamashita et al. (*92*) found higher PFNA concentrations in surface waters of the North Atlantic ocean (15−36 pg/L) than in the north central Pacific (1−16 pg/L) while the range of PFOS concentrations was similar in both oceans (9−36 and 1−20 pg/L, respectively), thus the geographical trends of PFNA and other PFCAs in polar bears cannot be explained by seawater concentrations in neighboring seas. Numerous linear correlations between concentrations of different PFSAs and PFCAs have been observed in humans and wildlife inhabiting different regions (*13*, *14*, *19*, *73*). These correlations suggest that PFS exposures occur simultaneously, probably through the same pathways, and thus may indicate a similar origin within geographical locations.

Temporal Trends. Many temporal trend studies on PFOS have shown increasing concentrations over time (Figure 6). A significant 4-fold nonlinear increase of PFOS concentrations in whole lake trout homogenates from Lake Ontario occurred between 1980 and 2001 (*42*). Temporal trend studies on guillemot eggs from the Baltic Sea indicate an increase of almost 30-fold in the mean PFOS concentration in eggs (a 7−11% increase per year) with a decrease after 2002 (*47*). Temporal trend in Arctic thick-billed murres showed a similar increasing pattern between 1987 and 2003 (*49*). An increase in PFSAs and PFCAs between 1987 and 1993 was measured in northern fulmar samples with relatively no changes in concentrations between 1993 and 2003 (*49*).

Results of a long-term assessment in ringed seals from Greenland have shown significant increases in PFOS, PFDA, and PFUA concentrations over the period 1982−2003 (*58*). PFCA (9−11 carbons) concentrations in Canadian Arctic ringed seal livers have also shown a steady increase from the 1970s and 2000s (*49*). PFOS concentrations, on the other hand, increased until the end of the 1990s but decreased after 2000; a pattern not observed with PFCAs. The same steadily increasing pattern has been reported for PFOS and PFCAs in livers of polar bears from the North Baffin Bay between 1972 and 2001 (*93*). The doubling time for PFOS concentrations in liver of these animals was similar to the doubling time of production of perfluorooctanesulfonyl fluoride (PFOSF)-based products during the 1990s (*93*). Tomy et al. have reported increasing trends in PFOS and PFOSA concentrations in the liver of beluga from the Canadian Artic between 1982 and 2002 (*94*). There is inconsistent evidence to indicate whether there has been a steady increase in PFS concentrations in humans. Olsen et al. (*68*) showed that PFOS, PFOA, and PFHxS concentrations were significantly greater in human serum collected in 1989 compared to that collected in 1974. However, comparison with additional data in 2001 did not suggest any increases since 1989 (*68*). Results

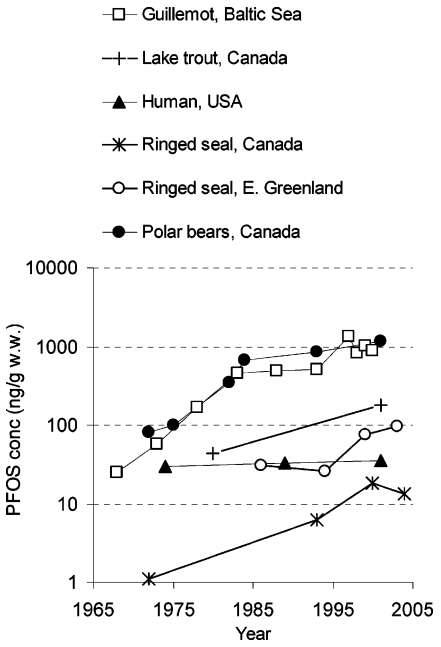

FIGURE 6. Temporal trend of PFOS (ng/g ww) in guillemot eggs (*47*), lake trout homogenates (*26*), human serum (*68*), and livers of polar bears/ringed seals from Arctic Canada and ringed seals from Greenland (*49, 58*).

presented by Saito et al. (*72*) demonstrated that PFOA increased by a factor of 4 between 1983 and 1999 in human serum from Kyoto and rural areas in Japan compared to PFOS which reached a plateau at the end of the 1980s.

Bioaccumulation and Biomagnification. Several biomonitoring studies have been conducted in which simultaneous concentrations in organisms and water have been measured in the field, thus enabling field-based bioaccumulation factors (BAFs) to be calculated (SI Table 7). The most elevated field-based BAF for PFOS was calculated in common shiner livers from Etobicoke Creek, Canada (BAF <125 000) following an accidental release of fire-fighting foam (*35*), but as the authors noted, this BAF may have been influenced by PFSA precursors that were not measured in water but which may have been metabolized to PFOS in the fish livers. A study on caged mink fed a diet composed of different percentages of contaminated carp from Michigan reported mink biomagnification factors (BMFs) of 11 to 23 from predator to prey (*62*). A field study calculated BMFs for bald eagle and mink predators and Chinook salmon prey of 5 to 10 (*22*) based on liver measurements.

Field-based BMFs and BAFs generally increase with increasing perfluoroalkyl chain-length, as observed in laboratory bioaccumulation studies (*36*, *37*). However, there is an extraordinary lack of agreement between laboratory and field BAFs/BMFs for PFSs. These discrepancies imply that numerous factors, such as organism size and unmonitored trophic concentrations, could affect the calculation of BAFs and BMFs. The monitored tissue analyzed for the calculation of these factors, rather than using whole body homogenates, is likely responsible for some of these differences.

It is possible to evaluate the trophic magnification of PFSs by plotting concentrations measured against trophic level (Figure 7) as determined by nitrogen stable isotope ratios (δ^{15}N). PFOS concentrations in an Arctic marine food web were positively correlated with trophic levels resulting in a trophic magnification factor (TMF) of 3.1 (*24*). Authors from this latter study stressed the fact that the presence and degradation of PFOS precursors, such as PFOSA, could result in overestimation of the BMF for PFOS. The same increasing observations have been reported for several PFCAs and PFSAs in a Lake Ontario food web (*26*) as well as in the food web of bottlenose dolphins (*63*). Moreover, significant positive relationships between PFOS concentrations in liver and muscle and δ^{15}N have also been observed in other species of marine mammals (*54*), indicating that animals feeding higher up in the food chain had greater PFOS concentrations.

The actual mechanism controlling the slow elimination, and hence bioaccumulation, of PFSs from organisms is not entirely clear, although enterohepatic recirculation of PFSs has been shown experimentally (*95*), as has the protein binding of many PFSs to albumin (*96*, *97*).

When assessing PFSs in food webs that include large top predators, such as birds and mammals, the use of concentrations measured in a specific predator tissue (e.g., liver) will bias the BAF, BMF, or TMF compared to use of whole organism homogenates. We suggest that whole-body-burden estimations for large predators, using estimated blood volume and whole tissue and body weights, will yield a more accurate and more useful measure of bioaccumulation. Unfortunately, this additional step requires data that are rarely available

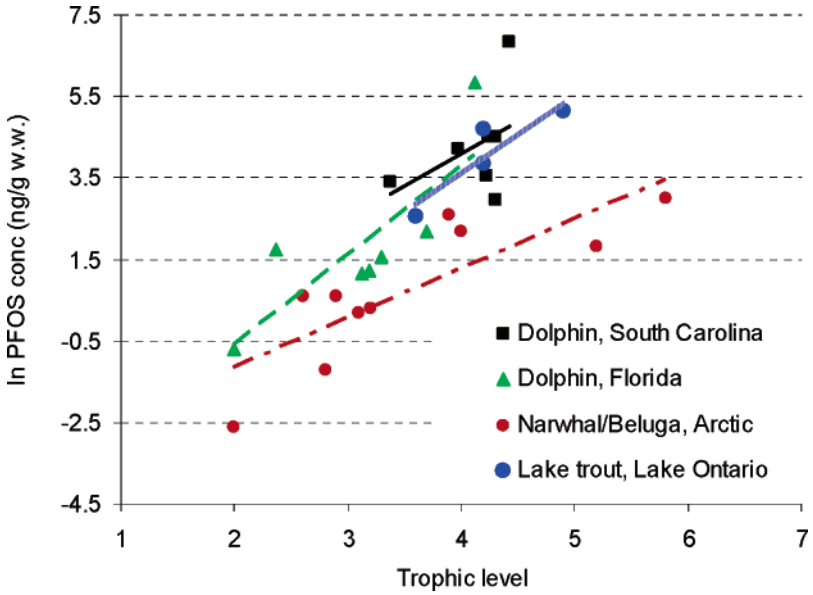

FIGURE 7. Natural logarithm-based PFOS concentration (ng/g ww) in relation to trophic levels for organisms in the food webs of bottlenose dolphins, narwhal/beluga and lake trout. Concentrations and trophic levels have been estimated from refs *24*, *26*, and *63*.

when conducting a biomonitoring assessment but that could be estimated based on the literature and/or observations in closely related species. These whole organism estimations have been conducted for bottlenose dolphins and beluga/narwhal (data from Tomy et al. (*24*)) based on plasma and liver values respectively (*63*). Comparisons showed that BMFs and TMFs were generally higher when calculated based on plasma or liver concentrations in top predators as opposed to whole body load estimate.

Summary and Recommendations

In general, it is clear from biomonitoring data that PFSs are globally distributed and that biota concentrations are higher when collected close to urbanized/industrialized regions. Detailed statistical comparison among studies is problematic, however, because of the variation in style of reporting PFS concentrations, i.e., ranges, geometric means, and arithmetic means. Field biomonitoring studies have provided strong evidence that PFOS, PFHxS, and C_8-C_{12} PFCAs can bioaccumulate and biomagnify through food webs, reaching elevated concentrations in higher trophic level species. Temporal trend studies using archived as well as recently collected samples have reported increases in PFOS and PFCA concentrations in wildlife, particularly during the 1990s. Less clear are the temporal trends of PFOS and PFOA in humans which do not parallel the observed trends in wildlife.

The phase-out of PFOSF-based products in 2001 and the reduction of global PFCA emissions (assuming PFOA is representative for all PFCAs) for the period 1999−2006 (*23*) has not yet been clearly detected by temporal trend studies but these changes offer a unique opportunity to use biomonitoring studies to test hypotheses about sources and fate of PFSs. A leading question for research today, which has major implications for the future environmental burden of PFSs and the associated environmental and human risk(s), is the importance of perfluoroalkyl polymer degradation to the emission of PFSA and PFCA precursors. If the environmental burden of PFSAs and PFCAs is the result of (i) emissions of nonpolymerized residual precursors, or (ii) release of PFSAs and PFCAs from multiple direct applications in aqueous fire-fighting foams or as processing aids, then it can reasonably be theorized that a phase-out or improvements in process technology should lead to a leveling off, or slow decrease, in the environmental burden of PFSAs and PFCAs. Alternatively, if the vast bulk of surface treatment polymers slowly degrades and continues to release PFSs either as acids, fragments of polymers, or other precursors, then the environmental burdens could be expected to increase over time, depending on the rate of degradation. Thus biomonitoring efforts will also be valuable in determining the effectiveness of this action.

Major gaps remain as exemplified by the lack of information on the sources, the transformation, distribution, and accumulation of PFCA and PFSA precursors, as well as the identification of new classes of PFSs (e.g., fluorotelomer olefins, perfluoro-ethers) in biological samples. Temporal and spatial trends of PFS data for wildlife and humans are also lacking for many regions and for the post-2001 time period following withdrawl of PFOSF-based chemistry and changes to fluorotelomer based-production. An appropriate and consistent selection of monitoring species for a particular ecosystem or food web and, if possible, nondestructively collected samples from top predator species that have a broad geographical distribution within a given ecosystem is required in such biomonitoring designs. Utilizing samples from existing archives and/or monitoring programs would also be beneficial. Future and continuing routine monitoring programs should aim to address hypotheses regarding the sources and environmental behavior of PFSs, rather than simply adding to the large existing database on biota concentrations. Whole body residues in wildlife should be estimated for more precise evaluation of biomagnification during the examination of PFSs in food webs. Finally, the sources of PFSs in humans, childhood exposure, and the variation among different ethnic groups need further study.

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Supporting Information Available

Definitions of acronyms and structures of PFCAs and PFSAs; mean PFS concentrations in algae and invertebrates; PFS concentrations in amphibians, reptiles, and fish; PFS concentrations in waterfowl and seabirds; PFS concentrations in mammals; PFS concentrations in humans; BCFs, BFAs, BMFs, and TMFs for PFSs. This material is available free of charge via the Internet at http://pubs.acs.org.

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