Concern about fluorinated organic compounds (FOCs), particularly perfluorinated (fully fluorinated) compounds (PFCs), is growing (1). The compounds are globally distributed, environmentally persistent, bioaccumulative, and potentially harmful. Moreover, the toxicity of these chemicals has yet to be extensively investigated, and, compared with chlorinated and brominated organic compounds, the environmental distribution of FOCs is poorly understood.

Analytical methods exist for investigating some PFCs, but further development of methods is required to more fully assess their presence in environmental matrices. Little is known, for example, about PFC air transport, and methods are needed for monitoring these compounds in air samples to understand their movement into remote regions. In this article, we examine what is known about this new class of persistent pollutants.

FOC properties
Organofluorine molecules have unique physical, chemical, and biological properties, and the environmental paradigm developed from organochlorine compound research is not directly applicable to them. The high-energy carbon–fluorine bond renders FOCs resistant to hydrolysis, photolysis, microbial degradation, and metabolism by vertebrates, and makes them environmentally persistent.

The distinctive properties of organofluorine molecules, such as their stability, arise from fluorine’s properties. The most electronegative element, fluorine attracts electrons in a chemical bond toward itself, conferring polarity and strength (∼110 kcal/mol) to carbon–fluorine bonds. Moreover, the fluorine atom has three pairs of negatively charged electrons in its outer electronic shell that are not involved in bonding with other atoms. In highly fluorinated systems, such as PTFE (Teflon), these nonbonding electrons act as a sheath, yielding highly fluorinated systems with...
high thermal and chemical stability. Monofluoroacetic acid, for example, withstands boiling in 100% sulfuric acid without defluorinating (2). Compared with hydrocarbon-based surfactants, fluorinated surfactants have greater chemical stability to degradation by acids, oxidizing agents, and alkalis.

Some naturally occurring FOCs are produced by higher plants and certain microorganisms; for example, monofluoroacetic acid is produced by plants of the genus *Dichapetalum*, and certain fluorine-containing antibiotics are produced by fungi. The naturally produced FOCs contain one fluorine atom, whereas synthetic FOCs often contain many fluorine substituents and some are fully fluorinated.

All PFCs found in the environment are anthropogenic. Although partially fluorinated hydrocarbons can undergo chemical breakdown at functional group bonds, many of the anthropogenic FOCs, such as PFCs, are stable. The U.S. Interagency Testing Committee (ITC) (www.epa.gov/opptintr/itc) identifies 50 PFCs of interest because of their potential for persistence and long-range transport. Perfluorinated carboxylates and perfluorinated sulfonates make up two major PFC classes of current concern.

The phase-partitioning behavior of perfluoralkanes differs from that of chlorinated hydrocarbons. When mixed with hydrocarbons and water, some perfluoralkanes form three immiscible phases, indicating that perfluorinated chains are oleophobic and hydrophobic—chlorinated and brominated organics are hydrophobic and lipophilic.

When attached to a perfluorinated chain, a charged moiety, such as carboxylic acid, sulfonic acid, or a quarternary ammonium group, imparts hydrophilicity. Such functionalized fluorochemicals have surfactant properties, selectively adsorbing at interfaces because of the presence of both hydrophobic and hydrophilic moieties. These molecules have polar and nonpolar domains that lessen water surface tension more than hydrocarbon-based surfactants and are therefore more powerful wetting agents. The hydrophobic portion repels water, oil, and fat.

Some PFC water solubility and vapor pressure data (from unrefined products) are available, but inaccurate information on physicochemical properties still prevents reliable prediction of the environmental fate and transport of most PFCs. The fugacity approach, which has been used to describe the environmental fates of organochlorines, is less useful for describing the fate of PFCs because of their hydrophobic and lipophilic nature.

**Production and use**

Carboxylated and sulfonated fluorochemicals have been produced and used for more than 50 years. Perfluorooctanesulfonyl fluoride (POSF), shown in Figure 1, is the basic building block of the perfluoroalkyl sulfonates, which are used as surfactants and surface protectors in carpets, leather, paper, packaging, fabric, and upholstery. POSF and POSF-based polymers ultimately degrade to perfluorooctane sulfonate (PFOS).

The fluorinated surfactants are primarily manufactured using electrochemical fluorination and telomerization techniques (3). Electrochemical fluorination products are a mixture of isomers and homologues. The process is inexpensive and generates PFCs with homologous series of even- and odd-number perfluorocarbons. Commercialized POSF-derived products contain ~70% linear and ~30% branched POSF-derived impurities.

Total carboxylated and sulfonated PFC global production is unknown. 3M produced 6.5 million pounds in 2000, of which ~37% was used in surface treatment applications and ~42% was used on paper products (4). Some sulfonated and carboxylated PFCs have been used in or as aqueous film fire-fighting foams (AFFFs), mining and oil well surfactants, acid mist suppressants, alkaline cleaners, floor polishes, photographic film, denture cleaners, shampoos, and ant insecticide (5). In 1985, the U.S. market for AFFF products containing perfluorinated compounds was 6.8 million liters (5).

**Analysis issues**

The fluorine content of organic molecules can be determined by destructive and nondestructive methods, such as neutron activation and X-ray fluorescence—low-sensitivity techniques that do not enable identification or quantification of individual organofluorine compounds.

Fluorine in organic compounds can also be determined by combustion, converting it to an inorganic...
fluoride; however, rigorous conditions are required for quantitative mineralization. These techniques have been used for determining total fluorine in environmental and biological samples (6, 7). In environmental matrices, tests that measure methylene-blue-active substances have been used to detect anionic PFCs, but the approach is nonspecific (8).

Perfluorinated surfactants can be determined using derivatization techniques coupled with gas chromatography followed by electron capture detection (9) and mass spectrometric detection (5, 10). PFOS has low volatility, and its derivatives are unstable. Perfluorocarboxylic acid concentrations in biological samples have been measured using high-performance liquid chromatography (HPLC) and fluorescence detection (11)—method application is limited to environmental samples.

Nuclear magnetic resonance (19F NMR) can also determine perfluorinated surfactant concentrations in biological samples. These NMR techniques also have been used to measure FOCs in contaminated water samples (12). In the 1970s, FOCs in human blood were analyzed using nonquantitative NMR techniques (9). Preconcentration is generally required, but it concentrates both target compounds and potential interferences, necessitating rigorous cleanup procedures. Compound-specific methods for analyzing PFCs using HPLC-negative ion electrospray tandem mass spectrometry (HPLC/MS/MS) (14–16) enable surveys of the environmental distribution of FOCs in wildlife at global scales (14–16), but further method improvements are needed to accommodate the range of PFCs in biological and environmental matrices and for monitoring PFCs in atmospheric media.

Transport uncertainties
The major route by which PFOS is transported to remote locations is unknown. The compound almost completely ionizes and is less volatile in this form—its vapor pressure is similar to those of other globally distributed compounds, such as polychlorinated biphenyls (PCBs) and DDT, but its high water solubility makes it less likely to partition to and be transported in air (Table 1).

The vapor pressures of PFOS parent compounds, such as n-ethyl perfluorooctanesulfonamidooethanol (n-EtFOSEA; C8F17SO2N(CH2CH3)CH2CH2OH) and n-methyl perfluorooctanesulfonamidoethanol (n-MeFOSEA; C9F19SO2N(CH2)3CH2CH2OH), may exceed 0.5 Pa—1000-fold greater than that of PFOS. Moreover, the water solubility of n-EtFOSEA (<1 mg/L) is more than 100-fold lower than that of perfluorooctanoic acid (PFOS) (300 mg/L). Possibly, volatile precursors reach remote locations through the atmosphere or hydrosphere (water currents) and are subsequently metabolized to PFOS in animals.

At several military bases in the United States, including Tyndall Air Force Base in Florida and Wurtsmith Air Force Base in Michigan, there are fluorochemical-contaminated groundwater plumes associated with past fire-training sites, during which AFFF wastewater entered groundwater without prior treatment (6, 10). Groundwater perfluorocarboxylate concentrations of 125–7090 µg/L have been found at Tyndall, with perfluorooctanoic acid (PFOA) the predominant compound (10). At Wurtsmith, perfluorocarboxylate concentrations in groundwater are 3–110 µg/L. PFOA transport may be affected by pH and ionic strength because of its weak acid strength—the chemical has a pKw of 2.8 (5). A recent study reported PFOS, perfluorohexanesulfonate (PFHS), and PFOA at 0.011–2270 µg/L concentrations in surface water samples collected near an AFFF spill (12).

**PFOS in animals**
The global biospheric distribution, bioaccumulation, and biomagnification potential of several perfluoro-compounds have been studied (14–16). The studies indicate that PFOS is commonly found in the tissues of wildlife and that perfluorooctanesulfonamide (FOSA), PFOA, and PFHS are present in the tissues of several species. Although PFOS is a metabolic product of various sulfonated perfluorochemicals, FOSA, PFOA, and PFHS are perfluorinated compound production intermediates, and FOSA and PFOA are also used in various industrial applications.

In most samples, including those collected from remote marine regions, PFOS is detectable at concentrations >1 ng/g (14). Concentrations in the blood of ringed and grey seals taken from the Canadian and Norwegian Arctic are 3–50 ng/mL (15) and are 2- to 10-fold greater (14–230 ng/mL) in seals taken from more contaminated locations, such as the Baltic Sea (14). As in seals, the blood sera of Laysan and black-

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**Table 1**

**Calculated properties of PFOS, PCB-153, and DDT**

The vapor pressure of PFOS is similar to those of PCB-153 and DDT, but its water solubility is much higher, making it unlikely to partition from water to air.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Vapor pressure (Pa at 20 °C)</th>
<th>Water solubility (mg/L)</th>
<th>K_{aw}</th>
<th>MW</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFOS</td>
<td>3.31 × 10^{-4}</td>
<td>300–600</td>
<td>&lt;2 × 10^{-4}</td>
<td>500</td>
</tr>
<tr>
<td>DDT</td>
<td>2.6 × 10^{-4}</td>
<td>0.003</td>
<td>3 × 10^{-6}</td>
<td>354</td>
</tr>
<tr>
<td>PCB-153</td>
<td>2.5 × 10^{-4}</td>
<td>0.038</td>
<td>0.0046</td>
<td>360</td>
</tr>
</tbody>
</table>

*As reported by 3M to U.S. EPA in 1999.

1. K_{aw} = C_a / C_w, IC = air concentration, C_a = water concentration.

2. Tetra-CB.
footed albatrosses collected from remote oceanic locations, such as Midway Atoll in the North Pacific Ocean, contain 3–26 ng/mL of PFOS, and concentrations in the blood of cormorants and herring gulls taken from the North American Great Lakes are ~10-fold greater than those in albatrosses taken from Midway Atoll. Although the liver of yellow-fin tuna taken from the North Pacific does not contain detectable (<7 ng/g) PFOS concentrations, livers of blue-fin tuna taken from the Mediterranean Sea have been found to contain up to 87 ng/g PFOS. Livers of Alaskan polar bears contain 180–680 ng/g PFOS (wet wt). Concentrations in Weddell seals taken from the Antarctic are below the quantification limit (35 ng/g). Bioconcentration factors and Henry’s law constants for several PFCs have been compiled by the ITC (see Table 2) (17). Taken together, this information suggests that although PFOS is found in remote marine environments, including polar regions, concentrations in wildlife taken from these areas are several-fold less than those taken from more industrialized and urbanized areas, such as the Baltic Sea and the North American Great Lakes.

The blood plasma of bald eagles collected from the midwestern United States when they were less than 200 days old contained up to 2570 ng/mL PFOS (16), and detectable PFOS concentrations >100 ng/mL have been found in the liver of other fish-eating birds, such as common loons and brown pelicans. Similarly, PFOS is detectable at 10–1000 ng/g in liver tissues of birds collected from Canada, Italy, Japan, and Korea (Figure 2). PFOS concentrations in black-tailed gulls (2–12 ng/mL) taken from Hokkaido, Japan, are lower than those found in albatrosses collected on Midway Atoll. The occurrence of PFOS in these birds suggests that the fish they consume are the likely exposure source. Supporting this conclusion, tissues of fish from the Great Lakes and the Mediterranean Sea contain 10–500 ng/g PFOS concentrations, and up to 300 ng/g of PFOS is found in the muscle of carp collected from Saginaw Bay, Mich.

Among aquatic mammals, mink from the Midwestern United States contain the greatest PFOS concentrations in their livers (40–5140 ng/g, wet wt). Fish are part of their diet, and in one study, average PFOS concentrations in Saginaw Bay carp fed to mink were 120 ng/g (wet wt), suggesting a biomagnification factor of 22 in mink.

Age- and sex-related changes in PFOS concentrations have been examined in several marine mammal and bird species (15, 16). Generally, insignificant variations in the concentrations are found between sexes and among different age groups. This observation differs from variations observed for neutral, lipophilic contaminants, such as PCBs (18), but is similar to those of protein-binding compounds, such as tributyltin (19). PFOS is also found in bird and fish eggs, suggesting possible maternal transfer during yolk formation.

Concentrations in the eggs of brown trout and lake whitefish from Michigan waters of the Great Lakes are as great as 250 ng/g (wet wt), and exceed PFOS levels in their liver and muscle tissue. PFOS concentrations in whole eggs of Caspian terns from Michigan waters of the Great Lakes were as great as 3350 ng/g (wet wt). High PFOS liver and blood concentrations suggest possible enterohepatic reabsorption from the gut after biliary excretion.

**Occurrence in humans**

Organofluorine in human blood was first reported in 1968 (20) and has since been measured in human blood in the United States and other countries (21). Earlier, it was postulated that the source was PFOA or a structurally related compound. In another study of occupationally exposed individuals, different forms of FOCs were analyzed in plasma (22). In one study of workers handling ammonium PFOA, blood contained up to 71 µg/mL organic fluorine (23).

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**Table 2**

<table>
<thead>
<tr>
<th>CAS number</th>
<th>Chemical name</th>
<th>BCF</th>
<th>HLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>000325-77-3</td>
<td>Perfluorodecanesulfonic acid</td>
<td>10</td>
<td>3.03 × 10⁻¹</td>
</tr>
<tr>
<td>001763-23-1</td>
<td>Perfluoroctanesulfonic acid</td>
<td>56</td>
<td>1.1 × 10⁻²</td>
</tr>
<tr>
<td>002795-39-3</td>
<td>Potassium perfluoroctanesulfonate</td>
<td>56</td>
<td>1.1 × 10⁻²</td>
</tr>
<tr>
<td>003825-26-1</td>
<td>Ammonium perfluorooctanoate</td>
<td>56</td>
<td>9.10 × 10⁻²</td>
</tr>
<tr>
<td>003871-99-6</td>
<td>Potassium perfluorohexanesulfonate</td>
<td>3</td>
<td>3.97 × 10⁻⁴</td>
</tr>
<tr>
<td>007054-91-6</td>
<td>Perfluoroctanesulfonamide</td>
<td>10,000</td>
<td>1.84 × 10⁻³</td>
</tr>
<tr>
<td>004151-50-2</td>
<td>N-ethyl perfluoroctanesulfonamide</td>
<td>500</td>
<td>5.37</td>
</tr>
<tr>
<td>001681-99-2</td>
<td>N-ethyl perfluorooctanesulfonamido</td>
<td>5543</td>
<td>5.72 × 10⁻⁷</td>
</tr>
<tr>
<td>024448-09-7</td>
<td>N-methyl perfluoroctanesulfonamido</td>
<td>26,000</td>
<td>4.3 × 10⁻⁴</td>
</tr>
<tr>
<td>034449-89-3</td>
<td>N-ethyl butanesulfonamido ethanol</td>
<td>206</td>
<td>7.50 × 10⁻⁷</td>
</tr>
<tr>
<td>034455-03-3</td>
<td>N-ethyl hexanesulfonamido ethanol</td>
<td>6331</td>
<td>2.07 × 10⁻⁵</td>
</tr>
<tr>
<td>000375-72-4</td>
<td>Nonafluorobutanesulfonyl fluoride</td>
<td>5364</td>
<td>8.91 × 10⁻²</td>
</tr>
</tbody>
</table>

Source: U.S. EPA (17).

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Footnote:

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Compound-specific analysis of blood sera has only recently been performed on employees in the fluorochromatic manufacturing industry. PFOS and PFOA were found up to 12.8 and 114 µg/mL, respectively (24, 25). HPLC/MS/MS has detected PFOS, FOSA, PFOA, and PFHS in blood sera of the general population, with PFOS concentrations four- to five-fold greater than those of PFOA (13).

**Toxicity issues and concerns**

Perfluorocarboxylates, such as PFOA and perfluorodecanoic acid (PFDA), can cause peroxisome proliferation and affect mitochondrial, microsomal, and cytosolic enzymes and proteins involved in lipid metabolism (26–28). Perfluorocarboxylates reportedly exert other toxic effects, including accumulation of triglycerides in liver (29), uncoupling of mitochondrial oxidative phosphorylation, and reduction of thyroid hormone in circulation (30).

There are significant sex-related differences in the effects of PFOA, but this is not reported for other perfluorocarboxylates. Toxic effects of the latter vary depending upon carbon chain length (28), and some studies suggest that urinary excretion plays a crucial role in reducing perfluorocarboxylate toxicity (28). Repeated administration of PFOA induces peroxisomal β-oxidation, 1-acylglycerophosphocholine acyltransferase, acyl-coA hydrolase, stearoyl-coA desaturase, and carnitine acyltransferase activities in the livers of male rats; however, little induction is observed in female rats (28). This difference is explained by rapid elimination of PFOA in female rat urine relative to that of males. Sex-related differences in the pharmacokinetics of PFOA are not evident in mice, monkeys, and dogs (31).

In blood plasma, liver, and testes, PFOA and PFDA covalently bind to proteins—possibly to sulfydryl groups (32). Despite being strongly protein-bound, PFDA can cross the blood–brain barrier and has been found in the brain tissue of exposed rats (33). Moreover, the sex-related difference observed in rats depends on sex hormones (34). Exposure of sexually mature males to PFDA results in a significant decrease in plasma androgen, testosterone, and 5α-dihydrotestosterone concentrations (35), while serum concentrations of estradiol increase following PFOA exposure, possibly because of aromatase (CYP19) activity induction (36). Exposure of rats to PFDA results in testicular necrosis and calcification, as well as decreased steroidogenesis—steroid hormone synthesis in rats (35). PFDA exposure causes Leydig cell (the cells that produce androgens) tumors in rats and modifies Leydig cell steroidogenesis in vitro (37).

Exposure of rats and rabbits to PFOS and n-EtFOSA results in reduced body weight gain, feed consumption, litter size, and fetal weight at doses >5 mg/kg/d. On the basis of a developmental toxicology (teratology) study, the maternal No-Observed-Effect Level (NOEL) for n-EtFOSA and PFOS in rabbits is 0.1 mg/kg/d, and the developmental NOEL is suggested to be 1 mg/kg/d (38). N-ethyl perfluorooctanesulfonamide (Sulfluramid) and its metabolite FOSA uncouple oxidative phosphorylation (39).

Like perfluorocarboxylates, several other PFCs are expected to be peroxisome proliferators. Peroxisomes are single-membrane organelles present in nearly all eukaryotic cells. One of the most important peroxisome metabolic processes is β-oxidation of long-chain fatty acids. The peroxisome is also involved in synthesis of bile acids, cholesterol, and plasmalogen and metabolism of amino acids and purines. Some peroxisome proliferators induce hepatocellular carcinomas in rats and mice (40). Alternatively, these compounds act as tumor promoters by inhibiting gap-junctional intercellular communication (41). The observation that peroxisome proliferators increase the level of peroxisomal fatty acid β-oxidation (which produces \( \text{H}_2\text{O}_2 \)) to a greater degree than the cellular level of catalase dismutes \( \text{H}_2\text{O}_2 \) to \( \text{H}_2\text{O} \) and \( \text{O}_2 \) leads to a peroxide metabolism imbalance. Peroxisome proliferators also alter the hepatic activity of glutathione S-transferase and epoxide hydrolase, indicating that the proliferators widely affect hepatic detoxification systems. Such

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**FIGURE 2**

**PFOS in aquatic mammals and birds**

(a) PFOS in the plasma (light blue) and liver (dark blue) of aquatic mammals ranges over a few hundred parts per billion, with the highest concentrations found in the liver. (b) In birds, the concentration range is similar, again with the highest concentrations occurring in the liver (brown) and lower concentrations in plasma (yellow).

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a combination of changes can increase intracellular oxidative stress, which may be involved in transformation, promotion, and progression processes.

Although PFOA produces hepatomegaly, local hepatocyte necrosis, hypolipidemia, alteration of hepatic lipid metabolism, peroxisome proliferation, induction of the cytochrome P450 superfamily, and uncoupling of oxidative phosphorylation in laboratory-exposed animals, epidemiological studies with occupationally exposed humans indicate no significant clinical hepatotoxicity at reported PFOA concentrations (42).

PFOS causes moderate to acute toxicity by an oral exposure route with a rat LD₅₀ of 251 mg/kg bw (4). On the basis of oral toxicity studies, a NOEL and Low-Observed-Effect Level for second-generation offspring of 0.1 and 0.4 mg/kg bw/d, respectively, is suggested (5). Studies of the reproductive effects of PFOS in rats suggest a NOEL of 47 µg/g serum, or 72.5 µg/g liver (43). These values correspond to a dietary concentration of approximately 15 µg/g.

Additional toxicity information and toxicity reference values are needed for other PFCs and for more exposed species. Only in this way can comprehensive risk assessments of multiple species exposures to multiple PFCs be conducted. In particular, knowledge of the critical mechanisms of toxic effects is needed to select appropriate endpoints and biomarkers of functional exposure and to assess complex PFC mixtures and their relationship to one another and to other environmental residues.

References

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