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Critical Review

PFAS Exposure Pathways for Humans and Wildlife: A Synthesis of Current Knowledge and Key Gaps in Understanding

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Abstract: We synthesize current understanding of the magnitudes and methods for assessing human and wildlife exposures to poly- and perfluoroalkyl substances (PFAS). Most human exposure assessments have focused on 2 to 5 legacy PFAS, and wildlife assessments are typically limited to targeted PFAS (up to ~30 substances). However, shifts in chemical production are occurring rapidly, and targeted methods for detecting PFAS have not kept pace with these changes. Total fluorine measurements complemented by suspect screening using high-resolution mass spectrometry are thus emerging as essential tools for PFAS exposure assessment. Such methods enable researchers to better understand contributions from precursor compounds that degrade into terminal perfluoroalkyl acids. Available data suggest that diet is the major human exposure pathway for some PFAS, but there is large variability across populations and PFAS compounds. Additional data on total fluorine in exposure media and the fraction of unidentified organofluorine are needed. Drinking water has been established as the major exposure source in contaminated communities. As water supplies are remediated, for the general population, exposures from dust, personal care products, indoor environments, and other sources may be more important. A major challenge for exposure assessments is the lack of statistically representative population surveys. For wildlife, bioaccumulation processes differ substantially between PFAS and neutral lipophilic organic compounds, prompting a reevaluation of traditional bioaccumulation metrics. There is evidence that both phospholipids and proteins are important for the tissue partitioning and accumulation of PFAS. New mechanistic models for PFAS bioaccumulation are being developed that will assist in wildlife risk evaluations. *Environ Toxicol Chem* 2021;40:631–657. © 2020 SETAC

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INTRODUCTION

Poly- and perfluoroalkyl substances (PFAS) are a class of thousands of anthropogenic substances containing an aliphatic fluorinated carbon chain (Buck et al. 2011; Organisation for Economic Co-operation and Development 2018). The PFAS family includes: 1) perfluoroalkyl substances, mainly perfluoroalkyl acids (PFAA) such as perfluoroalkyl carboxylates (PFCA) and perfluoroalkyl sulfonates (PFSA), as well as perfluoroalkane sulfonamide substances; and 2) polyfluoroalkyl substances such as fluorotelomer monomers, including fluorotelomer alcohols (FTOH), fluorotelomer olefins, and fluorotelomer iodides, and polyfluoroalkyl ether acids. Both perfluoroalkyl substances and polyfluoroalkyl substances can be polymers or nonpolymers. The extraordinary strength of the C–F bond in the perfluoroalkyl moiety imparts unique

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properties (Smart 2001; Biffinger et al. 2004) and has led to widespread industrial and commercial uses of PFAS. With over 7800 PFAS chemical structures identified to date (US Environmental Protection Agency 2020a) and thousands registered for regulatory purposes (e.g., chemical inventories; Organisation for Economic Co-operation and Development 2018), they play a prominent role in modern society.

These substances present a societal challenge. On the one hand, PFAS represent some of the most innovative developments in materials chemistry and provide innumerable societal benefits (Johns and Stead 2000). However, following decades of widespread global use and because many PFAS are highly persistent and mobile, concerns have been raised about the ecological and human health impacts of PFAS exposures. Categories of PFAS use include personal care products (PCPs), cosmetics, ski wax, aqueous film-forming foams (AFFF), textile treatments for stain and water repellency, food contact material, medical devices, membranes in fuel cells, and membranes in chloralkali processes. This list of PFAS applications, though not encompassing of the full scale of PFAS use, captures their diversity. Prior work established the concept of "essential uses" of PFAS by first reviewing where they are abundantly used and when such uses can be replaced by safer alternatives (Cousins et al. 2019).

Multiple strategies have been implemented to reduce emissions, production, and use of specific PFAS. Manufacturers have phased out production of certain PFAS and in some cases replaced them with new PFAS or chemical substitutes. For example, in textile treatments, many polymers containing long perfluoroalkyl side chains (more than 7 perfluorinated carbons) were replaced by analogues containing short perfluoroalkyl side chains (6 or 4 perfluorinated carbons) or fluorine-free moieties (e.g., siloxanes and hydrocarbon polymers; Schellenberger et al. 2019a). Further efforts are underway to constrain leachable content in fluoropolymers and side chain–fluorinated polymers. This leachable content consists of unbound monomers (such as FTOHs), oligomers, and other nonpolymeric PFAS used during the polymer manufacturing process (such as surfactants and chain transfer reagents). Governments have implemented plans to restrict the usage, manufacture, and import of certain PFAS, typically on a chemical-by-chemical basis and with certain exemptions. However, based on the recalcitrance of PFAS terminal products, their ubiquitous presence, and continued usage, PFAS exposure to humans and wildlife continues (Scheringer et al. 2014).

The volume of research publications over the past decade identifying PFAS in environmental media, humans, and wildlife is staggering, with several comprehensive review publications (Houde et al. 2011; Jian et al. 2018; Sunderland et al. 2019; Wang et al. 2019). However, our ability to quantify how production and environmental releases of PFAS translate into PFAS tissue burdens in humans and wildlife is still limited. The science of PFAS exposure was a key area explored in the Society of Environmental Toxicology Chemistry's (SETAC's) Focused Topic Meeting on Environmental Risk Assessment of PFAS held in Durham, North Carolina, USA, 12 to 15 August 2019.

In the present review, we synthesize current understanding of PFAS exposure sources for humans and wildlife and identify key knowledge gaps that inhibit the development of informed regulatory decisions based on sound science. Specifically, we review: 1) PFAS sources and environmental transport pathways, 2) analytical methods used to assess PFAS exposures and their strengths and limitations, 3) methods for assessing human exposures to PFAS, 4) current understanding of the relative importance of different human exposure pathways, and 5) current understanding of PFAS bioaccumulation in wildlife.

OVERVIEW OF PFAS SOURCES AND ENVIRONMENTAL PATHWAYS

Figure 1 provides a schematic of the sources and spatial scales of PFAS transport and accumulation. Releases to the environment occur during the production, use, and disposal of materials containing PFAS. For example, legacy emissions of perfluorooctanoic acid (PFOA) were dominated by its manufacture and use to manufacture fluoropolymer products (Prevedouros et al. 2006), whereas emissions of perfluorooctane sulfonic acid (PFOS) were dominated by its release during use of consumer and industrial products (e.g., surface treatments, AFFF, insecticides; Paul et al. 2009; Armitage et al. 2009b; Wang et al. 2017).

Existing chemical production and release inventories for PFAS have largely focused on PFCA, PFSA, and their precursor compounds (e.g., FTOH and perfluorooctane-sulfonamides and -sulfonamidoethanols [FASA]; Armitage et al. 2006, 2009a, 2009b; Prevedouros et al. 2006; Yarwood et al. 2007; Paul et al. 2009; Wang et al. 2014a, 2014b, 2017; Kotthoff et al. 2015; Shi et al. 2015; Boucher et al. 2019). A major shift in chemical production occurred between 2000 and 2002 with the voluntary phaseout of the base chemical perfluorooctane sulfonyl fluoride to PFOS and perfluorooctane sulfonamide (FOSA)–based chemistry by 3M, the major global manufacturer at the time (3M Company 1999). Stewardship programs for PFOA in the United States and Europe have similarly been very successful at phasing out releases of this compound. We now know that PFOS, PFOA, and other long-chain legacy PFAS compounds represent only a small proportion of the total number of PFAS (US Environmental Protection Agency 2020a). Understanding of the global environmental production and distribution of the legacy PFAS has been greatly facilitated by academic partnerships with industry that allowed the development of global emissions inventories for some compounds (Prevedouros et al. 2006; Paul et al. 2009; Armitage et al. 2009a, 2009b; Wang et al. 2014a, 2017). We thus recommend greater transparency and collaboration between academia, industry, and government to prioritize and improve our understanding of global environmental releases of the thousands of PFAS structures on the US Environmental Protection Agency's master list (2020a).

The effects of the phaseout in chemical production of PFOS and its precursors as well as the PFOA stewardship program are well documented and illustrate the potential benefits of

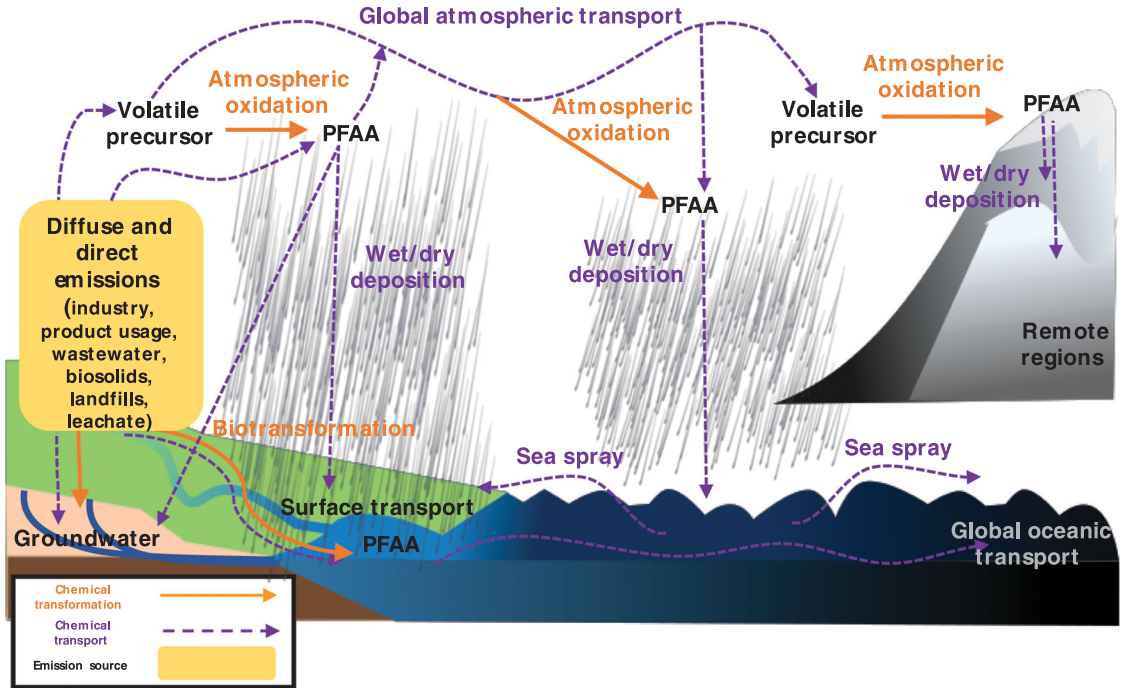

FIGURE 1: Conceptual representation of key emission sources and global transport pathways of perfluoroalkyl acids and their polyfluorinated precursors. PFAA = perfluoroalkyl acid.

coordinated action to curb chemical releases. For example, ocean modeling studies forced by changes in riverine discharges to the North Atlantic show a large decline in surface (0–10 m depth) seawater PFOS concentrations at their peak (median >60 pg L^{-1}) in approximately the year 2000 to <40 pg/L in 2020 (Zhang et al. 2017). In juvenile North Atlantic pilot whales, FOSA (a precursor to PFOS) accounted for 84% of the 15 targeted PFAS measured in the year 2000 but declined to 34% by 2013 (Dassuncao et al. 2017). Human cohort studies in Denmark, Australia, Japan, Germany, and the Faroe Islands all indicate large declines in PFAS exposure for the general population outside of contaminated areas over this same time period (Olsen et al. 2012; Okada et al. 2013; Yeung et al. 2013a; Toms et al. 2014; Bjerregaard-Olesen et al. 2016; Dassuncao et al. 2018).

Sources of local-scale contamination include fluorochemical manufacturing facilities, other manufacturing facilities where PFAS are used, PFAS-containing AFFF, wastewater-treatment plants, and landfills. High environmental concentrations of PFAS result in exposure through consumption of contaminated drinking water, agricultural products, or fish and game. For more diffuse PFAS exposures driven predominantly by use of consumer products, population has been established as a good proxy for contamination of surface waters and coastal ecosystems (Paul et al. 2012; Xie et al. 2013; Li et al. 2015; Zhang et al. 2017).

Environmental concentrations and human and wildlife exposures to PFAS are typically highest at contaminated sites (Paustenbach et al. 2007; Pistocchi and Loos 2009; Hoffman et al. 2011; Shin et al. 2011a; Shi et al. 2015). Fluorochemical manufacturing sites are responsible for a large proportion of global emissions of certain types of PFAS such as PFCA, but there are relatively few of these sites. One study reported the presence of 16 fluorochemical manufacturing plants in the United States (Hu et al. 2016), and another estimated that there were 33 fluoropolymer production plants worldwide as of 2002 (Prevedouros et al. 2006). High-volume emissions from such facilities can impact large geographic areas and correspondingly large populations. For example, releases into the Ohio River from a fluoropolymer production plant in the United States' state of West Virginia resulted in elevated levels of PFAS in drinking water in communities hundreds of miles downstream (Herrick et al. 2017).

Use of AFFF containing PFAS for fire suppression or training activities at military bases, commercial airports, and fire-training areas around the globe has contaminated many aquatic environments (Moody and Field 1999; Barzen-Hanson et al. 2017). Landscapes and water systems adjacent to areas of AFFF use often have high levels of PFAS in soil, sediment, groundwater, surface water, or drinking water (Karrman et al. 2011; Houtz et al. 2013; Anderson et al. 2016; US Department of Defense 2017). Concentrations of PFAS measured in different environmental media at 10 active US Air Force installations were highest for PFOS and included 4300 μg/L in groundwater, 8970 μg/L in surface water, 190 000 μg/kg in sediments, 9700 μg/kg in surface soil, and 1700 μg/kg in subsurface soil (Anderson et al. 2016).

Incidents of localized contamination have been linked to facilities that employ PFAS to produce goods such as plastic and textile coating (Vermont Department of Environmental Conservation 2016; New Hampshire Department of Environmental Services 2020; New York Department of Environmental

Conservation 2020) and leather tanneries (US Environmental Protection Agency 2020b). Numerous other industries are users of PFAS, and all of these have the potential to cause localized contamination. For example, major sources of PFAS contamination in surface waters in New York State and Rhode Island, USA, included mixed industrial sources that predominantly release PFOS and PFOA, metal plating industry sites, and landfills (Zhang et al. 2016). Such substances enter landfills as components of residual materials, can be released to the environment in leachate, and may contribute to elevated concentrations in wastewater (Huset et al. 2011; Lang et al. 2017; Masoner et al. 2020). Concentrations of PFAS in municipal solid waste vary substantially depending on the waste source (Solo-Gabriele et al. 2020).

Wastewater-treatment facilities receive PFAS in influent and discharge PFAS in treated effluent and biosolids (Sinclair and Kannan 2006; Coggan et al. 2019). Treated effluent can be a source of PFAS exposure if it is discharged to a water body that is used as a drinking water source. For example, the probability of detecting PFAS in United States public drinking supplies was significantly associated with higher numbers of wastewater-treatment plants within a watershed (Hu et al. 2016). Land application of biosolids or irrigation using reclaimed water can result in accumulation of PFAS in soils and underlying groundwater and uptake into food or fodder crops (Choi et al. 2019; Coggan et al. 2019; Lazcano et al. 2019; Letcher et al. 2020). Concentrations of PFAS are highest in effluent and biosolids for treatment plants that receive wastewater from industrial plants that use PFAS or facilities that use AFFF (3M 2001; Houtz et al. 2016).

Following decades of releases (ca. 1958 to present), PFAS are now ubiquitous in the global environment; and the ocean is thought to be the final sink for the terminal products (PFAA) associated with most global production (Armitage et al. 2009a, 2009b; Zhang et al. 2017). The spatial distributions of PFAS in the environment following releases reflect their physical–chemical properties (propensity for sorption vs transport in air and water) and types of releases (air, water, soil) during manufacturing, use, and disposal. The relative importance of the atmospheric transport/precursor degradation pathway versus the oceanic transport/terminal end product pathway has been assessed for some PFAA. Generally, aquatic discharges and oceanic transport are more relevant next to source regions in the United States, Europe, and Japan (Prevedouros et al. 2006; Armitage et al. 2009a; Zhang et al. 2017), whereas atmospheric transport is important in remote regions such as the Arctic and Southern Ocean for many compounds (Wang et al. 2015; Dassuncao et al. 2017; MacInnis et al. 2017; Yeung et al. 2017; Pickard et al. 2018). Accumulation of PFAS in the oceans reflects both contemporary and historic PFAS production because terminal PFAA are not known to appreciably degrade under environmental conditions, and the timescales associated with PFAS removal through burial in coastal and deep-sea sediment are long (Yamashita et al. 2008).

A major focus of PFAS research is better understanding the releases and environmental degradation pathways of precursor compounds that degrade into terminal PFAA. The majority of precursor compounds studied to date are neutral organics with appreciable vapor pressures. This means that they have a greater propensity for atmospheric transport, whereas most PFAA have low pK_a values and exist as stable ions in solution (Cheng et al. 2009). Significant effort is being dedicated to better understanding point source releases of atmospheric PFAS (both PFAA and precursor compounds), but stack testing methods and inventories are still limited. Ionizable precursors also exist, but data are scarce. Surface deposition of atmospheric PFAA emissions followed by leaching of PFAS to groundwater has been demonstrated at multiple industrial sites (Guelfo et al. 2018; New Hampshire Department of Environmental Services 2020; New York Department of Environmental Conservation 2020). Integration of PFAS measurements into routine atmospheric monitoring for pollutants by programs like the North American Deposition Program would thus be valuable for measuring changes in atmospheric PFAS concentrations, assisting atmospheric PFAS modeling efforts (Thackray et al. 2020), and identifying regions vulnerable to atmospheric PFAS contamination.

ANALYTICAL TECHNIQUES FOR MEASURING PFAS EXPOSURES

The ability of scientists and regulators to identify and rank the importance of different PFAS exposure sources is directly contingent on analytical methods available for measuring PFAS in a variety of environmental matrices and biological tissues. Analytical techniques for PFAS have advanced rapidly from an early focus on PFOA and PFOS to routine measurements of a suite of approximately 40 PFAS with commercially available analytical standards for detection using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Recent methods have been evolving for detecting volatile species, new compounds, and total fluorine in environmental and human samples. These advances have been critical for keeping pace with the rapidly changing chemical landscape of PFAS exposure sources.

Targeted PFAS analysis

Most studies report concentrations of nonvolatile PFAS measured using LC-MS/MS. This is commonly referred to as "targeted" analysis because it is based on setting up the instrumental analysis to collect data on specific substances, while confirmation of these substances relies on specific mass-to-charge (*m/z*) ratios and retention times based on parameters determined using commercially available chemical standards. This approach enables quantitative PFAS determination with high precision and high sensitivity. Targeted PFAS analysis is used for water (drinking water, surface water, groundwater), air/airborne particulates, food, solids (soil, sediment, house dust), and consumer products. The same techniques are also used to determine PFAS in diverse biological tissues including plasma, sera, whole blood, urine, breast milk, muscle, and other tissues. Over the past few decades, targeted PFAS measurement has improved substantially, with improved

instrument sensitivity and lower detection limits, numerous laboratory intercomparisons, standard operating procedures, and the addition of more PFAS that can be detected (Mills et al., 2019). A major analytical challenge is that synthesis of analytical standards for newer PFAS has lagged behind their production and release and a lack of reference materials for the major PFAS in routine analysis (Xiao 2017; Land et al. 2018).

Suspect screening and nontargeted analysis

Although targeted analysis is limited to a finite number of PFAS analytes, a comprehensive understanding of PFAS exposure calls for innovative techniques, specifically techniques that reveal the presence of emerging PFAS produced intentionally and unintentionally in various industrial processes as well as PFAS transformation products formed in natural and engineered systems. Suspect screening and nontargeted analysis using high-resolution mass spectrometry (HRMS) allow discovery and characterization of unidentified PFAS in the environment. High-resolution mass spectrometry provides highly accurate mass to charge ratios of the analytes (<±0.001 *m/z*), its fragments, and their isotopic patterns. Comparing such information with chemical databases that contain thousands of PFAS compounds enables identification of the molecular structure of analytes without analytical standards. Suspect screening and nontargeted analyses have led to the identification of emerging anionic, zwitterionic, cationic, and neutral PFAS in water (Strynar et al. 2015; Barzen-Hanson et al. 2017; Gebbink et al. 2017; Newton et al. 2017), sediment (Newton et al. 2017), soil (Baduel et al. 2017; Lin et al. 2017), airborne particulate matter (Yu et al. 2018), and biological samples (Rotander et al. 2015; Liu et al. 2018).

A drawback of HRMS methods is that such analyses are typically qualitative because of the absence of analytical standards. In addition, the PFAS congener can only be determined if the sample preparation has adequately recovered the analyte. Analyte spike and recovery validation is not possible without analytical standards. In addition, HRMS data analysis is labor-intensive and requires specialized analysts. However, it is increasingly recognized for its data-banking value, in which archived HRMS spectra for routine analyses can be reanalyzed when emerging analytes become a priority.

New methods for closing the fluorine mass balance in exposure studies

A major challenge in PFAS exposure assessment is that most studies employ targeted LC-MS/MS analyses and thus cannot assess the total burden of PFAS in environmental and biological samples. Even HRMS studies are limited by the sample preparation technique, which can be discriminatory toward certain classes of PFAS. Also, because HRMS analyses are qualitative or semiquantitative in nature, they cannot be used to develop mass budgets for total PFAS in the environment or the total burden of PFAS exposures. This has led to the development and use of several total fluorine measurements to better characterize the total burden of known and unknown PFAS in a sample.

Total fluorine methods rely on determinations of the concentration of atomic fluorine. Several strategies have been developed for the determination of the total organofluorine (TOF), extractable organofluorine (EOF), or adsorbable organofluorine (AOF) content to assess the total PFAS content, as reviewed in prior work (Koch et al. 2020). Known PFAS are typically determined using targeted LC-MS/MS techniques on the same sample extracts analyzed for EOF or AOF analyzed using combustion ion chromatography (CIC). The presence of organofluorine is indicative of anthropogenic substances because organofluorines are very rare in nature as a consequence of the high energy bond between carbon and fluorine. By contrast, inorganic fluoride is the most abundant halogen on Earth and must be quantified to assess the organofluorine content. The portion of unidentified organofluorine in a sample is calculated by subtracting the concentration of target PFAS, converted to moles of fluorine, from the total organofluorine content in the same extract (Figure 2). Because the quantity of unidentified organofluorine is dependent on the targeted analysis, it is challenging to compare unidentified organofluorine among different studies. In Figure 2B, the unidentified organofluorine is shown relative to the targeted analysis of 50 PFAS congeners in human blood. In general, studies on TOF and EOF/AOF indicate that a significant portion of organofluorine in biota and the environment is not captured by monitoring of the typical suite of PFAA congeners.

Different methods have been developed for total fluorine or organofluorine measurements in environmental samples and consumer products, including defluorination with sodium biphenyl (Musijowski et al. 2007), ^{19}F nuclear magnetic resonance (NMR; Moody and Field 2000), continuum source molecular absorption spectrometry (CS-MAS; Qin et al. 2012), inductively coupled plasma tandem mass spectrometry (ICP-MS/MS; Jamari et al. 2018), instrumental neutron activation analysis (INAA; Schultes et al. 2019), particle-induced gamma-ray emission spectrometry (PIGE; Ritter et al. 2017), CIC (Miyake et al. 2007a), and X-ray photoelectron spectroscopy (XPS; Tokranov et al. 2019). Although some methods can distinguish between organofluorine and inorganic fluoride (NMR, XPS), others give the total concentration of fluorine in a sample (for example, PIGE and CIC); therefore, a preextraction of inorganic fluorine is needed.

Assessing PFAS in consumer products presents an important challenge for fully understanding human exposure. Some studies have measured the fluorine concentration at the material surface or subsurface (PIGE, XPS, and INAA), whereas others consider the average concentrations throughout the sample analyzed (CIC). The unknown organofluorine content is useful for understanding total fluorine analysis in human tissues. Concentrations of organofluorine in human serum have been measured using the CIC method, both total fluorine before extraction (Miyake et al. 2007b) and EOF after extraction (Yeung and Mabury 2016). As an example of this application, one study targeted 52 PFAS congeners in human blood from Münster, Germany, including PFSA, PFCA, FASA, fluorotelomer acids

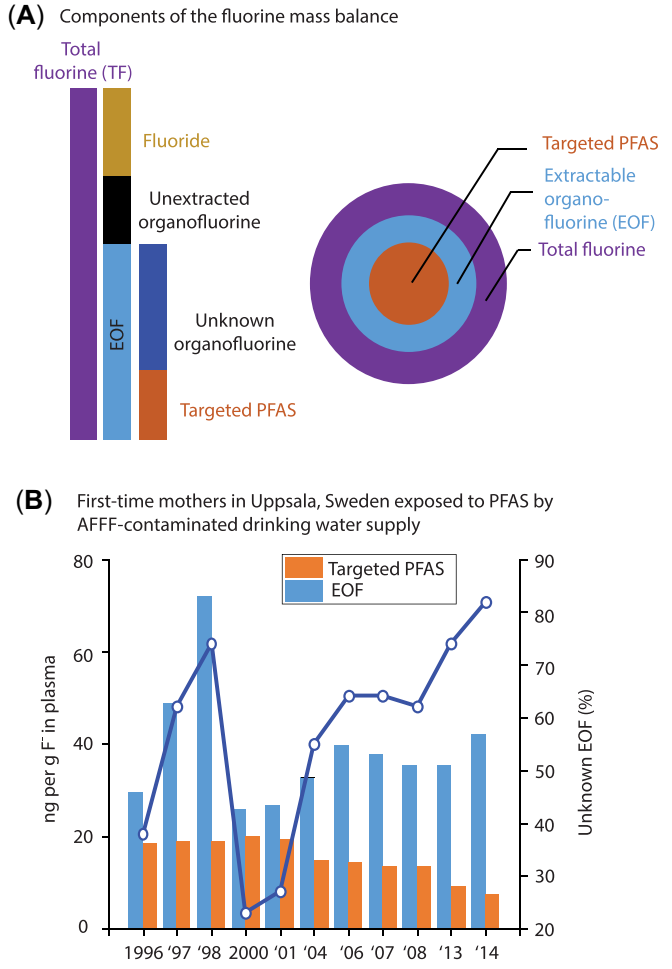

FIGURE 2: Components of the fluorine mass balance. (**A**) A conceptual diagram representing the relative fractions of total fluorine including fluoride, unextracted organofluorine, extractable organofluorine (EOF), and targeted poly- and perfluoroalkyl substances (PFAS). (**B**) Actual data where unknown EOF was determined using targeted analysis of 50 PFAS congeners in blood plasma of first-time mothers from Uppsala, Sweden (data from Miaz et al. 2020). AFFF = aqueous film-forming foam; TF = total fluorine.

(fluorotelomer unsaturated carboxylic acid and fluorotelomer carboxylic acid), and polyfluorinated phosphate esters (Yeung and Mabury 2016). Through total fluorine and EOF analysis, these PFAS accounted for approximately 80% of EOF from 1982 to 2006, and the unknown EOF increased to 50% from 2007 to 2009, further emphasizing that humans are being increasingly exposed to new organofluorine substances. Caution must be applied in ascribing the unknown EOF to PFAS because many pharmaceuticals contain fluorine. It may be possible to adapt methods to avoid coextraction of non-PFAS organofluorine. For example, a recent study (Figure 2B) used acetonitrile extraction followed by a dispersive graphitized carbon cleanup for human plasma (Miaz et al. 2020), which is likely to sorb the fluorine in pharmaceuticals that is typically in the form of a –F or $–CF_3$ moiety on an aromatic ring.

The total oxidizable precursor (TOP) assay provides another method for estimating unknown precursors. The method has been mainly applied to aqueous samples which are subjected to oxidation via hydroxyl radicals formed in a persulfate thermolysis, to transform PFAA precursors to their terminal products (Houtz et al. 2013, 2016). The oxidized extracts and unoxidized extracts are analyzed by LC-MS/MS for PFAS to quantify the concentrations of oxidizable precursors. The TOP assay highlights the relevance of PFAA precursors to PFAA concentrations in the environment. For example, one study determined that precursors in AFFF had significantly contributed to PFCA and PFSA in groundwater from a firefighting training area (Houtz et al. 2013).

Strengths and limitations of analytical techniques for assessing exposures

Table 1 compares the strengths and limitations of different analytical methods used to assess PFAS exposures. Comprehensive human exposure assessments need to consider a wider range of PFAS than available from targeted LC-MS/MS measurements, including precursors that transform to terminal PFAAs. Nontargeted screening for a variety of matrices and the TOP assay in aqueous samples have been proven useful for detecting additional PFAS. The utility of nontargeted analysis depends on identification strategies and available suspect lists. The TOP assay provides quantitative data on the contribution of oxidizable precursors and can provide some insight on the precursor structure (e.g., functional group and chain lengths). However, the TOP assay has only reliably been performed on aqueous samples because of matrix interference in soil and biota. Further, it is not able to oxidize certain emerging PFAS like per- and polyfluoroalkyl ether acids (PFEAs) such as 6:2 chlorinated perfluoroalkyl ether sulfonic acid and hexafluoropropylene oxide dimer acid (GenX). Nonspecific total fluorine methods add information on the magnitude of unknown PFAS that are not quantifiable using targeted analysis. However, some of the detected total fluorine or organofluorine may include compounds outside of those PFAS according to the current definition of the Organisation for Economic Co-operation and Development (OECD).

Pharmaceuticals and pesticides with a low atomic fraction of fluorine could result in moderate or high organofluorine content in water if present in high concentrations. Other PFAS classes could be excluded from the analysis during conventional sample extraction. For example, the nonpolar PFAS like perfluorobutyl side chain–fluorinated copolymer surfactant with molecular weight >1600 g/mol was only extracted from soil, wastewater sludge, and sediment using 1:1 hexane/acetone, whereas much lower recoveries were obtained using methanol or acetonitrile (Chu and Letcher 2017; Letcher et al. 2020). The removal of inorganic fluoride also needs to be validated, especially for natural waters and drinking water, where fluoride concentrations can be orders of magnitude higher than PFAS concentrations. Nonspecific total fluorine methods that target atomic fluorine thus risk overestimating the PFAS content of samples but nonetheless provide a useful screening metric for

TABLE 1: Comparison of analytical techniques for assessing poly- and perfluoroalkyl substance exposure[a]

Methods	Applicable matrices	Advantages	Limitations
Targeted analysis	All matrices	• Sensitive (0.1–1 ng/L) • High selectivity to the analysis targets	• Limited inclusivity • Variable recoveries • Potential bias from sample extraction
Nontargeted analysis[b]	All matrices	• High inclusivity • Elucidate unknown structures	• Not quantitative • Potential bias from sample extraction • Need expensive instruments and highly skilled users
TOP	Mainly aqueous samples	• Sensitive (0.1–1 ng/L) • High selectivity to PFAS	• Limited inclusivity • Variable recoveries
EOF (CIC)	All matrices	• High selectivity to organofluorine	• Less sensitive (0.1–0.5 ppm F) than targeted analyses • Potential bias from sample extraction
AOF (CIC)	Water	• High selectivity to organofluorine	• Not as sensitive (0.1–0.5 ppm F)
PIGE	Solids	• High-throughput • Nondestructive • No matrix effects • Surface measurement (100–250 μm)	• Not as sensitive (50 nmol F/cm^2) • Interference by fluoride
XPS	Solids	• High-throughput • Widely available instrumentation • Identification of perfluoroalkyl moiety • Etching of surface possible to create depth profiles • Surface measurement (~10 nm)	• High detection limits (~1% F) • Small area measurement • Can be affected by surface roughness and inhomogeneity

[a]A more comprehensive discussion of the strengths and limitations of different analytical techniques is reviewed elsewhere (Mills et al., 2019).
[b]For a more detailed discussion of the strengths and limitations of nontargeted analysis, please see the following viewpoints and response (Hites and Jobst 2018, 2019; Samanipour et al. 2019).
AOF = adsorbable organofluorine; CIC = combustion ion chromatography; EOF = extractable organofluorine; PFAS = poly- and perfluoroalkyl substances; PIGE = particle-induced gamma-ray emission spectrometry; TOP = total oxidizable precursor assay; XPS = X-ray photoelectron spectroscopy.

identifying the magnitude of unidentified organofluorine in an environmental sample.

METHODS FOR ASSESSING HUMAN EXPOSURE TO PFAS

Exposure pathways for PFAS can be examined as a chain of events, shown in Figure 3, linking sources to media (via fate and transport) to external exposure (via behavioral factors) to concentrations in blood, the body's central compartment (via toxicokinetics). Exposure routes that are typically examined for PFAS include dietary ingestion, water ingestion (particularly in contaminated communities), and inhalation of air and dust particles. Hand-to-mouth contact and dermal absorption can also be relevant pathways.

Approaches for PFAS exposure assessment

Exposures are typically estimated using 2 complementary approaches. The exposure factor ("bottom-up") approach relies on measured concentrations of certain PFAS in exposure media (e.g., food, water, air, dust) and uses estimates of exposure frequency and duration to estimate external exposure (mass per kilogram of body wt). Levels of PFAS in media (dietary items, drinking water, and the indoor environment) can also be estimated using multimedia modeling assessments of global or local sources, transport, and accumulation. An alternate method is the epidemiologic ("top-down") approach to exposure assessment, which typically involves regressing serum/blood levels against measured concentrations in different media (e.g., water, air, dust) and/or behavioral data (e.g., food consumption) to estimate the strength of association with one or more sources. With sufficient data regarding multiple pathways, either method can estimate the relative importance of different exposure routes.

Several studies have used the exposure factor approach to quantify the contribution of PFAS in the indoor environment,

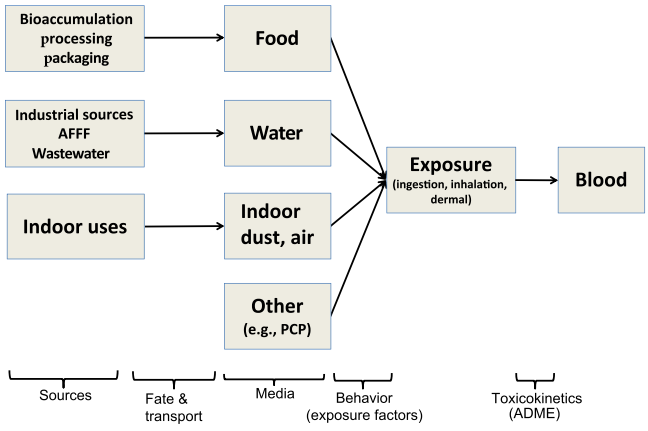

FIGURE 3: Schematic of exposure assessment steps for humans that relates poly- and perfluoroalkyl substance (PFAS) sources to exposure media and internal concentrations of PFAS in blood. Not all possible exposure routes (e.g., outdoor air) or arrows are shown. ADME = absorption, distribution, metabolism and excretion. AFFF = aqueous film-forming foam; PCP = personal care product.

seafood, drinking water, and food packaging to total exposures in humans (Trudel et al. 2008; Vestergren et al. 2008; Harrad et al. 2010; Gebbink et al. 2015; Dassuncao et al. 2018). Exposure to precursors has been linked to increased bioaccumulation in food webs (Kelly et al. 2009; Dassuncao et al. 2017; Boisvert et al. 2019; Zhang 2019). Associations between serum PFAS concentrations and exposure behaviors such as water district of residence, consumption of tap water, and fish consumption have also been characterized in prior work (Christensen et al. 2017; Herrick et al. 2017; Dassuncao et al. 2018; Barton et al. 2020).

The 2 exposure assessment methods each have strengths and weaknesses and are complementary. In the exposure factor approach, one or both elements may be uncertain. For example, whereas measuring PFAS in food can be analytically challenging with many nondetects, average food consumption rates are better known. In contrast, measuring PFAS in house dust is easier, but dust ingestion rates are uncertain, particularly for adults. Carrying out statistically representative (and therefore extrapolatable) sampling and characterizing the fraction of exposure originating from precursors are challenging for many exposure routes. One strength of the exposure factor approach is the potential for a direct link to chemical production and environmental concentrations that drive exposures (Armitage et al. 2009a). This information is critical for designing interventions that mitigate human and wildlife exposures.

The epidemiologic approach integrates both exposure and toxicokinetics but often must take into account potential confounding between exposure routes as well as exposure measurement error. For example, the latter can arise when regressing serum concentrations of persistent PFAS with media measured at one point in time. The long half-life of many PFAS in humans means that serum concentrations reflect cumulative exposures over a relatively long time period, whereas external exposure measurements often reflect a short exposure window. Hybrid models can be used to integrate and compare the 2 approaches. For example, one can use toxicokinetic models to estimate serum levels from exposure estimates (or vice versa), comparing the estimated and measured serum levels to determine how much of the total exposure has been captured (Trudel et al. 2008; Thompson et al. 2010; Haug et al. 2011; Lorber and Egeghy 2011; Dassuncao et al. 2018; Hu 2019).

Toxicokinetic models

Simplified one-compartment toxicokinetic models include 3 main parameters for each PFAS considered: absorption efficiency, elimination half-life, and volume of distribution (Trudel et al. 2008; Thompson et al. 2010; Lorber and Egeghy 2011; Hu et al. 2019). Limited data from human studies are available to characterize the absorption efficiency and the volume of distribution in toxicokinetic models. Instead, these have been estimated by extrapolating animal data, which can be problematic. Reliable PFAS elimination half-lives needed for one-compartment toxicokinetic modeling still only exist for 4 PFAS: PFOS, PFOA, perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS). Median elimination half-lives for these 4 PFAS range between 2.1 and 8.5 yr (Hu et al. 2019).

Many exposure assessments rely on relatively simple one-compartment toxicokinetic models to convert external doses to internal concentrations or the reverse. This is often done by assuming steady state. For individuals with changing metabolism and elimination processes for PFAS such as infants, children, and pregnant or lactating women, the steady-state assumption may be invalid depending on the half-life of a given PFAS and recent shifts in exposure. For example, time-dependent exposure assessments are needed for individuals who live in proximity to contaminated sites where exposure concentrations have changed because of either releases or site cleanup (Shin et al. 2011a; Verner et al. 2016; Balk et al. 2019). Given the long human half-lives of PFAS, constant exposures over years to decades (3–4 half-lives) are needed to reach approximate steady state.

One-compartment toxicokinetic models can provide reasonable estimates of serum concentrations. Additional modeling is needed to estimate tissue-specific PFAS concentrations (e.g., brain, liver, kidney) that may be relevant for interpreting different health outcomes associated with exposures. Empirical toxicokinetic data needed to describe PFAS partitioning among tissues, dermal absorption, facilitated transport, and elimination half-lives are still limited or nonexistent for many PFAS and represent an important research need. As the focus of PFAS research shifts toward issues associated with emerging compounds, additional data for parameterizing toxicokinetic models represent a critical research need.

Biomonitoring

Concentrations of PFAS have been measured in plasma, serum, and whole blood (Olsen et al. 2003a, 2003b, 2005; Kannan et al. 2004; Kärrman et al. 2006; Ehresman et al. 2007; Olsen and Zobel 2007). Noninvasive measurements for internal exposure, for example, dried blood spots, hair, and nails, are not typically reported for PFAS but have been measured in some studies and show promise for future work (Kim and Oh 2017; Jian et al. 2018; Wang et al. 2018; Poothong et al. 2019). Measured PFAS concentrations in human plasma and serum vary across different populations, from single- or double-digit micrograms per liter levels in the general population (Kannan et al. 2004; Olsen et al. 2005; Kärrman et al. 2006) to hundreds or even thousands of micrograms per liter in occupationally exposed workers and residents near contaminated sites (Olsen et al. 2003a, 2003b; Olsen and Zobel 2007). Observed concentrations also vary by geography, PFAS type, sex, and age.

The US National Health and Nutrition Examination Survey (NHANES) has included serum PFAS monitoring since 1999, which can now be used to describe nationally representative temporal changes in exposures. However, the small sample size (~2000 per cycle) means only a limited number of United States counties were included each year. Developing countries have even fewer serum measurements. Most published studies

are focused on communities that live near a manufacturing plant or individuals who have come to the hospital to seek care for another condition (usually pregnancy) and thus are not statistically extrapolatable to the general population or for specific demographic groups (Jiang et al. 2014; Ramli et al. 2020). Future PFAS researchers may benefit from establishing collaborations with existing representative population surveys such as the Demographics and Health Survey for developing countries (US Agency for International Development) and the Multiple Indicator Cluster Surveys (United Nations Children's Fund), which includes environmental health monitoring metrics such as PFAS exposure (Boerma et al. 2001; Corsi et al. 2012; Fabic et al. 2012).

In addition to representative sampling, there are a number of challenges in using biomonitoring data for assessing exposure to PFAS. Binding affinities of different PFAS vary (Ng and Hungerbuhler 2013), which affects how some PFAS partition between serum and whole blood (Poothong et al. 2017). Concentrations of PFAS in human blood/serum are the result of external exposures to a much larger mixture of compounds, including many PFAS precursors; but only a small subset of PFAS are routinely targeted in studies (Vestergren et al. 2008; Gebbink et al. 2015). For example, neutral volatile atmospheric precursors such as FTOH and FASA can biotransform in humans and wildlife, contributing to overall exposures of the terminal end products such as PFOS and PFOA. Without considering precursors, PFAS exposures and risks are likely underestimated. However, directly quantifying exposures to precursors is difficult because of in vivo biotransformation and the large number of unidentified compounds (Benskin et al. 2009; Ross et al. 2012; Yeung and Mabury 2016).

New analytical methods that measure total fluorine provide insights into the amount of PFAS that are not accounted for with targeted approaches (see section *Analytical Techniques for Measuring PFAS Exposures*). Studies with these newer analytical tools have shown that routinely monitored PFAS often comprise only a small fraction (<50%) of total PFAS in human exposure media such as textiles (Robel et al. 2017), food packaging (Schultes et al. 2019), and drinking water (Hu et al. 2019). Measurements of EOF in sediments and river water have shown similar results in the environment (Yeung et al. 2013b; Koch et al. 2019). In another study, focusing on the liver of marine mammals, targeted PFAS were observed to account for almost all EOF in tissues from Greenland, Iceland, and Sweden but only 30 to 75% of the EOF in tissues from the eastern United States (Spaan et al. 2020). An integrated approach using a combination of targeted, nontargeted, EOF, and total fluorine analytical techniques showed that although identifiable PFAS have decreased over the past 2 decades (Figure 2B), the percentage of unidentifiable EOF has increased (Miaz et al. 2020). These studies reinforce the importance of accounting for precursors when assessing biological exposures to PFAS. Additional research is needed to establish the link between precursor levels in exposure media (soil, dust, air, water, food, consumer products) and their overall contributions to biological exposures. The role of fluorinated polymers as a source of PFAS exposure to humans and wildlife continues to elude researchers because of the challenge of characterizing the polymers and isolating the contribution of PFAAs from polymers versus the residual unbound PFAS content in polymers (Rankin et al. 2014; Rankin and Mabury 2015; Washington et al. 2015; Li et al. 2017). In addition, questions about the presence of fluoropolymers in microplastics that are globally prevalent remain. Recent studies have reported the release of fluorinated polymers containing microplastic fibers during cleaning of outdoor jackets and the capacity of microplastics to sorb PFAS under environmental conditions (Schellenberger et al. 2019b; Llorca et al. 2020).

Estimating dietary PFAS exposures

Dietary exposure to PFAS has primarily been estimated using the exposure factor approach by measuring PFAS concentrations in various foods and multiplying by food consumption rates for a given population or demographic group. Food consumption rates vary by age, geographically, and culturally; but typical exposure factors are relatively well known (US Environmental Protection Agency 2011). Concentrations of PFAS have been reported in milk, meat, vegetables, fruits, and bread in the subnanogram to low nanogram per gram range, although the majority of food samples analyzed contained PFAS below detection limits (Ericson et al. 2007; Tittlemier et al. 2007). In homogenized whole meals, a similar concentration range was reported, although the maximum concentration observed was 118 ng PFOA/g of fresh food (Fromme et al. 2007). As discussed in the section *Ranking Sources of PFAS Exposure for Human Populations*, a number of studies have estimated dietary exposure to PFAS using the exposure factor approach, almost all European. However, the US Food and Drug Administration is undertaking a study of PFAS in food (de Jager 2019).

One challenge in extrapolating measured PFAS concentrations in foods to estimated exposures is that random sampling of foods in a statistically representative manner is generally unavailable. Sampling of PFAS concentrations in consumed food or individual ingredients can result in different exposure estimates because food contact material and cooking potentially alter PFAS concentrations. Early studies tended to focus on PFOA and PFOS, whereas later studies have started to report concentrations of other PFAS and precursors. New data on TOF and EOF would be useful.

Several studies have used the epidemiologic approach to associate serum PFAS concentrations with different food sources. For example, one study found associations between serum concentrations of several PFAS and fish/seafood consumption in Norway (Haug et al. 2010). In a cohort of 941 American adults with blood sampled between 1996 and 1999, investigators reported positive associations of several PFAS in plasma with consumption of "meat/fish/shellfish (especially fried fish and excluding omega-3 fatty acid rich fish), low-fiber and high-fat bread/cereal/rice/pasta, and coffee/tea" but inverse associations with some other foods such as vegetables and fruit (Lin et al. 2020). Another study reported associations

between serum PFOA and PFNA and fast food consumption and takeout coffee in the United States using data from the NHANES, suggesting a role for food contact material (Nelson et al. 2010). A different study also based on NHANES data reported associations between serum PFAS concentrations and fast food restaurant meals as well as microwave popcorn (Susmann et al. 2019). A small ($n = 61$) but remarkable Norwegian study examined food consumption using several approaches but reported few significant correlations with PFAS in blood (Poothong et al. 2020). Although diet is likely an important route of exposure for many people, it is difficult to estimate and thus uncertain. Statistically representative surveys of dietary exposure to PFAS are therefore needed as well as better data on the sources of PFAS found in food and links to those present in food contact material.

Indoor exposure via inhalation and dust ingestion

Most North Americans spend approximately 90% of their time in indoor environments, and PFAS are used extensively in products designed for indoor use such as stain-resistant coatings for carpet and furniture. They are found in indoor air and dust, although so far the connection to specific indoor sources has received little attention (Beesoon et al. 2012). Thus, there is the potential for indoor exposure to PFAS via inhalation, ingestion of dust, and dermally.

Investigation of indoor exposure to PFAS is more complicated than for many groups of compounds (e.g., polybrominated diphenyl ethers) because of the vast variety of physical–chemical properties for PFAS and the existence of precursors and polymers. Semivolatile organic compounds will tend to partition between the vapor phase, suspended particulate, dust, and indoor surfaces (including skin and clothing), depending in part on their octanol–air partition coefficients (Weschler and Nazaroff 2008). Some PFAS, such as FTOH and perfluorooctane sulfonamidoethanol, are relatively volatile and are found in the vapor phase indoors. Other PFAS, such as PFOA and PFOS, are found at high concentrations in dust. There is little information about the indoor presence and fate of fluorinated polymers (e.g., side-chain fluoropolymers used in some stain-resistance formulations). In part this is due to analytical difficulties (Rankin and Mabury 2015; Letcher et al. 2020). They may be released from products to dust via physical abrasion—as has been shown for other low-volatility compounds (Webster et al. 2009)—or potentially gradually break down over time, releasing the fluorinated side chains, as may occur in outdoor environments (Washington et al. 2015; Letcher et al. 2020). An important question is the amount of unidentified organic fluorine in air and dust. For example, total fluorine analysis in conjunction with HRMS may be a useful first step in examining polymers or other unmeasured compounds in dust.

Concentrations of PFAS in indoor environments are usually measured through filtration or adsorption to a solid phase (filters or sorbents) using either active air pumping or passive samples, followed by extraction of the solid phase to recover PFAS for quantification (Martin et al. 2002; Shoeib et al. 2008; Padilla-Sánchez et al. 2017; Guo et al. 2018; Rauert et al. 2018; Wong et al. 2018; Yao et al. 2018). In indoor air, concentrations can be an order of magnitude higher (nanograms per cubic meter levels) than outdoor environments (Shoeib et al. 2004, 2005; Yao et al. 2018). Indoor air sampling has tended to focus on the more volatile compounds such as the FTOH and FASA.

Concentrations of PFAS in dust can be very high and have been reported at the micrograms per gram level (Moriwaki et al. 2003; Kubwabo et al. 2005; Shoeib et al. 2005; Strynar and Lindstrom 2008; Eriksson and Karrman 2015; Lankova et al. 2015; Winkens et al. 2018). Dust sampling has found PFAA and other PFAS, including relatively large amounts of polyfluorinated phosphate esters (fluorotelomer phosphate diester; De Silva et al. 2012; Eriksson and Karrman 2015; Makey et al. 2017). Methods for dust sampling and processing (e.g., where and how to sample dust in homes, sieving size) are less standardized than for air. Bigger issues are the variety of indoor environments—home, workplace, childcare facilities, vehicles, etc. (with homes being a main focus)—and the difficulty of doing representative sampling (Goosey and Harrad 2012; Fraser et al. 2013; Zheng et al. 2020). Unlike the extraordinary efforts that have been made for representative biomonitoring (e.g., NHANES in the United States), most indoor sampling is convenience sampling, which may not be representative of exposures across the general population. Exposure factors for inhalation are well known, but exposure factors for dust ingestion are quite uncertain (US Environmental Protection Agency 2011). As a result, inhalation estimates are likely more reliable than those for dust ingestion. An additional source of uncertainty is the amount of conversion of precursors (e.g., FTOH, FASA) in terminal end products (e.g., PFCA, PFSA) found in serum/blood (Poothong et al. 2020). This issue is particularly important when trying to compare inhalation with dust ingestion or indoor routes of exposure to diet and other sources.

Two North American studies have found associations between serum levels of some PFAAs and the precursors FTOH and FASA, respectively, in indoor air (Fraser et al. 2012, 2013; Makey et al. 2017) but little association with PFAS concentrations in dust. A Norwegian study found associations between certain PFAS in whole blood and indoor air and/or dust (Poothong et al. 2020). The latter study also estimated that diet was more important than indoor exposure on average but that inhalation and dust ingestion dominated for some study participants, particularly the people with the highest blood concentrations. Some studies have found that serum PFAS concentrations increase with socioeconomic status, indicating that indoor and dietary exposure may be partly correlated as a result of purchasing decisions (Nelson et al. 2012). Relatively few studies have used epidemiologic techniques to examine air and dust or other pathways simultaneously (Haug et al. 2011; Fraser et al. 2013; Makey et al. 2017; Poothong et al. 2020).

In summary, some epidemiologic evidence suggests that indoor exposure is important enough to be empirically associated with serum/blood levels and may be the dominant

exposure route for some people (Fraser et al. 2013; Makey et al. 2017; Poothong et al. 2020). More research is needed on the differences in indoor exposure patterns between people as well as differences between countries and time trends. Relatively little research has been conducted on the connection between indoor levels and putative sources, total organic fluorine, the contribution of fluorine-containing polymers, and exposure of children.

Outdoor air exposures

Reported PFAS concentrations in outdoor air range from nondetectable or subpicogram per cubic meter levels to hundreds of picogram per cubic meter levels (Martin et al. 2002; Stock et al. 2004; Barber et al. 2007; Jahnke et al. 2007; Fromme et al. 2009; Rauert et al. 2018; Wong et al. 2018). Concentrations of PFAS are typically higher in urban areas than in rural areas (Martin et al. 2002; Stock et al. 2004; Barber et al. 2007; Jahnke et al. 2007). A few studies of general populations report that outdoor air PFAS concentrations are 1 to 2 orders of magnitude lower than indoors (Shoeib et al. 2011), presumably due to indoor sources. For such populations, we expect inhalation exposure indoors to exceed outdoor exposures.

Little is currently known about communities with major atmospheric point sources. In Parkersburg, West Virginia, USA, local drinking water sources were contaminated primarily by air emissions of PFOA emitted by the Washington Works facility, followed by deposition and groundwater transport (Davis 2007). In Fayetteville, North Carolina, USA, precipitation monitoring to assess the deposition of GenX via air emissions has been ongoing since 2018. Communities in Hoosick Falls, New York; Bennington, Vermont; and Merrimack, New Hampshire, USA, have had varying extents and types of monitoring conducted in response to concerns or documentation of groundwater or drinking water contamination. An important question in these scenarios is the relative importance of exposure via inhalation versus water ingestion. Using a sophisticated fate and transport model, researchers estimated PFOA concentrations in ambient air and water in the communities surrounding the Washington Works facility in West Virginia over time (Shin et al. 2011a, 2011b). Their results compared well with measured water values, and indoor air was assumed to be 10% of outdoor air because of partial infiltration. Transport of PFAS is faster in air than in soil and groundwater. Thus, for people living in areas with contaminated air, estimated inhalation exposure exceeded that via water ingestion in the early time period but was less than water ingestion later on (Shin et al. 2011a, 2011b). These results suggest that inhalation exposure to PFAS might exceed water ingestion in areas with continuing air emissions but mitigation of drinking water (e.g., via filtration).

Dermal exposures to PFAS

Dermal exposure to PFAS can result from contact with house dust, PCPs, and other consumer products. It has received relatively little attention, with 2 exceptions: dust and, more recently, cosmetics and other PCPs. For example, one study estimated dermal exposure of children to PFAS in dust in childcare settings using measured dust concentrations and an exposure factor for the amount of dust adhering to skin (Zheng et al. 2020). Poothong et al. (2020) used an alternative method for skin contact: measuring PFAS on hands using handwipes. Both then used the fraction dermal absorption approach, a model commonly used in risk assessment (Kissel 2011).

One study examined selected PCP with product labeling indicating PFAS ingredients such as polyfluorinated phosphate esters (PAPs) or other fluorinated compounds and reported PFCA in the micrograms per gram range but did not determine the levels of PAPs (Fujii et al. 2013). Another study that measured 39 PFAS, as well as EOF and total fluorine, detected PAPs at up to 470 μg/g in cosmetic products (Schultes et al. 2018). The measured PFAA accounted for only a small fraction of the EOF and total fluorine, implying the presence of unidentified compounds, potentially including polymers or inorganic fluorine. Skin contact with PCPs can depend on a number of factors including the amount of the product applied per unit area (loading), the surface area of exposed skin, the duration of use, and the frequency of washing the skin. Prior work has estimated dermal absorption of PFOA in foundation cosmetics, leading to an absorbed dose through dermal exposure of <0.006 to 3.1 ng/kg/d, with the high end exceeding dietary exposure in Sweden (Schultes et al. 2018). This dermal exposure estimate for PFOA does not include indirect exposure via PAP.

RANKING SOURCES OF PFAS EXPOSURE FOR HUMAN POPULATIONS

A major question discussed by the exposure assessment panel at the SETAC PFAS topic meeting was whether it is possible to rank the relative importance of PFAS exposure sources for different human populations at this time. Researchers and decision makers seek to understand the relative contributions of different exposure pathways to human exposure to inform risk assessments and prioritize interventions. The panel concluded that there were many gaps remaining in this area, especially for general populations that have diverse exposure pathways for PFAS. A summary of the present understanding is provided in this section.

Occupational exposures

Occupational health effects associated with human PFAS exposures have been reported for individuals who worked in fluorochemical production plants in the United States (Olsen et al. 1999), Italy (Girardi and Merler 2019), and China (Fu et al. 2016). Occupational exposure to PFAS occurs mainly through inhalation and dermal contact (Franko et al. 2012). Inhalation exposure to PFAS in a workplace situation can be important because of sublimation into the gaseous phase of volatile manufacturing intermediates that are hydrolyzed to

end-product PFAS (Kaiser et al. 2010). Firefighters working and training with AFFF did not show a relationship between internal exposure of PFOS and the self-reported frequency of direct skin contact with AFFF, indicating that dermal contact may not be an important pathway of exposure (Rotander et al. 2015). However, they had elevated blood levels of PFOS and PFHxS, which is consistent with the composition of legacy electrochemical fluorination AFFF. Elevated levels of PFNA and other long-chain PFCAs have been connected to occupational exposure for firefighters (Laitinen et al. 2014; Trowbridge et al. 2020). Professional ski wax technicians showed elevated blood levels of PFCA, which was associated with number of working years. Ski wax contains both precursor semifluorinated n-alkanes and PFCA (Plassmann and Berger 2013; Carlson and Tupper 2020) and is often applied using heat (130–220 °C), which results in gaseous compounds and particles. An exposure study with internal dose measurement and personal and ambient air including airborne particles showed that inhalation of both precursor compounds and terminal end products contributed to the internal dose (Nilsson et al. 2010).

Communities near contaminated sites

Near facilities that manufacture or process fluorochemicals PFAS have been detected in both surface water and groundwater sources. Concentrations in aqueous matrices in areas without point sources generally occur below detection limits or at the subnanogram per liter (parts per trillion) level but are commonly detected at the micrograms per liter (parts per billion) level or higher in contaminated areas (Chen H et al. 2017; Cai et al. 2018; Pan et al. 2018; Park et al. 2018; Janda et al. 2019). These include sites with historical releases of AFFF, such as military bases and airports, and wastewater-treatment plants that have received industrial wastes (Herrick et al. 2017; Worley et al. 2017; Barton et al. 2020). These sites have been associated with contamination of drinking water across the United States, with at least 6 million people estimated to have been exposed to levels above the US Environmental Protection Agency health advisory for PFOS and PFOA of 70 ng/L (Hu et al. 2016). The total number of people exposed to PFAS in the United States is greater because this estimate does not include populations exposed through small drinking water systems or private wells or exposure to other PFAS.

Many biomonitoring studies have shown that PFAS in drinking water near contaminated sites have led to population blood levels that are much greater than background levels (Daly et al. 2018; Ingelido et al. 2018; Li et al. 2018). In such areas, serum levels are associated with concentrations in drinking water (Hoffman et al. 2011). Drinking water has been estimated to contribute up to 75% of exposures near contaminated sites (Vestergren and Cousins 2009). The US Agency for Toxics Substances and Disease Registry is currently conducting biological monitoring at over 15 sites with contaminated drinking water across the country, following comparable methods for collecting blood and administering exposure questionnaires. This work will generate further information about the contributions of drinking water exposures across a diverse set of communities near contaminated sites.

Production and use of the most common legacy PFAS (PFOS, PFOA, PFHxS) have decreased in the United States, but an increasing number of sites contaminated with these compounds have been identified over the past decade. Data compiled by Northeastern University's Social Science Environmental Health Research Institute (2020) show that as of May 2020 there were 393 known contaminated public drinking water systems in the United States. As background levels of legacy PFAS decrease, the relative contribution of their exposure from drinking water sources near these contaminated sites will increase (Bao et al. 2017). Furthermore, replacement compounds, such as PFEA, including GenX, have already been detected in drinking water near manufacturing facilities (Hopkins et al. 2018). Newer methods that measure EOF and total fluorine are beginning to be used on drinking water with the goal of quantifying the exposure of unidentified PFAS (Hu et al. 2019). However, the large-scale implications of changes in production have yet to be fully understood.

General population PFAS exposures

The relative importance of different PFAS exposure sources varies dramatically across general populations with diverse PFAS exposure sources. Table 2 summarizes some prior literature estimates of source contributions to overall PFAA exposures for adult populations without occupational exposure and not living in close proximity to point sources of PFAS contamination. Large variability in the relative importance of different exposure sources across studies reflects variable concentrations in environmental media and differing assumptions regarding exposure sources, frequencies, duration, and consideration of precursors.

Several studies have shown that exposure to PFAS in children differs from that in adults because of behavioral and dietary variability. Breast-feeding is known to be an important source of early-life exposure to PFAS (Mogensen et al. 2015; Kang et al. 2016; Papadopoulou et al. 2016). A study from the Faroe Islands showed that hand-to-mouth contact with carpeting was an important exposure source for children but not adults based on the contrasting composition of PFAS measured in serum (Hu et al. 2018). The 2020 European Food Safety Authority (EFSA) report found that toddlers and children had a 2-fold higher exposure than adults, in part due to maternal exposure (European Food Safety Authority 2020).

There is general agreement that dietary exposure is the major contributor to population exposure for PFOS and PFOA (Table 2) but more limited evidence for perfluorohexanoic acid, perfluoroheptanoic acid, PFNA, perfluorodecanoic acid, and PFHxS. In 2018, the EFSA estimated that the main contributors to adult dietary exposure to PFOS were fish, meat, eggs, and products with these ingredients (European Food Safety Authority 2018). The greatest sources of exposure to PFOA were eggs and dairy and products containing these ingredients. The youngest population groups were estimated

TABLE 2: Literature estimates of source contributions (percentage) to adult exposures to poly- and perfluoroalkyl substances[a]

		Exposure medium[b]				Exposure route[b]				
PFAS	Carbon length	Diet	Dust	Water	Consumer goods	Inhalation	Dermal	Indirect	Study location	Ref.
PFBA	4		4	96					NA	[c]
PFHxA	6	38	4	38		8		12	NA	[c]
PFHxA	6	87	4			2			Norway	[d]
PFHxS	6	57	38			5			Finland	[e]
PFHxS	6	94	1						Norway	[d]
PFHpA	7	93	1						Norway	[d]
PFHpS	7				100				Norway	[d]
PFOA	8	16	11		58	14			NA, EU	[f]
PFOA	8	85	6	1	3			4	Germany, Japan	[g]
PFOA	8	77	8	11		4			Norway	[h]
PFOA	8	66	9	24		<1	<1		USA	[i]
PFOA	8	41		37				22	Korea	[j]
PFOA	8	99		<1					China	[k]
PFOA	8	47	8	12		6		27	NA	[c]
PFOA	8	95	<2.5			<2.5			Finland	[e]
PFOA	8	89	3			2			Norway	[d]
PFOA	8	91		3		5			Ireland	[l]
PFOS	8	66	10	7		2		16	NA	[c]
PFOS	8	72	6	22		<1	<1		USA	[m]
PFOS	8	96	1	1		2			Norway	[h]
PFOS	8	81	15		4				NA, EU	[f]
PFOS	8	93		4				3	Korea	[j]
PFOS	8	100		<1					China	[k]
PFOS	8	95	<2.5			<2.5			Finland	[e]
PFOS	8	75				3			Norway	[d]
PFOS	8	100							Ireland	[l]
PFOPA	8		100						Norway	[d]
PFNA	9	79	5			1			Norway	[d]
PFDA	10	51	2	4		15		28	NA	[c]
PFDA	10	78	1			2			Norway	[d]
PFDS	10		89		4				Norway	[d]
PFUnDA	11	61	4			1			Norway	[d]
PFDoDA	12	86	2	2		4		5	NA	[c]
PFDoDA	12	48	15						Norway	[d]
PFTrDA	13	89	1						Norway	[d]

[a]Adapted from Sunderland et al. (2019) and updated with more recent publications.
[b]Where available, central tendency values are presented.
[c]Data from Gebbink et al. (2015). Data shown are based on the intermediate exposure scenario in figure 3 in their article.
[d]Data from Poothong et al. (2020).
[e]Data from Balk et al. (2019). Values represent modeled exposures for children at 10.5 years of age.
[f]Data from Trudel et al. (2008). Values are based on the high exposure scenarios from figures 2 and 5 of their article.
[g]Data from Vestergren and Cousins (2009). Values are for the background population exposure from figure 4a in their article.
[h]Data from Haug et al. (2011). Values are based on the 50th percentile exposure scenario for women and the midrange scenario for dust exposure.
[i]Data from Lorber and Egeghy (2011). Data are based on pathway-specific intake estimates for adults.
[j]Data from Tian et al. (2016). Data are for adult exposures based on figure 4 in their article.
[k]Data from Shan et al. (2016). Data are based on summed estimated daily intakes.
[l]Data from Harrad et al. (2019).
[m]Data from Egeghy and Lorber (2011). Values represent the typical environmental exposure scenario shown in figure 3 in their article.
EU = Europe; NA = North America; PFAS = poly- and perfluoroalkyl substances; PFBA = perfluorobutanoic acid; PFDA = perfluorodecanoic acid; PFDoDA = perfluorododecanoic acid; PFDS = perfluorodecane sulfonic acid; PFHpA = perfluoroheptanoic acid; PFHpS = perfluoroheptane sulfonic acid; PFHxA = perfluorohexanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOPA = perfluorooctylphosphonic acid; PFOS = perfluorooctane sulfonic acid; PFTrDA = perfluorotridecanoic acid; PFUnDA = perfluoroundecanoic acid.

to have the highest dietary exposure to PFOA and PFOS. In 2020, the EFSA expanded its analysis of exposures to PFAS in foods and reported that the sources contributing to PFAS exposure to adults and children were consistent with the findings from 2018. They concluded that PFOA contributed 21%, PFNA 4%, PFHxS 10%, and PFOS 66% to the sum of PFAS exposures, based on the median of the mean lower-bound estimates. The EFSA was unable to draw meaningful conclusions about the contributions of PFAS from food contact material.

Comparing water and serum samples from 1989 and 1990, one study estimated that drinking water contributed approximately 20% of total exposure of several legacy PFAS in the general United States population (Hu et al. 2019). There are still large uncertainties related to the fraction of PFAS exposure in the general population that originates from dust, consumer products, inhalation, and other pathways. For example, exposures to PFAS precursors in dust that degrade into terminal PFAA have not been well characterized (Balk et al. 2019; de la Torre et al. 2019; Harrad et al. 2019). Table 2 suggests that for

the general population indoor exposures to PFAS through inhalation, dermal contact, or incidental ingestion of dust and air contribute less to exposure than dietary ingestion on average, although the balance may be different for subpopulations. Without rigorously conducted exposure studies, it is challenging to rank order the most important human exposure pathways; and without these data, our ability to design evidence-based exposure intervention strategies will be limited.

CURRENT UNDERSTANDING OF PFAS EXPOSURE IN WILDLIFE

PFAS occurrence and temporal trends in wildlife

Elevated exposures of wildlife to PFAS represent a concern for their health directly and for human populations that consume wildlife (Fair et al. 2019; Guillette et al. 2020). In 2001, the first report on the global occurrence of PFOS in wildlife was released, illustrating widespread presence in biological tissues even in remote regions such as the Arctic (Giesy and Kannan 2001). Concentrations of PFOS and other PFAA have been detected in invertebrates, fish, amphibians, reptiles, birds, and mammals worldwide (Ahrens 2011; Reiner and Place 2015; Penland et al. 2020). Several comprehensive reviews (Houde et al. 2011; Reiner and Place 2015; Muir et al. 2019) have synthesized data from available biomonitoring studies.

The highest PFAS concentrations in wildlife tend to be associated with proximity to contaminated sites. For example, one of the highest reported fish PFOS concentrations (maximum 9349 ng/g dry wt in whole fish tissue) was from an AFFF-impacted site downstream from Barksdale Air Force Base in Louisiana (Lanza et al. 2017). Many biomonitoring studies have identified elevated exposures to legacy and emerging PFAS as the result of industrial activities (Custer et al. 2012, 2014; Liu et al. 2017; Groffen et al. 2019; Lopez-Antia et al. 2019; Guillette et al. 2020). Legacy PFAS such as PFOS are still abundant at many contaminated sites, and novel PFAS are increasingly being detected. For example, one study reported that PFOS was the predominant compound in fish (mean 263–348 ng/g wet wt in muscle) adjacent to a major fluorochemical production facility in Wuhan, China (Zhou et al. 2013). Suspect and nontarget screening subsequently revealed a suite of 330 novel fluorinated structures belonging to 10 different chemical classes in fish liver from the same region (Liu et al. 2018). The profile of specific PFAS released at each contaminated site affects the accumulation of different compounds in biota and may also be relevant for determining exposure risks such as near AFFF-contaminated regions (Yeung and Mabury 2013; Custer et al. 2014; Munoz et al. 2017; Larson et al. 2018; Salice et al. 2018; Langberg et al. 2019; Munoz et al. 2020).

Biological time series data for specific ecosystems suggest variable temporal changes in PFAS across compounds and ecosystems. In the Arctic, there are sustained or increasing (post-2010) PFAA levels in some wildlife (Muir et al. 2019). Following the phaseout of the parent chemical to PFOS and its precursors circa 2000 to 2002, several studies have noted rapid declines in FOSA, an atmospheric precursor to PFOS that is biotransformed by most mammals, but less consistent declines or even increases in PFOS (Smithwick et al. 2006; Ahrens et al. 2009a; Dassuncao et al. 2017; Sun et al. 2019; Schultes et al. 2020). This likely reflects the rapid response of atmospheric concentrations to changes in chemical production but a lagged response of most aquatic ecosystems. Most time series studies have focused on targeted PFAS, but recent work has shown that trends in total fluorine indicated by EOF and other methods differ from the legacy compounds (Schultes et al. 2020). Understanding temporal and spatial trends in emerging PFAS compounds in biota is thus an important research need (Spaan 2020).

PFAS bioaccumulation metrics

The bioaccumulation potential of persistent organic pollutants (POPs) is commonly reported based on several metrics: bioconcentration factor (BCF; the direct uptake of a chemical by an organism from water or air, i.e., $BCF = C_{fish}/C_{water}$ in a controlled laboratory experiment with no dietary intake); biomagnification factor (BMF; the concentration of an organism relative to its diet, i.e., C_{fish}/C_{prey}); bioaccumulation factor (BAF; the combined effects of all uptake pathways). Bioconcentration factors are commonly measured in laboratory experiments, whereas BMFs and BAFs are typically field-based measurements. The trophic magnification factor (TMF) is an indicator of dietary biomagnification and is generally established empirically using the slope of the relationship between trophic position in a food web based on stable nitrogen isotopes and chemical concentrations in organisms from a field-based food web. A large body of work has established that for neutral, hydrophobic POPs, simple partitioning between lipid and water indicated by their octanol–water partition coefficient (K_{OW}) or octanol–air partition coefficient (K_{OA}) provides a reasonable proxy for bioaccumulation propensity.

By contrast, processes governing the uptake of PFAS into organisms and partitioning across tissues are less understood, even for commonly studied PFAAs (Figure 4). The pK_a values of long-chain PFAAs are thought to range from less than 0 to 1, indicating that they are almost completely ionized at environmentally and biologically relevant pH (Goss 2008). Despite being ionized, PFAS are bioavailable, and long-chain PFAAs can accumulate in specific biological media to levels equivalent to lipid accumulation of neutral POPs. Given these observations, the question emerges of whether and how existing metrics for chemical accumulation in wildlife can be used to describe diverse PFAS. This formidable data gap hampers efforts to develop mechanistic models for exposure and risk assessment of PFAS and stands as a major limitation to ecological exposure assessment of PFAS.

A synthesis of 513 laboratory-based and 931 field-based measurements indicates that long-chain PFCAs with a 12 to 14 carbon-chain length generally exhibit the highest

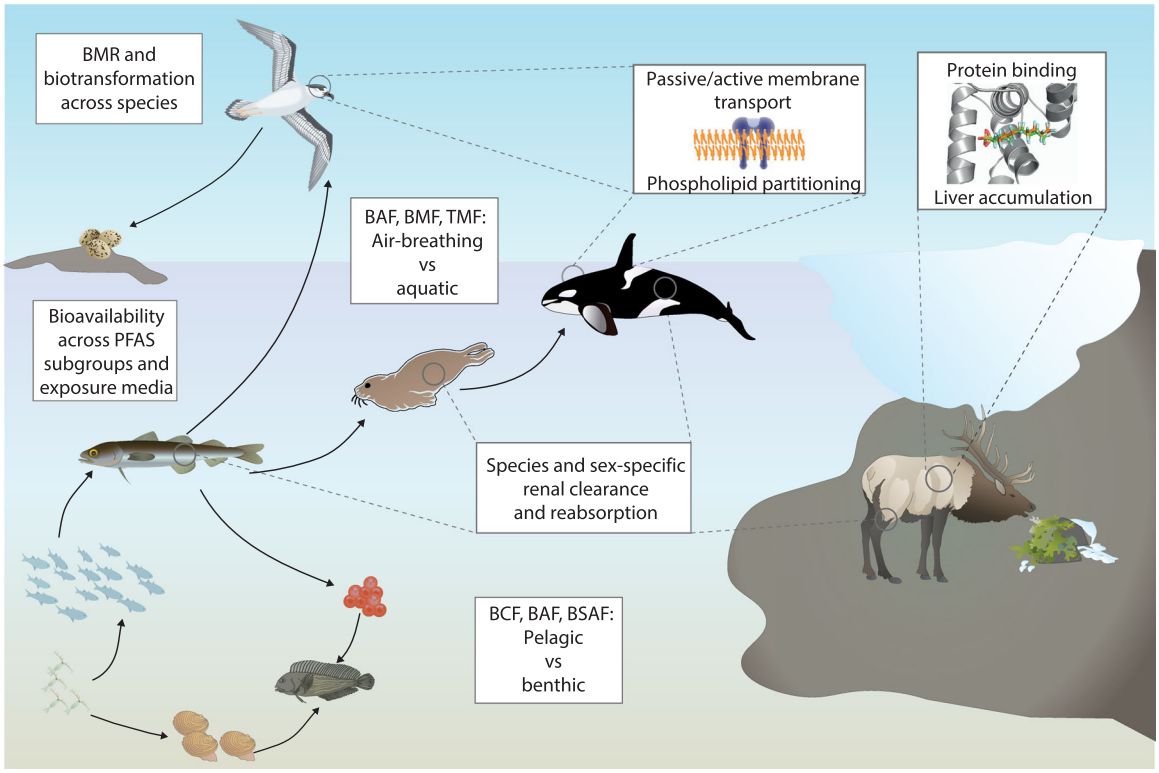

FIGURE 4: Key bioaccumulation processes, metrics, and gaps associated with poly- and perfluoroalkyl substances in wildlife. BAF = bioaccumulation factor; BCF = bioconcentration factor; BMF = biomagnification factor; BMR = basal metabolic rate; BSAF = biota-sediment accumulation factor; PFAS = poly- and perfluoroalkyl substances; TMF = trophic magnification factor.

bioaccumulation potential, with whole-body BCF values ranging between 18 000 and 40 000 L/kg (Gobas 2020). Laboratory-based whole-body BCFs of PFCA with 8 to 11 carbon-chain lengths are generally much lower (BCF range 4.0–4900 L/kg). Similarly, PFOS exhibits relatively low laboratory-based whole-body BCFs, generally in the range of 100 to 1000 L/kg. Field-based BAFs are generally in agreement with the laboratory-derived BCF values but in some cases are somewhat higher, reflecting dietary accumulation. Generally, BCFs and BAFs (liters per kilogram) of individual PFAAs in plankton, aquatic gill-ventilating invertebrates, and fish increase with increasing perfluoroalkyl chain length and hydrophobicity (Condor et al. 2008), though exceptions have been identified (Munoz et al. 2017; Zhang et al. 2019).

Avian and marine mammalian food webs exhibit the highest reported TMFs for PFAA (Kelly et al. 2009; Tomy et al. 2009). For example, the TMF for PFOS in these relatively long food webs containing air-breathing wildlife (e.g., marine birds and mammals) is approximately 20. In aquatic piscivorous food webs TMFs tend to be much lower. For example, TMFs of PFOS in the Lake Ontario aquatic piscivorous food webs range between 1.9 and 5.9 (Martin et al. 2004; Houde et al. 2008). Other studies have reported negligible biomagnification of PFOS in aquatic piscivorous food webs, with TMFs not substantially different from 1 (Loi et al. 2011; Penland et al. 2020). This behavior mirrors previous observations of food web–specific biomagnification of low K_{OW} and high K_{OA} moderately hydrophobic organic chemicals (Kelly et al. 2007). In particular, PFOS and several other PFAS of concern, which are likewise moderately hydrophobic and poorly metabolizable substances, may not biomagnify extensively in aquatic food webs because of efficient respiratory elimination to water via gills. Conversely, these substances can biomagnify to a high degree in food webs containing air-breathing animals because elimination of these substances via lung–air exchange is negligible. More data are needed to refine these hypotheses and address variability across current data sets. Observed variability in TMFs for PFAA is likely due to selection of species, tissues, concentration normalization techniques, as well as the influence of site-specific conditions, life history stage, trophic condition of sampled individuals, and tissues and techniques used for stable isotope analyses.

The contribution of PFAA precursors to field-based measurements of BAFs represents a major gap in understanding of PFAS bioaccumulation. For example, one study noted higher than expected accumulation of PFCA with 5 and 6 carbons in marine plankton from the northwestern Atlantic and posited that this reflects the accumulation of degraded precursor compounds (Zhang et al. 2019). Another study that included liver tissues from marine mammals from the same region found a large fraction (30–75%) of unidentified organofluorine (Spaan et al. 2020). Shrimp from a subtropical food web in Hong Kong were similarly noted to have a high fraction of unknown fluorinated compounds (Loi et al. 2011). Some precursor compounds behave more similarly to traditional POPs and may thus have enhanced bioaccumulation propensity (Dassuncao et al. 2017).

Additional data on bioaccumulation potential and health risks associated with unidentified organofluorine are thus needed, particularly because chemical manufacturing has shifted away from the legacy PFAS typically detected in biota (see section *Overview of PFAS Sources and Environmental Pathways*).

Modifications to bioaccumulation metrics for POPs needed for PFAS

Table 3 illustrates some potential modifications to key bioaccumulation metrics that better reflect the behavior of PFAS in biological systems. In deciding the appropriate metric to use and how it is to be defined (in what tissue, with what type of normalization), a key guiding question is "For what purpose?" If a TMF is being calculated to understand the exposure of a predator organism to PFAS in its prey, it makes the most sense to use the concentration in the portion of the prey consumed by that organism to define the denominator. For example, one study calculated the BMF for PFAA in polar bears using the ratio of polar bear liver to ringed seal blubber concentrations (Boisvert et al. 2019). Similarly, when considering BCFs in sport fish, PFAS concentrations in muscle tissue may be most relevant in establishing dietary guidelines for humans, but liver-specific BCFs may provide better insight for potential health consequences to the fish population itself.

Refining metrics to better capture the behavior of PFAS in biological systems requires a better understanding of how PFAS are transferred from external exposure sources to the internal environment and how, once internalized, they distribute to different tissues and are eliminated (Figure 5). Presently there is little consensus on the tissue type (e.g., liver, kidney, muscle) that best represents PFAS bioaccumulation in wildlife and whether normalization of concentrations to protein or phospholipid is needed. For example, using tissue-specific measurements in fish, there were large variations in blood BCF and blood BAF compared to the analogous whole-body BAF and BCF, whereas liver-based BCF and BAF were on the same order of magnitude for the whole-body accumulation parameters (Martin et al. 2003; Shi et al. 2018).

The PFAA are acidic compounds with low pK_a, which means they are often associated with proteins (e.g., serum albumin) and phospholipids rather than storage lipids (Armitage et al. 2012, 2013, 2017; Ng and Hungerbuhler 2013, 2014; Chen et al. 2016; Dassuncao et al. 2019). As a result, PFAA accumulate primarily in the blood, liver, kidney, and brain of organisms rather than adipose tissue (Martin et al. 2003; Ahrens et al. 2009b; Borg et al. 2010; Kowalczyk et al. 2013; Dassuncao et al. 2019). The affinity of different PFAA for proteins varies widely, suggesting binding site–specific interactions and facilitated transport of some compounds. PFAA interact with protein molecules through a combination of polar, nonpolar, and electrostatic interactions and not through covalent binding. Hence, sorption and desorption are dependent on thermodynamic gradients (i.e., chemical activity differences) in biological systems (Bischel et al. 2010). Distribution of PFAA to structural (muscle) proteins is generally low, while binding to specific proteins (e.g., serum albumin, liver fatty acid binding protein [L-FABP]) leads to tissue-specific accumulation patterns (Luebker et al. 2002; Jones et al. 2003; Martin et al. 2003; Ahrens et al. 2009b; Ng and Hungerbuhler 2014). Phospholipids also play an important role in tissue-specific partitioning (Armitage et al. 2012). This is

TABLE 3: Modifications to persistent organic pollutant bioaccumulation metrics for poly- and perfluoroalkyl substances

Metric	Traditional indicator	PFAS-specific recommendation
K_{OW}, K_{OA}	Used as surrogates for equilibrium partitioning of neutral organic chemicals to lipid tissues of aquatic and air-breathing organisms	D_{OW}: Octanol–water distribution ratio (takes degree of ionization into account) D_{MW}: Membrane–water partition ratio; chemical activity ratios K_{PW}: Protein–water partition coefficient K_A, K_D: Equilibrium association and dissociation constants for specific proteins (e.g., albumin, liver fatty acid binding protein) *Key gap: Relevant metric for air-breathing organisms*
BCF: bioconcentration factor (waterborne or airborne exposure only) BAF: bioaccumulation factor (waterborne/airborne and/or dietary exposure)	Concentration in organism (whole body, lipid-normalized)/concentration in water (freely dissolved)	Concentration (chemical activity)[a] in serum/concentration in water; concentration in liver/concentration in water; concentration in organism (whole body)/concentration in water *Key gap: 1) Selecting appropriate tissue to represent accumulation in organism, 2) accounting for contributions of precursors to field-based BAFs*
BMF: biomagnification factor TMF: trophic magnification factor	Concentration in predator (whole body, lipid-normalized)/concentration in prey (whole body, lipid-normalized)	Concentration in predator liver/concentration in prey liver; concentration in predator (whole body)/concentration in prey (whole body) *Key gaps: Selecting appropriate predator and prey tissues across food webs*

[a]Emerging approach: activity-based metrics. See section *PFAS bioaccumulation modeling*.
PFAS = poly- and perfluoroalkyl substances.

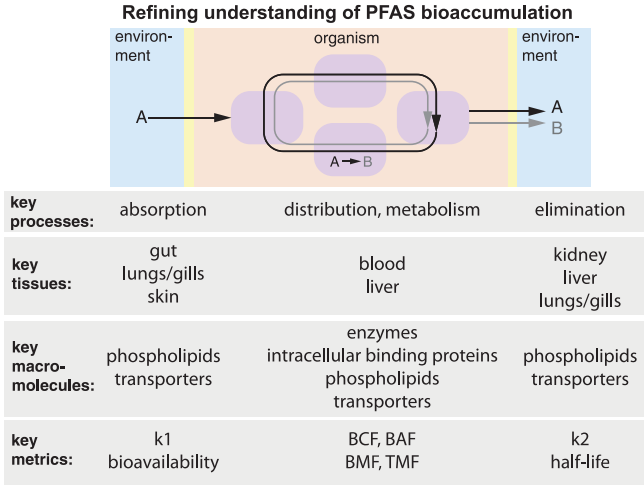

FIGURE 5: Key elements for predicting the relationship between external exposure and internal dose of wildlife and human to poly- and perfluoroalkyl substances (PFAS). The internal distribution and dose are driven by the balance of absorption, distribution, metabolism, and elimination. For PFAS, unlike for neutral organic chemicals, internal distribution is substantially influenced by protein binding and transporter uptake and efflux, leading to accumulation in the liver and blood and species- and sex-specific elimination half-lives. BAF = bioaccumulation factor; BCF = bioconcentration factor; BMF = biomagnification factor; TMF = trophic magnification factor.

particularly true for the long chain PFAS and brain tissue, which is very high in phospholipid content (Dassuncao et al. 2019). Thus, more refined approaches to account for tissue-specific uptake in bioaccumulation assessments are needed.

PFAS bioaccumulation modeling

Mechanistic bioaccumulation models developed for neutral lipophilic contaminants such as polychlorinated biphenyls and organochlorine pesticides have been widely used by academics, risk-assessment professionals, and regulatory authorities (Arnot and Gobas 2004). Applications of these models include substance prioritization, screening-level risk assessments, development of environmental quality guidelines, and determination of total maximum daily loads. They use information on the physical–chemical properties of the compound of interest as well as environmental and biological properties of the site and organisms. The success of these existing mechanistic approaches relies on good data quality on the partitioning properties of neutral compounds in biological media and tissues. Thus, a major challenge for PFAS is suitable data on their partitioning in biological compartments.

One available approach for modeling fish bioaccumulation of ionizable organic compounds (IOCs, including PFAA) takes into account the role of thermodynamic gradients in tissue partitioning for PFAS (Armitage et al. 2013). Specifically, the model is based on pH-dependent distribution ratios, including the chemical's octanol–water distribution ratio and membrane-water distribution ratio (D_{MW}), as well as the estimated distribution ratio between nonlipid organic matter (NLOM) and water. It provides a simple partitioning-based equation to predict steady-state concentrations of PFAA and other IOCs in aquatic organisms.

Strong relationships between empirically derived bioaccumulation metrics (BCF, BAF, TMF) and distribution ratios for protein–water (D_{PW}) and membrane–water (D_{MW}) of individual PFAA have been demonstrated for some ecosystems (Kelly et al. 2009; Chen et al. 2016). The relatively high degree of bioaccumulation of long chain PFCA with 12 to 14 carbons in fish is likely attributable to high D_{MW} and D_{PW} (estimated values of 10^5–10^6 D_{MW} and 10^4–10^6 D_{PW}). Thus, D_{PW} and D_{MW} are 2 key parameters that may be useful for predicting PFAS bioaccumulation potential (Table 3).

The NLOM component of the IOC model represents endogenous protein (Armitage et al. 2013). Although it performs well for many IOCs, it tends to underestimate the bioaccumulation capacity of some PFAA. This is likely due to the complex association of PFAS with proteins. Thus, a key to parameterizing this model is the difference in distribution ratios between neutral and ionized forms of the specific PFAS congener, which may require challenging experimental determinations. Further, different protein types can exhibit different sorptive capacities for IOCs (Henneberger et al. 2016). For some compounds, the D_{PW} in plasma protein (e.g., albumin) can be orders of magnitude greater than that in structural proteins (e.g., muscle protein). Thus, application of simple equilibrium partitioning-based models may require utilizing a series of distribution coefficients for different proteins (e.g., transporter protein–water distribution ratios and structural protein–water distribution ratios). This approach was used to assess tissue-specific bioaccumulation of PFAA and other IOCs in laboratory exposed fish (Chen FF et al. 2016, 2017).

A chemical activity–based approach to ecological risk assessment bridges some gaps between traditional empirical modeling efforts and mechanistic models (Gobas et al. 2017, 2018). This approach was used to assess bioaccumulation and exposure risks of several PFAS in wildlife at AFFF-impacted sites (Gobas 2020). The chemical activities of PFOS and other PFAA indicated that these compounds tend to primarily biomagnify in food webs composed of air-breathing wildlife (birds, mammals, terrestrial reptiles) compared to those comprising only aquatic organisms. For example, activity-based BMFs in upper–trophic level wildlife (birds and mammals) were found to range between 10 and 20, and those in aquatic organisms were close to 1, indicating negligible biomagnification. An advantage of this approach that is particularly relevant to PFAS is that it can be used effectively for both neutral and ionic substances, including anionic, cationic, and zwitterionic compounds. A limitation of this approach is that solubility estimates and hence calculated activities are based on numerous assumptions regarding physicochemical properties, phase partitioning, protein-binding, and toxicokinetic.

Beyond simple partitioning-based models for substance screening, more sophisticated approaches may be required for higher-resolution modeling. For example, IOC binding to intra- and extracellular protein (serum albumin, L-FABP), as well as

membrane-associated organic anion transporters, may act to provide both enhanced sorption capacity and advective transport across biological membranes (Ng and Hungerbuehler 2013). This affects uptake and elimination rates as well as tissue distribution and helps explain the long elimination half-lives of PFAA in organisms.

Physiologically based toxicokinetic (PBTK) models incorporating absorption, distribution, metabolism, and excretion metrics have been developed to assess the toxicokinetic of PFOS and PFOA in various animal models, including fish and mammals (Andersen et al. 2006; Tan et al. 2008; Consoer et al. 2014, 2016; Fabrega et al. 2014, 2016; Cheng and Ng 2017; Khazaee and Ng 2018). Such models are particularly useful for assessing the influence of membrane transporters and revealing important challenges in equilibrium modeling of PFAS bioaccumulation. For example, in laboratory-based evaluations of bioconcentration (e.g., the OECD 305 test), a kinetic BCF can be defined as the ratio of uptake and elimination rates (k_1/k_2). However, the elimination rate for PFAS can be affected by saturable transporter-mediated renal uptake and clearance, as has been observed in rats (Han et al. 2012) and monkeys (Andersen et al. 2006), so that the k_2 rate becomes dose-dependent. Therefore, observations both in the laboratory and in the field (e.g., at highly contaminated sites) may be concentration-dependent and thus not representable by first-order kinetics.

In vitro and in silico methods to support modeling and assessment

As more focus is placed on molecular interactions between PFAS and biomolecules including proteins, transporters, and phospholipids, a variety of in vitro and analytical methods have been developed to support both laboratory assessments and the parameterization of mechanistic models. In vitro methods include cell- and vesicle-based assays to estimate and compare uptake rates into cells via passive diffusion and active transport (Luebker et al. 2002; Katakura et al. 2007; Nakagawa et al. 2008; Weaver et al. 2010; Herédi-Szabó et al. 2012) and protein-binding assays using equilibrium dialysis (Bischel et al. 2010, 2011), fluorescence displacement (Chen and Guo 2009; MacManus-Spencer et al. 2010; Yang et al. 2020), and other methods (MacManus-Spencer et al. 2010). A key challenge of these approaches is high variability across studies, which can lead to order-of-magnitude differences in estimated binding affinities for the same PFAS–protein combinations (MacManus-Spencer et al. 2010; Ng and Hungerbuehler 2014). Recently, a hybrid approach used size exclusion column coelution with nontarget mass spectrometry to identify L-FABP ligands from complex PFAS mixtures (Yang et al. 2020). The method identified 31 new L-FABP ligands from AFFF. Given the known importance of this protein to liver accumulation of PFAS in diverse organisms, this method illustrates the potential for combining nontarget analysis with bioaccumulation potential screening.

In silico methods have been developed to predict the behavior of PFAS at the molecular level in biological systems. These methods have an advantage of high-throughput testing and are not hindered by the lack of available standards and samples. Molecular docking and molecular dynamics are computational approaches originally developed for drug discovery and powerful tools for the prediction of protein–ligand interactions.

They have now been used to screen a number of legacy and emerging PFAS for binding with serum albumin (Salvalaglio et al. 2010; Ng and Hungerbuehler 2015), L-FABP (Zhang et al. 2013; Ng and Hungerbuehler 2015; Cheng and Ng 2018; Yang et al. 2020), and peroxisome proliferator–activated receptors, which are thought to be linked to some of the toxic effects of PFAS (Li et al. 2019). Predicted binding affinities from these kinds of studies are highly correlated with experimental observations and can be used to help parameterize mechanistic PBTK models. However, we note that the predicted binding affinities are overestimated for perfluoroalkylsulfonamide and may still require anchoring to some experimental binding data.

The role of phospholipids and related application of D_{MW} in PFAS toxicokinetic and tissue has not been fully realized. In vitro assay protocols to assess phospholipid partitioning using laboratory-prepared liposomes (Escher et al. 2000) are applicable to determining D_{MW} for PFAS. Solid-supported phosphatidylcholine membranes can also be applied for generating empirical data for D_{MW} for PFAS such as TRANSIL-XL membrane affinity assay kits (Droge 2019).

Finally, more empirical computational methods attempt to build predictive relationships between PFAS structure and their bioaccumulation potential or toxicity based on available data rather than mechanistic process–based approaches. These include quantitative structure–activity relationships (QSARs) for predicting key physicochemical properties for PFAS, as recently reviewed (Lampic and Parnis 2020) and a machine learning–based approach to classifying the potential bioactivity of thousands of PFAS (Cheng and Ng 2019). Hybrid in vitro/in silico approaches that generate data with which to develop a QSAR have also been used, for example, to tackle the important subject of PFAS mixture toxicity (Hoover et al. 2019).

SUMMARY AND KEY RESEARCH GAPS

We have reviewed current understanding of: 1) PFAS sources and environmental transport pathways, 2) analytical methods used to assess PFAS exposures and their strengths and limitations, 3) methods for assessing human exposures and the relative importance of different sources and pathways, and 4) PFAS bioaccumulation in wildlife. Changing geographic locations of PFAS manufacturing and the shifting chemical landscape pose a number of challenges for exposure assessments for humans and wildlife. Synthesis of analytical standards for newer PFAS has lagged behind their production and release, and thus nontargeted methods, suspect screening, and total fluorine assessments have all emerged as essential tools for understanding the total burden of PFAS in the environment,

humans, and wildlife. Although such data are now appearing across all media, more data are needed, particularly for food items, PCPs, dust, drinking water, and wildlife tissues that contain PFAS. For both humans and wildlife, additional research is needed to characterize the fraction of exposure originating from precursors that degrade into terminal PFAAs that have been linked to adverse health effects. Existing literature on time trends in PFAS in biological tissues suggest that although some legacy PFAS have decreased over the past 2 decades, the percentage of unidentifiable EOF has increased. There is a need for greater constraints on residual content (i.e., unbound fluorinated surfactants, monomers) in fluoropolymers, side-chain polymers, and ether-based polymers and for more data on their contribution to PFAS exposure. Measurement of polymers in environmental media remains an important challenge.

A major focus of past research has been contaminated sites where the highest concentrations in the environment and biota are often found. Moving forward, a better understanding of atmospheric PFAS sources and potential resulting exposures is needed, particularly as treatment systems are introduced for contaminated drinking water supplies. Integration of PFAS measurements into long-term atmospheric monitoring for pollutants would be valuable for measuring changes in atmospheric PFAS concentrations, aiding model development, and identifying vulnerable regions.

Occupational health effects associated with human PFAS exposures have been reported for individuals who work in fluorochemical production plants. There is a reasonable consensus that near contaminated sites drinking water is often the main pathway for human exposure to PFAS. However, data are still sparse on exposure sources for the general population and for communities where drinking water contamination has been remediated. Presently, there is a paucity of data on the indoor environment where many PFAS-containing products are found. Dermal exposures to PFAS from dust and PCPs warrant additional consideration given the extremely high concentrations reported for some PCPs and dust. There is general agreement that dietary exposure is the major contributor to population exposure for PFOS and PFOA, but there is more limited evidence for other PFAS, including that contributed by food processing and packaging. More information is needed about the contribution of food processing and packaging to PFAS in food.

Most prior work on human exposure pathways has not included statistically representative population surveys. Future PFAS researchers may benefit from establishing collaborations with existing representative populations. The field needs total exposure studies seeking to characterize all pathways and routes of exposure to PFAS including precursors. Empirical toxicokinetic data needed to describe PFAS partitioning among tissues, facilitated transport, and elimination half-lives are still limited or nonexistent for many PFAS and represent an important research need. As the focus of PFAS research shifts toward issues associated with emerging compounds, additional data for parameterizing toxicokinetic models represent a critical research need.

For wildlife exposures, a major challenge is adapting existing metrics for chemical accumulation to describe diverse PFAS. This data gap hampers efforts to develop mechanistic models for exposure and risk assessment of PFAS. Early PFAS bioaccumulation modeling suggested that some PFAS are efficiently eliminated though the gills of water-breathing organisms but biomagnify to a greater degree in air-breathing organisms because of limited lung–air exchange (Kelly et al. 2007). Mechanistic bioaccumulation models for PFAS are needed to understand the tissue accumulation patterns for novel PFAS, including neutral precursors and intermediates. Nontraditional approaches to probing molecular mechanisms of bioaccumulation such as protein association have important impacts on predicting tissue distribution and internal dose but also can have organismal effects if PFAS are able to perturb endogenous functions. Tissue and cellular partitioning of PFAS can be used to inform models; current wildlife monitoring is primarily limited to liver or muscle or blood.

Early research on PFAS releases and global transport was conducted as a partnership between industry and academia. We thus recommend greater transparency and collaboration between academia, industry, and government to prioritize and then improve understanding of global environmental releases of the thousands of PFAS structures present in global commerce. One example of improved transparency could be a commitment by industry to release information on the chemical structures and analytical standards for new PFAS used in commerce. Better characterizing PFAS exposure sources for humans and wildlife is an essential first step in the design of effective risk-mitigation strategies.

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