

Critical Review

Environmental Sources, Chemistry, Fate, and Transport of Per- and Polyfluoroalkyl Substances: State of the Science, Key Knowledge Gaps, and Recommendations Presented at the August 2019 SETAC Focus Topic Meeting

Jennifer L. Guelfo,^{a,*} Stephen Korzeniowski,^{b,c,1} Marc A. Mills,^{d,1} Janet Anderson,^e Richard H. Anderson,^f Jennifer A. Arblaster,^g Jason M. Conder,^g Ian T. Cousins,^h Kavitha Dasu,ⁱ Barbara J. Henry,^j Linda S. Lee,^k Jinxia Liu,^l Erica R. McKenzie,^m and Janice Willeyⁿ

^aDepartment of Civil, Environmental, & Construction Engineering, Texas Tech University, Lubbock, Texas, USA

^bAmerican Chemistry Council, Washington, DC, USA

^cAssociated General Contractors of America, Exton, Pennsylvania, USA

^dOffice of Research and Development, US Environmental Protection Agency, Cincinnati, Ohio, USA

^eGSI Environmental, San Antonio, Texas, USA

^fAir Force Civil Engineer Center, San Antonio, Texas, USA

^gGeosyntec Consultants, Huntington Beach, California, USA

^hDepartment of Environmental Science and Analytical Chemistry, Stockholm University, Stockholm, Sweden

ⁱBattelle Memorial Institute, Columbus, Ohio, USA

^jWL Gore & Associates, Elkton, Maryland, USA

^kDepartment of Agronomy, Purdue University, West Lafayette, Indiana, USA

^lDepartment of Civil Engineering, McGill University, Montreal, Quebec, Canada

^mDepartment of Civil and Environmental Engineering, Temple University, Philadelphia, Pennsylvania, USA

ⁿNaval Sea Systems Command, Laboratory Quality and Accreditation Office, Goose Creek, South Carolina, USA

Abstract: A Society of Environmental Toxicology and Chemistry (SETAC) Focused Topic Meeting (FTM) on the environmental management of per- and polyfluoroalkyl substances (PFAS) convened during August 2019 in Durham, North Carolina (USA). Experts from around the globe were brought together to critically evaluate new and emerging information on PFAS including chemistry, fate, transport, exposure, and toxicity. After plenary presentations, breakout groups were established and tasked to identify and adjudicate via panel discussions overarching conclusions and relevant data gaps. The present review is one in a series and summarizes outcomes of presentations and breakout discussions related to (1) primary sources and pathways in the environment, (2) sorption and transport in porous media, (3) precursor transformation, (4) practical approaches to the assessment of source zones, (5) standard and novel analytical methods with implications for environmental forensics and site management, and (6) classification and grouping from multiple perspectives. Outcomes illustrate that PFAS classification will continue to be a challenge, and additional pressing needs include increased availability of analytical standards and methods for assessment of PFAS and fate and transport, including precursor transformation. Although the state of the science is sufficient to support a degree of site-specific and flexible risk management, effective source prioritization tools, predictive fate and transport models, and improved and standardized analytical methods are needed to guide broader policies and best management practices. *Environ Toxicol Chem* 2021;00:1–27. © 2021 The Authors. *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

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¹These authors contributed equally to this work.

* Address correspondence to jennifer.guelfo@ttu.edu

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INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) are a broad group of chemicals that pose challenges on multiple fronts including identifying and prioritizing sources, identifying exposure pathways, characterizing their fate and transport, accurately detecting and quantifying their presence in various media, and grouping them in a pragmatic way that facilitates consistent communication of scientific results, risk communication, risk assessment, and regulatory decisions. In response to these and other challenges, the Society for Environmental Toxicology and Chemistry (SETAC) organized a PFAS Focus Topic Meeting (FTM) entitled “Environmental Risk Assessment of PFAS” in August 2019 in Durham, North Carolina, USA (Johnson et al., 2020). The objective of the FTM was to “review new and emerging information on PFAS and to formulate a roadmap for a risk assessment approach for PFAS.” The meeting sessions and workgroups were (1) environmental sources, chemistry, fate, and transport; (2) exposure assessment; (3) ecological toxicity; (4) human health toxicity; and (5) risk characterization. For each of the five topics, the meeting included a half-day of presentations from invited experts followed by one day of breakout group discussion. Session presentations addressed charge questions determined during FTM planning by the session chairs. More information on the meeting can be found in manuscripts associated with each meeting session in the

March 2021 issue of this journal (<https://setac.onlinelibrary.wiley.com/toc/15528618/2021/40/3>) and at the meeting link.

The present manuscript, authored by the session chairs and presenters, summarizes the FTM outcomes from “Session 1: Environmental Sources, Chemistry, Fate, and Transport.” We provide an overview of information presented to address the charge questions, and we synthesize key knowledge gaps and recommendations from the breakout groups. The structure of Session 1 is summarized in Table 1. Consistent with the Session 1 topics, the present manuscript summarizes outcomes of presentations and breakout discussions related to (1) primary sources and pathways in the environment, (2) sorption and transport in porous media, (3) precursor transformation, (4) practical approaches to the assessment of source zones, (5) standard and novel analytical methods with implications for environmental forensics and site management, and (6) classification and grouping from multiple perspectives. Notably, SETAC FTMs are intended to capture the state of the science and to facilitate exchange of information. As a result, this synopsis has several key characteristics the reader may wish to note: (1) studies that formed the basis of presentations and discussions are presented in more detail than other supporting literature or literature included in previous reviews; (2) information exchange captured diverse perspectives of business, government, and academia, as evidenced by the author affiliations; and (3) the manuscript does not represent a consensus on all aspects of the key state of the science by all

TABLE 1: Session 1: Environmental Sources, Chemistry, Fate, and Transport of Per- and Polyfluoroalkyl Substances (PFAS)^a

Charge question	Presentation
1. What are the primary sources/pathways of PFAS in the environment? Can we prioritize or rank exposure pathways from various sources?	PFAS in the Environment: Key Challenges and Strategies for Source-Pathway Evaluation and Prioritization (Jennifer L. Guelfo)
2. What chemical–physical properties are most useful in predicting fate and transport for PFAS? What patterns emerge that can be used to develop empirical models to estimate environmental fate and transport?	PFAS Source-Zones: How to Define Source-Strength? (Richard H. Anderson)
3. When characterizing the range of PFAS potentially in the environment, do we consider long-term transformation of PFAS precursors to perfluoroalkyl acids (PFAAs) and related degradation products?	Addressing Long-term Transformation of PFAS Precursors in the Environment (Linda Lee)
4. Are current analytical chemistry techniques adequate? What improvements could be made to improve process and precision (“future chemistry”)? What methods are needed in the toolbox to manage/remediate PFAS-impacted sites?	Analytical Techniques for Detecting and Measuring PFAS (Marc A. Mills) Identification of PFAS in the Environment (Mark Strynar) An Overview of PFAS Forensic Approaches (Kavitha Dasu) Analysis and Site Management (Janice Wiley)
5. How do we group PFAS that are potentially in the environment? How should fluoropolymers be categorized?	Toward a Systematic Characterization and Categorization of PFAS (Ian Cousins) How Should Polymers Be Categorized (Barbara Henry)
6. How can classification and grouping of PFAS be used in environmental risk assessment?	Classification and Grouping of PFAS for Environmental Risk Assessment (Jason Conder)

^aSession chairs: Jennifer Guelfo, Stephen Korzeniowski, and Marc A. Mills.

authors. We have summarized the science presented and captured key aspects where knowledge gaps or challenges still need to be addressed to move the scientific community closer to a consensus.

SOURCES AND PATHWAYS

PFAS sources and exposure pathways

A primary reason for the ubiquitous distribution of some PFAS in the environment is the diverse number of products and applications in which they are used, such as firefighting foams, textile and carpet products, food packaging, and nonstick and stain-repellant coatings (Buck et al., 2011; Kissa, 2001). However, the environmental occurrence of many of the 4730 PFAS identified by the Organisation for Economic Co-operation and Development (OECD) synthesis study on PFAS (OECD, 2018) remains unknown. Historically, PFAS were generated by both electrochemical fluorination (ECF) and telomerization (e.g., fluorotelomers or fluorotelomer-derived PFAS). More thorough reviews of PFAS synthesis, uses, and environmental presence are available elsewhere (e.g., Buck et al., 2011; Glüge et al., 2020). Sources of environmental release of PFAS include training, testing, equipment calibration and emergency response with aqueous film-forming foams (AFFF; Anderson et al., 2016; McGuire et al., 2014), industrial or manufacturing activities (Barton et al., 2006; Davis et al., 2007), solid waste disposal (e.g., landfills; Lang et al., 2017), wastewater treatment residuals (e.g., effluent, biosolids; Ahrens et al., 2011; Schultz et al., 2006; Sepulvado et al., 2011), and others. Collectively, releases have led to PFAS in surface water, groundwater, soil, and air. These direct exposures along with uptake in plants (Blaine et al., 2013, 2014) and other organisms (Christensen et al., 2017) followed by subsequent exposure at higher trophic levels have created human and ecological risks (De Silva et al., 2020).

Source data in the United States

When one is assessing exposure and risk, it is necessary to characterize known or potential sources of PFAS release to the environment. Currently there is not a consolidated, comprehensive, publicly available database of known and/or potential PFAS release sources on a national scale in the United States. However, there are databases that may be of use in assembling information on potential PFAS sources in the United States (Supporting Information, Table S1). Data from these sources require manual compilation by the user, and historical data are limited. Finally, we note that the US Environmental Protection Agency (USEPA) has made efforts to build a publicly available, interactive map of potential PFAS sources in the United States as part of their 2019 PFAS Action Plan (USEPA, 2019a).

Additional information related to known or potential PFAS release sources may be available through other federal, state, and local agencies in the United States. For example, a recent study that presented a risk-based geospatial framework for

investigation of PFAS impacts in groundwater using maps and data on airports, fire stations, and solid waste facilities is available from the Rhode Island Geographic Information System (Guelfo et al., 2018), and some states such as Florida (Florida Department of Environmental Protection, 2020) and Ohio have publicly available maps of approved biosolids application sites (Ohio Environmental Protection Agency, 2020). As mentioned, historical data regarding sources of PFAS release are limited. To address this gap, prior studies (Berenbaum et al., 2019; Guelfo et al., 2018) have used manufacturing directories, which are hard-copy archives. Using this technique, a database of manufacturing and industrial facilities was compiled for Rhode Island for a period encompassing the entire history of PFAS use and then filtered by North American Industry Classification System codes pertinent to PFAS by converting scanned copies of manufacturing directories to digital databases using the open-source data processing tool GEOREG (Guelfo et al., 2018). Information available from alternate sources may vary regionally and between databases; however, these regional and local resources may be able to fill important gaps in current US data sets.

Source prioritization approaches

Given the diversity and number of facilities that may be associated with PFAS synthesis, use, and disposal, a need exists for approaches to prioritize sources and to facilitate more efficient designs of monitoring and sampling programs. Prioritization approaches should recognize that not all facilities of a given sector will use or discharge PFAS. To date, few peer-reviewed studies have focused on source prioritization. Guelfo et al. (2018), used a geospatial approach to predict the likelihood of PFAS impacts on aquifers in Rhode Island using the source database just described. Sources in the database were sorted by type (e.g., landfills, fire training areas), and each source type was assigned a rank based on the likelihood of causing groundwater impacts. This was evaluated using literature data regarding the numbers and concentrations of PFAS (considering any PFAS identified in the literature) in groundwater impacted by each source type. The resulting ranks were coupled with the duration of operation of each facility to yield a score known as a Hazard Index (HI) for each source. Next, sources were assigned to a Vulnerability Index (VI) based on aquifer use. The HI and VI were combined to calculate a Risk Index, and these were mapped to identify areas with the highest likelihood of PFAS aquifer impacts. Geographic regions with an elevated density of sources situated in recharge zones were considered to have a greater likelihood for PFAS impacts relative to those with a lower source density and/or for which there is no beneficial use of aquifer resources (Guelfo et al., 2018). The resulting maps were compared with drinking water data in Rhode Island for the PFAS listed in the USEPA (2012a) Unregulated Contaminant Monitoring Rule 3 (UCMR3). The UCMR3 detections were shown to overlap areas of the region with the highest Risk Indices, or likelihood of PFAS impacts on the aquifer.

Hu et al. (2016) took a retrospective approach by evaluating how various major PFAS sources in the United States may have contributed to concentrations reflected in the nationwide UCMR3 database. Source locations compiled included military fire training areas (MFTAs), wastewater treatment plants (WWTPs), AFFF-certified airports, and the 16 industrial sites that participated in the USEPA Perfluorooctanoic Acid (PFOA) Stewardship program. Using a combination of geospatial and statistical analyses, the authors found a statistically significant relationship between the number of industrial sites, MFTAs, and WWTPs and increasing PFAS concentrations within a watershed (Hu et al., 2016). This approach can be applied to determine geographic regions that should conduct additional drinking water monitoring for public water systems and/or private wells not included in the UCMR3. These tools may also be used to identify watersheds where a significant fraction of PFAS impacts are not explained by existing sources and thus may be screened for additional sources of PFAS release.

Source prioritization synopsis

Existing approaches using publicly available data hold promise for large-scale screening of aquifer impacts (Guelfo et al., 2018). Validation of the resulting maps using a larger set of regional sampling data is needed, and the framework has only been applied for evaluating aquifer impacts. In addition, some sources of PFAS release such as biosolids application were not considered. Similarly, Hu et al. (2016) noted several potential limitations to their source prioritization approach including uncertainty in the locations of drinking water intakes and a lack of data regarding some source types (e.g., landfills and smaller industrial/manufacturing facilities). To our knowledge, similar studies investigating impacts on other media (e.g., air) and inclusion of other sources (e.g., biosolids application) are lacking, although there is potential for extension of similar approaches to these scenarios.

Challenges in source identification and prioritization

Historical releases of PFAS present a challenge in terms of assembling source databases. Because certain PFAS were unregulated for much of the history of use, this information is not always available. An additional complexity is the numerous types of facilities that could be linked with PFAS manufacturing, use, or disposal. Overall, information regarding *known* associations with PFAS and the historical information are limited. Historical and current information is available for regulated facilities; however, small facilities or those not associated with the relevant regulated activities (e.g., some agricultural facilities, biosolids application) will not be captured. Although state and local resources may be able to fill in some of these knowledge gaps, depending on the scale of the study, the information that such databases will cover may be limited. Considerable effort will be required to identify and compile available resources across multiple geographic regions (e.g., databases from regulatory agencies in multiple states)

including the basics of locating, assessing, and digitizing information. Additional information on releases associated with other sources (such as gray water reuse, compost application in home gardens, septic systems, and emergency response locations) and impacted by atmospheric deposition would even pose greater challenges. Lastly, in some cases, regulatory agencies may have access to information that is considered confidential business information and cannot be shared publicly.

SORPTION AND TRANSPORT IN POROUS MEDIA

When PFAS are discharged to the environment (incidentally or otherwise), their ultimate fate and transport are still considered critical knowledge gaps, which particularly applies to less or unstudied compounds (e.g., most polyfluorinated compounds) and to a lesser extent to more studied compounds including the perfluoroalkyl acids (PFAAs), which are not well predicted by available models. The PFAS include both polymers and nonpolymers. Nonpolymeric PFAS reflect a range of volatilities and solubilities such that transport in the air and water has occurred, and more soluble compounds are generally characterized by at least one ionic functional group and a highly fluorinated alkyl chain. The combination of the charged head group(s) with the hydrophobic tail results in surfactant-like behavior whereby the charged head group(s) interacts favorably with water whereas the hydrophobic regions of the PFAS do not, as discussed by the Interstate Technology and Regulatory Council (ITRC, 2018). These dual hydrophobic–hydrophilic properties are a key characteristic that has led to their multiple and diverse commercial and consumer uses and one that significantly affects PFAS fate and transport.

The retention of PFAS on soils has often been observed at field sites (e.g., Filipovic et al., 2015; Moody & Field, 1999), and the extent of retention is associated with PFAS hydrophobicity. Sorption of PFAS to a range of environmental solids has been studied for over a decade; most efforts have evaluated PFAA sorption, but more recent efforts have included a wide range of polyfluorinated compounds (e.g., Zhi & Liu, 2018). Both laboratory and field evaluations have determined that retention reflects multiple mechanisms across several phases, which include a wide variety of geochemical conditions and fluid–fluid interfacial partitioning. As discussed below, this research has demonstrated that subsurface transport depends on the molecular characteristics of the specific PFAS, fluid–fluid interfacial abundance, solution chemistry, and the amount and composition of both soil organic matter and variably charged clay minerals. Transport may be further complicated by kinetic limitations that prevent a system from reaching equilibrium.

The dual hydrophobic–hydrophilic surfactant behavior leads to interfacial accumulation processes that limit interactions between the fluoroalkyl chain and water. This can result in the formation of self-assemblages (e.g., micelles, hemimicelles, lamella, etc.) in which the alkyl chains are isolated within the self-assembled structures, span the air–water interface with the hydrophobic chain extending into the gas phase, or are sorbed

to a solid through a limited penetration mechanism whereby the polar head group(s) remains in the aqueous phase and the tail is sequestered within or onto a solid (e.g., soil mineral surface) or soil organic matter (e.g., as depicted in Guelfo & Higgins, 2013). Owing to the influence of the hydrophobic tail, increased PFAS chain length (or molar volume) has been associated with increased accumulation at air–water, oil–water, and soil–water interfaces (e.g., Brusseau, 2020; Guelfo & Higgins, 2013; Ju et al., 2008; Li et al., 2018; Lyu et al., 2018). Isotherms, conducted to evaluate the impacts of PFAS concentration on equilibrium sorption capacity, reveal that nonlinear Freundlich and Langmuir isotherm models often better describe experimental data (e.g., as discussed in Zareitalabad et al., [2013] focusing specifically on PFOA and perfluorosulfonic acid [PFOS]).

The seminal paper by Higgins & Luthy (2006) revealed that long-chain PFAA sorption under saturated conditions is strongly influenced by sediment organic carbon content (f_{OC}) and solution chemistry (i.e., polyvalent cations and pH); the f_{OC} -based trend was consistent with the traditional organic carbon–water distribution coefficient (K_{OC}) approach to evaluating hydrophobic organic contaminant sorption. Although other studies have observed similar trends among equilibrium sorption rates, that is, with f_{OC} , and solution chemistry factors (e.g., McKenzie et al., 2015; 11 PFAAs), these trends have not been universal (e.g., reviewed in Li et al., 2018; McKenzie et al., 2015). Similarly, PFOS sorption to mineral phases depends on surface composition, pH, ionic strength, and polyvalent cation concentration (e.g., Tang et al., 2010). The observed trends with chain length, organic carbon content, pH, and cation composition, suggest that a combination of hydrophobic, electrostatic, and ion exchange mechanisms collectively contribute to PFAS sorption to solids. To evaluate the relative importance of these factors, Li et al. (2018) statistically evaluated published saturated batch sorption results for 14 PFAAs and three polyfluorinated compounds and determined that, although individual studies observed trends with organic carbon, soil characteristics, or solution chemistry, these trends were not statistically significant when all studies were collectively considered and were better described by multiple regression models including organic carbon, pH, and total clay content as explanatory variables. In contrast, a meta-analysis of field data from hundreds of AFFF-impacted sites considering 15 PFAAs, perfluorooctane sulfonamide (PFOSA), and the 6:2 and 8:2 fluorotelomer sulfonates clearly demonstrated the importance of soil organic carbon content and implicated air–water interfacial sorption as significant retention mechanisms within the vadose zone (Anderson, Adamson, et al., 2019). This variability among equilibrium batch studies and field observations suggests that the sorption mechanisms and their kinetics are not fully understood and that multiple environmental parameters (i.e., air–water interfacial sorption) likely play a significant role in determining PFAS sorption capacity and resulting soil retention. Further studies are warranted to adequately develop the conceptual model and the relative importance and potential interaction among the multiple mechanisms.

As just mentioned, accumulation of some PFAS at air–water and nonaqueous phase liquid (NAPL) interfaces have also been studied and have revealed that multiple factors impact interfacial accumulation for nonsolid phases as well. Freundlich models were a better fit for five perfluoroalkyl carboxylic acids (PFCAs), three perfluoroalkyl sulfonic acids (PFSA), and the 6:2 fluorotelomer thioether amido sulfonate (FtTAoS) air–water interfacial uptake (Schaefer et al., 2019). Dissolved solids have also been consistently observed to increase PFAS surface uptake (Costanza et al., 2019; Schaefer et al., 2019). In the presence of NAPL, batch study results indicated that PFAS partitioned into the NAPL and also accumulated at the immiscible fluid interface (McKenzie et al., 2016). To overcome data gaps, Brusseau et al. (2019) developed a quantitative structure–property relationship to relate PFAS molar volume to air–water and oil–water interfacial adsorption for a range of structurally diverse PFAS for potential use in transport models that incorporate interfacial partitioning.

Although much uncertainty remains regarding the ultimate fate and long-term transport behavior of PFAS mixtures found at contaminated sites, there is consensus that most terrestrial PFAS contamination originates at the ground surface given the operational context of commercial and industrial uses (e.g., AFFF discharge from fire-training and emergency response actions and deposition from atmospheric manufacturing emissions (see ITRC [2020] for further discussion). Moreover, unsaturated soils are increasingly recognized as a significant reservoir of the total PFAS mass at contaminated sites due to the various soil retention processes just discussed (see Brusseau [2020] for a comprehensive meta-analysis of published data). Notwithstanding potential transient volatile intermediates resulting from polyfluorinated precursor biotransformation (e.g., Chen et al., 2019), this terrestrial PFAS contamination largely consists of nonvolatile PFAS (by definition due to the operational context) and, although influenced by multiprocess partitioning (see previous discussion), exclusively occurs in the dissolved phase (as depicted and described in Guelfo & Higgins, [2013]). Thus, the entire unsaturated soil profile is inherently relevant to PFAS site management, and the cumulative effect of all applicable soil retention processes defines the source strength of groundwater contamination as opposed to rate-limiting phase transfer kinetics typical for common hydrophobic organic contaminants. Notwithstanding the importance of the surface water transport pathway, this is important to the management of these sites because most tools and models have been developed for these more common hydrophobic organic legacy contaminants.

It follows, therefore, that the PFAS mass discharge (the cumulative mass flux, or mass flow/unit of cross-sectional area, over a given period of time) from soil to groundwater be considered as the primary metric of the vadose source strength. In fact, the groundwater remediation industry has long recognized groundwater mass flux/discharge as the authoritative metric of plume strength and the associated risk to down-gradient receptors (see ITRC [2010] for a comprehensive review and practical implementation guidance). Similarly, for

PFAS, mass flux across the capillary fringe reflects the cumulative effect and rate of all applicable vadose zone processes. Given that efforts to characterize the full nature and extent of PFAS contamination in the United States are still in their infancy, it seems prudent to capitalize on the benefits of flux-based assessments that have emerged from decades of groundwater remediation of petroleum hydrocarbons and chlorinated solvents (Horneman et al., 2017).

Conceptually, soil-to-groundwater mass discharge estimates (i.e., vertical flux from the vadose zone to the groundwater) could be compared with groundwater mass discharge estimates (i.e., horizontal flux within the saturated zone) across multiple control planes with increasing distance from the source, to prioritize remedial efforts. For example, if mass discharge from soil to groundwater exceeds the groundwater mass discharge, contaminated vadose zone soils should be prioritized for remediation to prevent ongoing leaching to groundwater and plume expansion. Conversely, if the groundwater mass discharge exceeds the soil-to-groundwater mass discharge, management and mitigation of the groundwater plume should be prioritized. Such flux-based comparisons provide a starting point for site management efforts that universally apply and are not complicated by evolving regulations.

In practice, soil-to-groundwater contaminant mass discharge is typically estimated using various vertical transport models (e.g., VLEACH, HYDRUS, etc.). These models are often parameterized based on total soil contaminant measurements with depth along with various soil physical and chemical property measurements and hydrologic parameters (e.g., precipitation) and are typically based on equilibrium partitioning (i.e., partition coefficient [K_d] = $K_{OC}f_{OC}$) for hydrophobic organic contaminants. Alternatively, analytical extraction methods are routinely used to simulate porewater concentrations from soil samples and use a variety of different protocols. However, these methods are likely overly conservative for PFAS, because of the multiple retention mechanisms (see previous discussion), the nonideal PFAA transport behavior due to complex sorption/desorption kinetics (Brusseau et al., 2019; Brusseau, 2020), and most importantly the fact that synthetic extraction protocols use (1) liquid-to-solid ratios in excess of pore volume (eliminating all air–water interfacial area), and (2) aggressive agitation, which disperses water-soluble aggregates and colloids.

Moreover, there are currently no universal methods to assess the extent and rate of precursor biotransformation, and linear isomers are retained to a greater extent than branched isomers for a given PFAS (e.g., Kärman et al., 2011; Labadie & Chevreuil, 2011). In the present report, precursors refer to polyfluorinated PFAS that may transform to intermediate PFAS and eventually to terminal, PFAA endpoints, thus affecting PFAA mass discharge (see discussion in the following main section, *Precursor Transformation*). Finally, air–water interfacial partitioning is highly dependent on the air–water interfacial area in soil voids (Brusseau, 2018), which is highly transient and complicated by soil structure (Peng & Brusseau, 2005), making vertical transport model parameterization operationally difficult. Although research is under way to develop methods to account for this multiprocess retention with nonideal behavior (e.g., Guo et al.,

2020), much uncertainty remains, and thus field validation is a prerequisite prior to a large-scale application. Alternatively, mass discharge can be estimated more directly by physically sampling soil porewater above the capillary fringe (or as deep as practicable) using lysimeters because PFAS concentrations in soil porewater with depth represent the PFAS fraction subject to migration to groundwater. Multiple soil lysimeters within vadose zone sources sampled at multiple time points have yielded rigorous estimates of contaminant mass discharge without modeling uncertainty (e.g., Del Campo et al., 2019).

Challenges

Accurately and reliably predicting PFAS retention in vadose zone soil continues to be a challenge. Among the mostly highly studied compounds (e.g., PFOA, PFOS, and to a lesser extent, other PFAAs), substantial variability in partitioning behavior (discussed previously) has been observed to date. The contributing factors are likely numerous and potentially include: (1) nonlinear sorption; (2) competition among PFAS and potentially other contaminants and constituents (e.g., other hydrophobic organic contaminants competing for soil organic matter, or ions—most notably anions such as chloride, sulfate, and carbonate—for ion exchange mechanisms); (3) soil organic matter characteristics (e.g., quality and accessibility); (4) differences between sorption/desorption kinetics; and (5) potential interactions among these considerations. The state-of-knowledge on air–water interfacial sorption is rapidly developing, but more studies that focus on complex systems (e.g., flow-through, poorly sorted media) are needed. Data are sparse for other PFAS including cationic, zwitterionic, and polymeric PFAS, which are frequently assumed to be less mobile, but supporting data are largely lacking. Furthermore, differences between laboratory-derived and field-derived equilibrium values have been observed, suggesting that poorly flushed sites can result in elevated K_d values, as observed by Anderson, Adamson, et al. (2019). Finally, field-scale heterogeneities coupled with challenges of unbiased field sampling at environmentally relevant concentrations will likely require substantial site knowledge, a carefully devised site conceptual model, and a supporting sampling plan to enable robust mass discharge estimates.

PRECURSOR TRANSFORMATION

Understanding the factors affecting the long-term transformation of precursors is important in predicting PFAA plume development and characterization, and necessary for site management. The term precursor is used loosely to refer to any polyfluoroalkyl substances, in part because there are typically multiple transformation steps to the terminal PFAAs with some relatively stable intermediates. The PFAA precursors should be limited to PFAS that have been experimentally proven to produce PFAAs. Otherwise, “suspected” PFAA precursor is the more proper term. Degradation rates, metabolites, and metabolite yields are a function of the individual PFAS chemical structure as well as environmental factors commonly known

(FtTAoS), sulfonamidoalkyl betaine (6:2 FTAB), and sulfonamidoalkyl amine (6:2 FTAA; Supporting Information, Table S2). For these fluorotelomers, transformation typically occurred at the hydrocarbon head, resulting in a range of polyfluoroalkyl products including fluorotelomer sulfonates (x:2 FTSA), which are common transformation intermediates (Figure 1B). Subsequent FTSA degradation requiring C–S cleavage is often the rate-limiting step, thus resulting in slow formation of PFAAs and consequently very low PFAA yields (Van Hamme et al., 2013; Wang et al., 2011; Zhang, Lu et al., 2016). Desulfonation is likely strongly linked to the presence or absence of desulfurizing bacteria, enzymes associated with the sulfur-regulated metabolism, and available sulfur sources (Shaw et al., 2019; Van Hamme et al., 2013). For example, 6:2 FTSA had a $t_{1/2}$ of less than 5 days in an aerobic sediment, resulting in high molar yields of perfluorohexanoic acid (PFHxA; 21%), PFPeA (20%), and 5:3 acid (16%; Zhang, Lu et al., 2016) as well as with a *Gordonia* sp. Pure culture in a sulfate-free media (Shaw et al., 2019). In contrast, 6:2 FTSA $t_{1/2}$ values were several months to years in aerobic sludge and soils (Wang et al., 2011). This may explain why elevated and persistent FTSA concentrations are often observed at sites where fluorotelomer-based AFFFs were used (Field et al., 2017).

Aerobic biotransformation summary for ECF-derived PFAS

Mixtures derived from ECF result in numerous structures and diverse mixtures. They often contain a sulfonamide group immediately prior to the perfluoroalkyl chain ($F(CF_2)_n-S(O)_2NH-$), or similar amide-containing equivalents ($F(CF_2)_n-C(O)NH-$), and biotransformation typically ends with PFSA or PFCAs (Benskin et al., 2013; Mejia-Avenidaño et al., 2016; Chen et al., 2020; Figure 1C). Some ECF-derived PFAS also contain hydrolysable groups, for example, perfluorooctane sulfonamido ethanol-based phosphate esters (mono-, di-, and tri-). The initial transformation, often microbially mediated, produces N-ethyl perfluorooctane sulfonamido ethanol (EtFOSE; Figure 1; Benskin et al., 2013; Mejia-Avenidaño et al., 2015; Liu et al., 2019). Subsequent EtFOSE biotransformation involves breakdown of its nonfluorinated segment to produce acid, aldehyde, or amine intermediates that lead to PFOS (Figure 1D); the highest PFOS molar yield reported was 34% in an 81-d soil-carrot mesocosm (Zabaleta et al., 2018). Likewise, perfluorooctane amido quaternary ammonium salt (PFOAAmS) and perfluorooctane sulfonamide quaternary ammonium salt (PFOSAmS) undergo aerobic transformation despite strong sorption to soil, to produce PFOA or PFOS, respectively. It is reasonable to assume that most ECF-derived PFAS will eventually break down, but with $t_{1/2}$ varying vastly depending on the nonfluorinated structure and environmental conditions. The ECF-derived PFAS contain branched isomers, which has been proposed as a forensic approach for source tracking (Benskin et al., 2009). However, unique and varying isomer-specific biotransformation kinetics of PFOS precursors strongly influence PFOS isomer ratios and may limit source tracking potential (Liu, Zhong, et al., 2019).

Anaerobic biotransformation summary

Anaerobic transformation potential remains mostly unknown except for a few fluorotelomers, which indicates low transformation potential to PFAAs (Supporting Information, Table S3). For example, methanogenic FTOH biotransformation yielded primarily x:2 or x:3 polyfluoroalkyl acids and less than 1% yields to PFCAs (Zhang et al., 2013; Zhang, Lohmann, et al., 2016). Only minor changes to 6:2 FtTAoS was observed under nitrate-, sulfate-, and iron-reducing and methanogenic conditions, with the perfluoroalkyl chain remaining intact and no production of FTOH or PFCAs (Field et al., 2017; Yi et al., 2018). The compound 6:2 FTSA did not undergo any detectable transformation in anaerobic sediment after a 100-d incubation. The ECF-derived PFAS are likely also highly persistent under anaerobic conditions.

Field observations

Our understanding of PFAS transformation and temporal trends from field observations are confounded by the occurrence of numerous PFAS species, changing formulations and sources, sample heterogeneity, and multiple environmental processes and pathways. Nevertheless, limited studies have provided evidence that in situ precursor transformation occurs including higher PFAA levels in wastewater effluents than influents (Anderson et al., 2016). Mejia-Avenidaño et al. (2017) tracked the PFAS patterns in AFFF-impacted surface soils. The summed concentrations of 33 target PFAS were much lower after 2 years, but the relative proportion of PFAAs reflected an increase, consistent with precursor transformation. McGuire et al. (2014) concluded that historical remedial activities influenced spatial distributions of PFAS in a former fire-training area. Notably, the unexpected elevated ratio of perfluorohexanesulfonic acid (PFHxS) to PFOS was best explained by precursor transformation likely caused by biosparging-enhanced microbial activities.

Other observations and data gaps

Little is known about factors that lead to a particular degradation pathway among several that have been observed. Limited laboratory data suggest that some PFAS may degrade from natural abiotic processes or become more strongly or irreversibly bound over time, but little is known about these mechanisms and their influence on their fate and transport or impacts on remediation systems (Dasu et al., 2012; Liu et al., 2007, 2010; Wang et al., 2009). Changing redox states within groundwater also adds additional complexity. Shifts from aerobic to anaerobic due to degradation of co-contaminants may slow precursor degradation, whereas PFAS-contaminated anaerobic groundwater entering an aerobic receiving water might be expected to increase biotransformation of mobile intermediates. Likewise, remedial activities such as biosparging for enhanced biotransformation of other contaminants may result in an expanded PFAA plume (e.g., Weber et al., 2017).

Key challenges

The complex dynamics involved in biotransformation, particularly at the field scale, make it difficult to accurately predict the strength of a precursor source zone of varying age to downstream concentrations of the more mobile PFAAs. To improve predictability, better characterization of biotic and abiotic degradation pathways in relevant media are needed for both legacy and newly emerged precursors. Overarching success will be limited by the availability of adequate analytical methods and standards to support PFAS biotransformation research.

ANALYSIS

The PFAS analysis required to characterize sources, delineate contaminated sites, manage emission and discharges, and understand their fate and transport is challenging due to their unique chemical and physical properties. Their uniqueness has led to a suite of specific considerations for environmental sample collection, sample processing, and analytical measurements in complex environmental matrices. In addition, industrial innovation has led to a growing number of PFAS subclasses, and site investigations have revealed precursor transformations to other PFAS as well as releases of previously unknown PFAS. Due to the widespread use and disposal of PFAS-containing materials in a broad variety of consumer and industrial products, PFAS are found in many environmental compartments, and thus exposures to humans and ecological receptors may occur via many pathways and media. Finally, a growing body of exposure routes and toxicological effects is being documented with potential adverse human and ecological impacts at low concentrations relative to other environmental contaminants.

Environmental measurements for PFAS have largely relied on mass spectrometry (MS)-based techniques following chromatographic separation of media extracts (Lai et al., 2018; Nakayama et al., 2019; Schwichtenberg et al., 2020). Extraction techniques utilize sorbents and/or solvents to isolate and concentrate the PFAS analytes, which is necessary due to the low concentrations of concern and interferences commonly found in these complex media. The most common methods of extractions are effective for a limited number of target analytes based on the chemical structure and associated functional groups. Although further research may result in some additional innovations and expansion of target analyte lists, methods will continue to be challenged to fully characterize sources, fate, and transport, and to evaluate the effectiveness of management strategies.

Chromatographic separation techniques, such as liquid and gas chromatography, allow for resolution of the resulting complex mixture in the solvent extracts such that they can be detected and either quantified in targeted analysis or identified in nontargeted analyses (NTA). Targeted analyses are used to quantify the concentrations of specific PFAS within a matrix for monitoring, source characterization, and managing PFAS in environmental media and during treatment and remediation. The NTA method allows for identification of unknown

compounds or compounds not identified for quantification. Chromatographic separation enables a more accurate identification of unknown compounds for which higher levels of confirmation are attained by matching both MS and tandem MS (MS/MS) spectra with an appropriate MS/MS library, with the highest level of confirmation being attained when matched with a standard, if one is available (Schymanski et al., 2014).

Standard methods

Standardized methods available for quantifying PFAS in relevant environmental matrices are limited. The USEPA has developed, validated, and published three analytical methods for drinking water matrices only, to support the targeted analysis of a combined total of 29 PFAS using methods 533, 537, and 537.1 (Supporting Information, Table S4; USEPA, 2020a). These methods use solid-phase extraction (SPE) to isolate the target analytes from the drinking water samples. The USEPA method 537 was first published in 2008 in support of the USEPA's (2015) UCMR3. In 2019, the USEPA revised method 537, with the addition of analytes and methodological updates, and published the update as method 537.1 (USEPA, 2019b). In 2019, the USEPA published method 533 to allow for quantitation of shorter chain PFAS in drinking water (USEPA, 2019c). These USEPA drinking water protocols were developed to provide accurate, precise, and robust methods; they have been validated by many laboratories and peer reviewed for drinking water matrices only.

For nonpotable aqueous samples, the USEPA (2019d) recently released a draft multilaboratory-validated protocol, "EPA SW-846 method 8327: Per- and polyfluoroalkyl substances (PFAS) using external standard calibration and liquid chromatography/tandem mass spectrometry (LC/MS/MS)," in a two-phase study for 24 PFAS analytes and 19 isotopically labeled PFAS surrogates in four aqueous matrices of reagent water, surface water, groundwater, and wastewater effluent. The protocol is based on direct-injection LC-MS. After the public comment period, the USEPA will adjudicate comments and revise the method accordingly before finalizing and incorporating the method into the Test Methods for Evaluating Solid Waste: Physical/Chemical Methods compendium (EPA SW846).

For other environmental matrices, methods have been published in the peer-reviewed literature as well as through ASTM International (formerly known as the American Society for Testing and Materials). The ASTM International methods for solids (D7979) and waters (D7968) have been successfully single-laboratory validated. In addition, other international organizations are developing methods and protocols; however, many will require further testing and validation. Finally, the US Department of Defense (DoD, 2019) has published quality assurance guidance for PFAS as part of the DoD/Department of Energy (DOE) Quality Systems Manual for Environmental Laboratories, under Table B-15. The guidance is currently being used by commercial laboratories to meet quality assurance requirements in support of the DoD.

With PFAS' unique properties, their widespread use, and their effects at low levels, environmental measurements for PFAS continue to be a challenge and require novel methods, rigorous quality assurance and quality control measures, and state-of-the-art equipment operated by highly trained analysts. Currently, the analytical methods for PFAS are evolving quickly as the need has expanded to include additional matrices, more target analytes as well as NTA, and evolving chemical formulations. Currently, there are standard analytical methods for selected PFAS in drinking water matrices. However, there are on-going efforts by federal and state agencies, academia, and other groups to provide more methods and tools to efficiently and cost-effectively characterize PFAS and manage PFAS-impacted media.

Analysis and site management

In addition to targeted analyses that currently rely primarily on LC–MS/MS methods, analytical techniques such as total oxidizable precursor (TOP) assay, particle-induced gamma-ray emission (PIGE), adsorbable organic fluorine (AOF) or extractable organic fluorine (EOF) paired with combustion ion chromatography (AOF/CIC; EOF/CIC), and high-resolution mass spectrometry (HRMS) for NTA can aid in source delineation and treatment monitoring efforts (Koch et al., 2021; Schultes et al., 2019; Schulze et al., 2020).

The TOP assay estimates the oxidizable precursors in a sample that transform into a defined targeted list of PFAAs (Houtz & Sedlak, 2012; Houtz et al., 2013). Its ability to determine total PFAS concentration of a sample is limited by the list of PFAAs quantified, the ability of the process to oxidize every precursor in the sample to the limited targeted analytes, and the ability to achieve complete oxidation of precursors. It should be noted that oxidative conversions that occur as a result of the TOP assay may not be environmentally relevant (e.g., conversion of PFSA precursors to PFCAs). Commercially available TOP assays have generated data used in designing treatment processes by estimating the PFAS load the system will encounter and the change-out frequency of treatment media.

The PIGE technique determines the total elemental fluorine content present on a solid surface (0–0.22 mm). Therefore, liquid samples must undergo an extraction process prior to analysis (Ritter et al., 2017). Additional steps can be added to both solid (e.g., soil) and liquid extraction procedures to remove inorganic fluorine prior to analysis, rendering it a useful tool to determine the total organofluorine content of a sample. However, it is important to consider that the sample may contain other sources of organofluorine beside PFAS (e.g., pharmaceuticals, pesticides).

The EOF technique utilizes solvent extraction processes to separate organic fluorine from inorganic fluoride in a solid or aqueous sample, whereas with AOF, an aqueous sample is passed through a sorbent material that retains PFAS (Wagner et al., 2013). Both sample preparation procedures have limitations. The individual PFAS that are extracted by EOF are dependent on their affinity for the solvent used, and AOF is

limited by the affinity the individual PFAS has for the sorbent used. The organofluorine compounds extracted by both techniques are then combusted and quantified as fluoride by ion chromatography. The AOF/CIC method is not currently widely utilized for PFAS investigations due to its inability to distinguish between PFAS and non-PFAS fluorine-containing compounds and relatively high detection limits (parts per billion range) compared with contemporary targeted methods.

The NTA technique using HRMS methods is rapidly becoming available as new and innovative approaches are being used to identify previously unknown PFAS. More details on NTA are provided in the next section, *High-resolution mass spectrometric tools for identification of PFAS*. These methods can tentatively identify a much greater number of analytes within samples compared with targeted methods. A statistically significant identification of a compound in the sample provides qualitative information on a more diverse list of analytes but may not be able to be quantified similar to a targeted method. However, if the response of the tentatively identified PFAS is compared with the response of known PFAS, a semi-quantitative estimate can be determined (Nickerson et al., 2020). Due to the lack of standardization of the protocols required for consistent identification and qualitative determination using HRMS, use of data generated by these techniques has been greatly limited to investigative and research efforts. The utility and acceptance of these innovative NTA analytical techniques could be widely expanded through the further optimization, validation, and publication as standard methods. Utility and acceptance are further facilitated through documentation of the method's performance over a suite of samples exhibiting the range of characteristics that may be encountered for the media type included in the scope of the method and the standardization of the protocols required for consistent identification and qualitative determination by HRMS systems obtained from different manufacturers.

In addition to the formal standardization of these techniques, additional analytical method needs have been identified. Screening methods that could be deployed in the field to produce fast, reliable, qualitative, and/or quantitative determination of individual PFAS and total PFAS could reduce costs, time, and the number of off-site sample analyses. It is anticipated that screening techniques would be primarily useful in evaluating high-concentration samples or in routine monitoring of treatment systems requiring routine operational data. Additional sampling techniques such as passive sampling protocols optimized for PFAS, are needed to understand the spatial and temporal variability of groundwater and surface water. Evaluation of PFAS in other media has also been identified as an immediate need. The determination of PFAS in ambient air, as well as gaseous emissions and products of incomplete combustion (PICs), is of particular interest given the use of thermal treatment technologies for end-of-life disposal of spent treatment media, PFAS-contaminated media, and PFAS-containing products (e.g., plastics and AFFFs). In addition to both targeted and nontargeted PFAS analysis, the investigation of non-PFAS byproducts resulting from the thermal treatment of PFAS is of concern.

HRMS tools for identification of PFAS

Many individual compounds found in mixtures of legacy and new alternatives PFAS are unknown, and/or information on their chemical composition is proprietary. The HRMS method can be applied to identify the structures of unknown PFAS present in environmental samples. The HRMS tools include a combination of two techniques, offering better selectivity and sensitivity. These instruments can perform a full scan in addition to the multistage MS fragmentations (MSⁿ) experiments and provide high mass resolution, which is the ability to distinguish between ions slightly different in mass-to-charge ratio, and thus give accurate mass measurements. An advantage of the HRMS data acquired in full-scan mode is that it can be archived, and retrospective analysis or data mining can be performed for compounds of interest in the future. The discovery of a new alternative, hexafluoropropylene oxide dimer acid (HFPO-DA) in the surface water near Cape Fear River, North Carolina (USA), resulted from such retrospective analysis (Strynar et al., 2015). The NTA tools are often used for the qualitative analysis and complete characterization of the unknown analytes or nontargeted analytes with high mass accuracy.

Commonly used HRMS instrumentation applied for aqueous and extractable PFAS includes LC/quadrupole–time of flight/ion trap coupled to time-of-flight (QTOF/IT–TOF)–HRMS. Alternatively, to identify more volatile PFAS present in the samples, gas chromatography (GC) coupled to TOF–HRMS techniques can be applied (Rewerts et al., 2018). For example, GC–TOF–HRMS techniques are applicable to measure the volatiles generated as PICs during the thermal treatment of PFAS.

Sample preparation for NTA

Most environmental samples require preconcentration steps, and it is essential to understand the importance of sample preparation to avoid bias from extraction for NTA. Different functional moieties, chain lengths, degrees of fluorination, linear or branched chains, and so on, make identification of detected, unknown compounds a challenge. Researchers have used novel techniques to capture a broader range represented by these chemistries and minimize unintended bias during sample preparation (Liu, D'Agostino, et al., 2019). D'Agostino and Mabury (2017) developed two mixed-mode ion-exchange SPE methods (to be used before analysis) to fractionate PFAS as cationic and zwitterionic, anionic, and neutral fractions followed by direct infusion analysis in both the negative and positive electrospray (ES) ionization modes. Backe et al. (2013) reported a nonaqueous large-volume direct injection method and applied novel chromatographic separation of different ionic species in AFFF by orthogonal chromatography using cation exchange (silica) and anion exchange (propylamine) guard columns connected in series to a reverse-phase (C18) analytical column. However, in a recent field study in which the groundwater samples were extracted using the weak anion exchange solid-phase cartridges, the authors found capture of all the anionic, neutral, zwitterionic (6:2 FTAB),

and cationic species (fluorotelomer sulfonamide propyl N,N-dimethyl amine, 6:2 FTSaAM) with recoveries greater than 50% (Dauchy et al., 2019). That study indicates that the routine PFAS extractions using weak anion exchange cartridges are also capable of capturing both amphoteric and cationic species with decent recoveries.

The ability to more completely characterize the broad PFAS mixtures depends on the functional groups present on the individual PFAS and their ability to accept or lose a proton (cation) in positive and negative ionization modes, respectively. Functional groups (anionic species) such as carboxylates and sulfonates lose a proton (cation), and the cationic and zwitterionic functional groups (e.g., species containing amines) tend to accept a proton. For the targeted analysis of the known anionic PFAS, such as carboxylates and sulfonates, MS/MS is commonly operated in ES-negative ionization mode. However, given the complex PFAS chemistry commonly found in products and the environment, performing NTA only in negative ionization mode may not detect some PFAS. For example, AFFF and other commercial surfactant formulations contain zwitterionic, cationic, anionic, and neutral fluorinated chemicals (Barzen-Hanson et al., 2017; D'Agostino & Mabury, 2017; Ruyle et al., 2021), some of which are better detected with other ionization modes. Given that many PFAS formulations and environmental mixtures contain diverse chemistries and to ensure a better and more complete characterization of unknown PFAS, samples should be analyzed in both ionization modes.

NTA analysis data filtering

While NTA is being performed, data are acquired using a full-scan mode, resulting in acquisition of a large complex MS data set for each run. These dense, complicated file sets are challenging to process and filter. Therefore, informed data filtering approaches are used by many researchers to identify the unknown compounds of interest from the acquired data (Barzen-Hanson & Field, 2015; Barzen-Hanson et al., 2017; Bugsel & Zwiener, 2020; McCord & Strynar, 2019; Strynar et al., 2015; Yu et al., 2020). Approaches developed in the pharmaceutical fields to identify drug metabolites and proteins from environmental samples commonly use mass defect filtering of complex MS data acquired using HRMS tools (Sleighter & Hatcher, 2007; Zhu et al., 2007). An important feature characterizing the majority of PFAS is a negative mass defect (Bugsel & Zwiener, 2020), and elements in PFAS include those with a negative mass defect (F, Cl, Br, I, O, S, and P). Given the high degree of fluorination of most PFAS, the negative mass defect is more resolved and is a useful feature for identifying individual PFAS.

Another common NTA approach is exploiting a homologous series. A homologous series occurs in certain chemical classes that differ by an exact mass of a chemical unit that occurs as repeating units (for example, a mass difference of 14 m/z for CH₂ in petroleum hydrocarbons of different chain lengths; Hughey et al., 2001). Similarly, PFAS containing repeating units of CF₂ groups with a mass difference of

49.9968 Da have been used to identify homologous series by calculating the CF_2 -normalized Kendrick mass defect (KMD; Barzen-Hanson & Field, 2015; Barzen-Hanson et al., 2017; Newton et al., 2017; Strynar et al., 2015). The KMD analysis of other repeating chemical units can also be performed, for example, CH_2CF_2 units (64.0125 Da) for fluorotelomer chemistry or CF_2O (65.9917 Da) units for PFAS with ether oxygen homologs (Newton et al., 2017; Strynar et al., 2015). Many researchers have applied automated data filtering tools such as R-Homolog script (Barzen-Hanson et al., 2017; Loos & Singer, 2017) or MATLAB (Yu et al., 2020) to identify the homologous series. Some of the characteristic fragment ions, adducts, and dimers have been identified to aid in PFAS structural elucidation and confirmation, such as CF_3^- , C_2F_5^- , C_3F_7^- , $\text{C}_2\text{F}_5\text{O}^-$, CO_2^- , SO_3^- , CF_2SO_3^- , and HF^- (Supporting Information, Table S5; Barzen-Hanson et al., 2017; Strynar et al., 2015). Further confirmation of the structures can be performed by comparing the structures and the fragmentation pattern with available comprehensive databases (e.g., the USEPA CompTox Chemistry Dashboard [USEPA CompTox database; 2020b] or the Network of Reference Laboratories, Research Centres, and Related Organisations for Monitoring of Emerging Environmental Substances [NORMAN] Suspect List; Getzinger et al., 2021). Suspect screening analysis allows for *in silico* MS/MS predictions and matching with the available PFAS databases. However, the complete structural confirmations and quantitative measures can only be performed with the authentic standards. The HRMS tools are often qualitative, and data processing is time consuming and labor intensive, which limits their use in routine sample analysis.

Application of analysis and fate/transport principles to PFAS environmental forensics

Distinct distributions of specific compounds associated with individual sources are referred to as source fingerprints or signatures. These source signatures can be related to environmental samples to identify, allocate, or characterize the fate and transport of PFAS from specific sources of contamination at a particular site. Historically, forensic approaches are commonly used for legacy contaminants, such as petroleum hydrocarbons, for which a more extensive selection of target analytical standards are available to fully and accurately define the contaminant source profile. Forensic analysis of these legacy contaminants is performed using source contaminant distribution patterns or diagnostic ratios for compounds within a given source signature profile (Riccardi et al., 2013; Wang & Fingas, 2003). Applying these approaches, however, is not as straightforward for PFAS source identification compared with more traditional environmental contaminants. The knowledge of PFAS chemistry is important for understanding the sources of PFAS present at a particular site. To assess source attribution for the PFAS found in environmental matrices, understanding the manufacturing history, timing of release, potential sources, degradation products, isomer profiles, environmental fractionation, and fate and transport is very important (Benotti et al., 2020; Dorrance et al., 2017).

Typically, environmental samples consist of comingled PFAS sources. For example, at an AFFF-impacted site, there could be different AFFF formulations from the two primary manufacturing-based sources (ECF or telomer based), as well as from different sources (e.g., landfill leachates). For example, WWTP influents contain a mix of multiple domestic and industrial waste sources of PFAS. Landfills also contain a mix of domestic, industrial, and construction and demolition waste, which may all contain PFAS from varying sources and formulations. Forensic analysis of such complex comingled sources requires multiple lines of evidence to better understand source identifications and differentiations. These include (1) PFAS isomer profiles and chain length ratios; (2) unique source-specific markers (Charbonnet et al., 2021; Guelfo & Adamson, 2018; McGuire et al., 2014; Swedish Chemicals Agency [KEMI], 2015); and (3) advanced analytical tools, such as HRMS (e.g., NTA and suspect screening methods) to identify and characterize a broad suite of PFAS analytes (Charbonnet et al., 2021; Ruyle et al., 2021). Selection of a broad suite of analytes will be helpful for understanding the signatures of multiple PFAS sources. These advanced MS tools are needed for the structural identification of unknown PFAS chemicals, which may provide the necessary information about precursors, unknown new alternatives, or the biodegradation products (Hopkins et al., 2018; Lin et al., 2017; Munoz et al., 2017). Using only targeted PFAS analysis does not provide sufficient information, because many of the sources have the same persistent PFAAs, making it difficult to effectively differentiate sources using such limited data.

Isomer profiles and ratios of chain lengths

The chemical signature of PFAS varies based on the manufacturers, intended applications, and fate and transport once released into the environment. The PFAS are commonly produced by two methods: ECF and telomerization. The ECF process results in a mixture of linear and branched fluorinated molecules of various carbon chain lengths (ratio of linear to branched ~70:30), and both even and odd carbon chains, whereas the telomerization process produces linear isomers with an even number of carbon chains (Buck et al., 2011). Isomer profiles, such as branched or linear isomers, and the odd or even chain lengths provide the primary information about PFAS manufacturing sources. An analysis of concentration ratios of several PFAS pairs was performed on a nationwide occurrence data set collected for UCMR3 by the USEPA, and it was found that PFAS mixtures in groundwater were likely dominated by PFASs, based on the ratio of PFSA and perfluoroalkyl carboxylic acid (PFCA) concentrations to total PFAS concentrations (Guelfo & Adamson, 2018).

Enrichment of linear compared with branched PFOA isomers in environmental samples may indicate the telomer source attribution (Benskin et al., 2009). Branched and linear isomers will have different physical and chemical properties (water solubility, sorption, transport behavior, and bioaccumulation potentials) and, hence, are expected to show different fate and transport behavior (Kärman et al., 2011). The isomer

profiles present at the source of contamination will change and redistribute after a certain distance from the source, and in addition, the transformation of different precursor isomers may be different (Adamson et al., 2020; Anderson et al., 2016; Guelfo & Higgins, 2013; Liu, Zhong, et al., 2019; Nickerson et al., 2021). Therefore, measuring PFAS at a distance from the source may show different isomer profiles compared with the source, resulting in misinterpretation of sources. The environmental partitioning of the isomers might be different, because the branched isomers tend to enrich in the water phase, whereas the linear isomers are held back in the soil, indicating telomerization sources in the soil profile (Kärman et al., 2011). Most studies have reported mainly on linear PFAS isomers, because many of the branched isomers are unknown, and standards are not available. However, quantifying only linear isomers leads to underestimation of PFAS concentrations; hence, it is important to include the quantitation of branched isomers during analysis following USEPA Method 537.1 guidelines (USEPA, 2018). Similarly, precursor transformation at the source can occur, resulting in the formation of PFAAs. These precursor transformation products, with different physical and chemical properties, tend to redistribute at a distance from the source, showing different concentration and composition profiles (McGuire et al., 2014). Evidence also suggests that air deposition of some PFAS could be considered (Ahrens et al., 2011; Dauchy et al., 2012). The aerosols produced over the aeration basin from WWTPs could also result in emissions to the atmosphere and nearby soil contamination (Ahrens et al., 2011; Dauchy et al., 2017). Hence, it is important to consider the environmental transport/fractionation of PFAS to assess the source attribution of PFAS at a contaminated site. This indicates that the signature at the sources might be different compared with the sample locations away from the sources; hence, many factors and lines of evidence need to be considered in understanding and differentiating the source attributions.

Source-specific markers

The knowledge of PFAS manufacturing methods and source-specific signature chemistries is important to understand the source attribution to a particular PFAS-contaminated site. The variety of commercial and industrial applications in which PFAS are used leads to an array of potential sources and source signatures. Polyfluoroalkyl phosphate esters and PFCAs are found predominantly in personal care products, such as cosmetics and sunscreens (Fujii et al., 2013). For surface treatments of commercial products, side-chain fluorinated polymers, polyfluoroalkyl phosphate esters/phosphonic acids, perfluorinated/polyfluorinated methacrylate polymers/monomers, perfluorinated/polyfluorinated alkyl sulfonamide derivatives, and perfluorinated/polyfluorinated alkyl thiols are found as the dominant analytes for many of these applications, prior to the switch to alternate chemistries (KEMI, 2015). These alternate chemistries include some of the shorter chains of these chemistries, 6:2 fluorotelomer derivatives, and perfluoropolyesters (KEMI, 2015). The phase-out

of the longer chain PFAS by global manufacturers and increasing use and purity of shorter chain PFAS have led to quantifiable increases in concentrations of shorter chains and decreases in longer chains at some of the areas investigated. Hence the changes in manufacturing of PFAS over time complicate evaluations of site data that may have been impacted historically.

Many PFAS end up in the WWTPs and landfills by either use or disposal. Some of the precursors undergo biotransformation in the landfills and during the WWTP processes, resulting in higher concentrations of persistent PFCAs and PFSA in effluents compared with the influents (Loganathan et al., 2007; Schultz et al., 2006; Xiao et al., 2012). As discussed in *Precursor Transformation*, commonly found biotransformation products are n:3 fluorotelomer acids, n:2 fluorotelomer acids, and N-alkyl perfluoroalkylated sulfonamidoacetic acids. The latter are the precursors of PFOS and intermediate transformation products of FOSE (Rhoads et al., 2008). Detection of these biotransformation products could be considered as source-specific markers indicating the waste-related sources such as WWTP and landfills (Lang et al., 2017).

Application of statistical tools for source identification

Many statistical analysis tools have been applied to identify sources of PFAS contamination. Bivariate and multivariate analyses, principal component analysis (PCA), and grouping/clustering of the PFAS analytes under different sources along with geospatial analytical tools have been used to understand source attribution (Guelfo & Adamson, 2018; Hu et al., 2016; Kibbey et al., 2021; Zhang, Lohmann et al., 2016). Multivariate statistical analysis is commonly used to identify the composition profiles of PFAS analytes associated with different sources. Analysis by PCA allows for the visualization and analysis of data by revealing clusters of data associated with similar source profiles. Hierarchical clustering is used to generate clustered subgroups associated with similar source profiles. Zhang, Lohmann et al., 2016 applied a combination of PCA and hierarchical clustering and identified three statistical groups of PFAS clusters. Furthermore, source attribution of these three clustered groups was performed based on the geospatial analysis data of watersheds (Zhang, Lu, et al., 2016). The application of generalized source clustering based on geospatial analysis for probable broader source categorization, might have limitations due to the lack of knowledge about the unique signatures of diverse sources based on the common persistent PFAAs (few known analytes) and the presence of comingled sources (Charbonnet et al., 2021).

Advanced statistical tools such as the supervised machine learning tools have been applied to identify the source of PFAS using targeted analysis concentration data for a few PFAS (PFOS, PFHxS, PFOA, PFHpA, and PFHxA; Kibbey et al., 2020, 2021). Among the different machine learning tools explored, the Extra Trees approach and the deep neural network have exhibited high performance for classification of samples from a

range of AFFF and non-AFFF sources (Kibbey et al., 2020, 2021). The Extra Trees method creates extremely randomized decision trees by selecting random thresholds for features, rather than searching for optimal values (Kibbey et al., 2020; Strozier et al., 2016). These decision trees are based on binary choices; trees are trained through dividing training data sets by identifying the magnitude of a single feature that most completely separates the data set into two parts (Kibbey et al., 2020; Strozier et al., 2016). However, the composition of the limited PFAS analytes measured can vary substantially at a site as a result of mobility differences based on the environmental and site-specific conditions. By considering the broad suite of data collected from HRMS, although the influence of the many components included in the broad data set may be small, they still might be important for classification of sources. Hence, consideration of a broad suite of PFAS analytes to perform advanced statistical analysis might provide better information about the classification of sources (Charbonnet et al., 2021; Strozier et al., 2016).

Overall analytical methods conclusions

Due to the complex chemistries used in PFAS formulations in commercial and consumer uses, multiple analytical techniques and approaches are needed to fully characterize the fate and transport of PFAS in the environment and during management actions to remediate PFAS-impacted sites. These tools include more traditional targeted analyses using chromatographic MS-based methods as well as more innovative tools such as those used to characterize total PFAS and precursors. In addition, more recent developments have resulted in HRMS tools for PFAS analysis in complex matrices and the determination of previously unknown or nontargeted analytes based on high mass accuracy approaches. Given the proprietary information in the production of PFAS, and the lack of analytical standards for most PFAS, HRMS tools shed light on the PFAS present in the chemical formulations of consumer and commercial products (e.g., AFFF), as well as in the environmental media at contaminated sites. In addition, the NTA can be used to identify precursors, as well as their degradation metabolites present in the environmental samples. Similarly, NTA could be applied to understand the end products formed during the remedial treatments and in the apportionment and tracking of PFAS sources.

Overall, the multitude of applications resulting in ubiquitous PFAS contamination, proprietary PFAS source chemistry information, complex chemistry of PFAS, many comingled sources, and availability of a limited list of analytes for PFAS-targeted analysis pose many challenges for forensic PFAS investigations. Although the ratios of different chain length PFAS, isomer profiles, and use of statistical analysis employing the monitoring data on a limited list of PFAS analytes have been applied to differentiate some sources, the presence of comingled sources and PFAS environmental fractionation complicates such assessments in understanding the signature at these sites, and is a major area of concern because of our limited understanding. Recent developments

in HRMS tools show great promise for an understanding and delineation of PFAS sources; however, these tools are often qualitative. This information on the broad range of analytes, along with multiple lines of evidence, needs to be considered to identify PFAS source attribution and help manage contaminated sites.

Analytical methods challenges

The need for the availability of PFAS analytical standards has been a challenge for advancing the understanding of PFAS sources, fate and transport, and toxicity. A broad list of PFAS analytical standards is needed to accurately quantitate PFAS and acquire data to support decision-making. With an ever-growing number and diversity of PFAS subclasses, analytical methods development for targeted analysis will continue to be challenging. Some of the currently used total PFAS methods have limitations, which are applicability to limited matrices, lack of differentiation between organic and inorganic fluorine, relatively poor sensitivity (compared with targeted methods), and nonstandardized methods. There is a need for the multilaboratory-validated methods in different environmental and biological matrices to fully characterize sources, fate and transport, and effectiveness of management strategies.

To work around the limitations of targeted PFAS quantitation, many novel analytical tools have been developed to quantify total organofluorine; these tools have been applied with the aim of understanding the total PFAS concentrations for different sources (Houtz et al., 2013; Martin et al., 2019; Robel et al., 2017; Schaider et al., 2017; Wagner et al., 2013). However, these techniques are not standardized and have some limitations such as variable recoveries, lack of differentiation between organic and inorganic fluorine, and applicability to limited matrices. Hence, these novel techniques should be used with caution for forensic PFAS investigations.

The HRMS tools are often qualitative and need to be coupled with the development of standards, for the insights gained from those analyses to be applied in more standardized protocols to ensure reproducible and defensible data for decision makers. Due to the lack of standardized protocols required for consistent identification and qualitative determination using HRMS, these techniques have been limited to research and selected in-depth investigations. Complex chemistry and environmental behavior complicate the understanding of PFAS compositions at sites with comingled sources. Forensic tools are in the early stages of development, but the application of HRMS and statistical tools shows great promise for understanding and delineating PFAS sources. With the recent advances in HRMS tools, many new classes of PFAS have been discovered and detected in environmental samples. However, it is important and challenging to prioritize which chemicals require development of analytical standards for further quantitation, routine monitoring, and study of the toxicological effects of these new classes.

GROUPING AND CLASSIFICATION

Importance of terminology

In a milestone publication (Buck et al., 2011), offered harmonized terminology, names, and acronyms for use by the global scientific, regulatory, and industrial communities to describe PFAS in an effort to address confusion caused by inconsistent communication. For example, prior to the Buck et al. (2011) publication, the same substance could be given a variety of different names and acronyms, or a given acronym could be used to represent different substances. Since this publication, studies have identified additional individual PFAS for which harmonized terminologies do not exist. However, expanding on the (Buck et al., 2011) nomenclature is only one of several possible approaches. For example, there is an ongoing international effort under the leadership of the OECD/United Nations Environment Programme (UNEP) Global Perfluorinated Chemicals (PFC) Group to establish a harmonized terminology for PFAS. The USEPA (Patlewicz et al., 2019) is developing an approach that combines expert knowledge and in-house cheminformatics. Barzen-Hanson et al. (2017) have used a simplified, manual International Union of Pure and Applied Chemistry (IUPAC)-based naming system, and Sha et al. (2019) have explored the potential of open cheminformatics approaches for the systematic categorization and naming of PFAS (Barzen-Hanson et al., 2019).

The PFAS universe

Having a clear definition of PFAS is critical for many stakeholders given that the structural definition often determines whether certain substances are included or excluded for regulatory purposes. In some jurisdictions, all substances defined as PFAS are treated as a single class of substances for regulatory purposes (European Commission, 2019). However, although there are some structural similarities between PFAS (i.e., they all contain per- and/or polyfluoroalkyl moieties), they are also structurally diverse and as a result have diverse behavior in the environment and within organisms.

Buck et al. (2011) defined PFAS as “highly fluorinated aliphatic substances that contain 1 or more C atoms on which all the H substituents ... have been replaced by F atoms, in such a manner that they contain the perfluoroalkyl moiety C_nF_{2n+1} .” Note that when $n = 1$, then $F = 3$, and thus according to the Buck et al. (2011) definition, an organic substance is a PFAS only if it contains at least one CF_3 – group. The OECD (2018) have argued that many substances containing perfluoroalkyl moieties would not be considered PFAS according to the Buck et al. (2011) definition and that the “PFAS universe” should be expanded. Examples of exclusions based on the Buck et al. (2011) definition are those: (1) in which a perfluoroalkyl chain is connected with functional groups on both ends (e.g., perfluoroalkyl dicarboxylic acids, $HOOC-C_nF_{2n}-COOH$); and (2) containing aromatic ring(s) but also perfluoroalkyl moieties. As a result, the widely cited OECD (2018) list of 4730 substances used a different working PFAS definition than the Buck et al. (2011) definition. Specifically, they focused on substances “including

perfluorocarbons, that contain a perfluoroalkyl moiety with three or more carbons (i.e., $-C_nF_{2n}$, $n \geq 3$) or a perfluoroalkylether moiety with two or more carbons (i.e., $-C_nF_{2n}OC_mF_{2m}$, n and $m \geq 1$).”

Although the OECD report (2018) recognized that some PFAS with shorter chain perfluoroalkyl(ether) moieties are present in products as intended ingredients or as impurities, and/or in the environment, they were excluded from the scope of the study. No justification was provided for excluding substances with shorter chain perfluoroalkyl moieties. However, this may be due to the numerous pharmaceuticals, pesticides, and other commercial chemical products that contain single $-CF_3$ groups or ultrashort perfluoroalkyl chains. For example, a recent (May 15, 2020) online search using SciFinder (<https://scifinder-n.cas.org/>) revealed 78,535 “commercially available” substances with assigned Chemical Abstracts Service (CAS) numbers containing the CF_2CF_2 moiety (when $n = 2$ in the OECD definition), whereas for higher values of n the number of substances was greatly reduced (e.g., 19,000 CAS numbers containing the $-CF_2CF_2CF_2-$ moiety). The ultimate environmental degradation products of PFAS that contain these shorter chain perfluoroalkyl (ether) moieties may be ultra-short-chain PFAAs or perfluoroether acids (PFEAs). Whereas these shorter chain PFAAs and PFEAs are persistent and mobile in the environment, and thus some will have the potential to pollute groundwater and drinking water (Barzen-Hanson & Field, 2015), they are not bioaccumulative in wildlife or humans (Conder et al., 2008). The existence of multiple PFAS definitions is unhelpful to stakeholders, and we therefore recommend that a new definition be broadly agreed on by multiple stakeholders.

Existing PFAS lists

The Supporting Information of Buck et al. (2011) lists 42 families and subfamilies of PFAS and 268 selected individual compounds, providing recommended names, acronyms, structural formulas, and CAS numbers. In compiling the list, the co-authors consulted publicly available information sources such as industry reports, patents, and scientific publications.

The Swedish Chemicals Agency (KEMI, 2015) compiled a list of 2060 PFAS with annual volumes greater than 100 kg in Sweden using all data sources available to the agency. These data sources included the Swedish products register, databases from the European Union, North America, and Asia, scientific publications and reports, and patents. The KEMI noted that the largest group among the PFAS identified in their list of 2060 was comprised of polymers. In compiling the list of PFAS, KEMI (2015) used the Buck et al. (2011) PFAS definition with $n = 1$, which resulted in another large number of PFAS (more than 1000) that included only shorter perfluoroalkyl fragments, principally the CF_3 – group.

The OECD (2018) identified 4730 PFAS-related CAS numbers. In compiling this list, the OECD study utilized publicly accessible information sources, including (1) two lists of PFAS (and other highly fluorinated substances) by national or international regulatory bodies, (2) nine public national/regional inventories of chemicals, (3) two public national/regional

inventories of chemicals in specific uses, (4) four public national/regional inventories of chemicals subject to specific regulations, and (5) one scientific database. The full OECD list is available online along with a report outlining the methodology used in more detail. The number of individual PFAS identified increased compared with the earlier compiled lists partly because a broader definition of PFAS was applied (see the previous section, *The PFAS universe*), and due to the broader definition, several new groups of PFAS were identified (OECD, 2018). The USEPA (2020b) has a curated list of more than 9000 PFAS that were included based on structures in the CompTox Chemicals Dashboard (Williams et al., 2017). In compiling this list, the USEPA used the OECD definition of PFAS, that is, that the structure should contain at least one perfluoroalkyl ($-C_nF_{2n-}$) moiety.

The NORMAN (2021) Network Suspect List Exchange was established in 2015 as a central access point for members of the NORMAN Network (and others) to find suspect lists relevant for their environmental monitoring questions. In recent activities, a suspect list of PFAS has been compiled that includes identified PFAS from NTA studies as well as the OECD list of PFAS. The database includes names, structural formulas, CAS numbers, the simplified molecular-input line-entry system (SMILES), the International Chemical Identifier (InChI), and necessary information for analysis by MS. The NORMAN PFAS Suspect List can be continually expanded on as new information arises.

PFAS with common terminology

An IUPAC name can be assigned to all PFAS, but these names are impractical and not commonly used in the PFAS literature. The Supporting Information of Buck et al. (2011) therefore provided a simplified harmonized naming system for certain PFAS. Those with a common simplified terminology mainly include PFAS derived from perfluoroalkane sulfonyl fluorides (i.e., ECF-derived PFAS) and perfluoroalkyl iodides (i.e., $n:2$ fluorotelomer PFAS), which are two of the major PFAS chemistries used (Buck et al., 2011). In their 2018 report, the OECD attempted a manual categorization of PFAS, but it is recognized that this needs to be revisited in a more systematic way.

PFAS without common terminology

As a result of the recent increasing application of HRMS for nontarget and suspect screening of environmental and biological samples, as well as the recent efforts of the OECD (2018), a wider range of PFAS has been identified. These individual substances are too many to list here, and no harmonized terminology exists for many of the new PFAS identified. For example, PFAS in the OECD list that are excluded from the Buck et al. (2011) terminology include: hydrofluorocarbons (HFCs; $C_nF_{2n+1}C_mH_{2m+1}$), hydrofluoroethers (HFEs; $C_nF_{2n+1}OC_mH_{2m+1}$), and hydrofluoroolefins (HFOs; $C_nF_{2n+1}C_mH_{2m-1}$), perfluoroalkyl alkenes (C_nF_{2n}) and their derivatives, perfluoroalkyl ketones ($C_nF_{2n+1}C(O)C_mF_{2m+1}$), semifluorinated ketones ($C_nF_{2n+1}C(O)C_mH_{2m+1}$), and their

derivatives, side-chain fluorinated aromatics (C_nF_{2n+1} -aromatic ring(s)), perfluoroalkyl alcohols ($C_nF_{2n+1}OH$), silanes ($C_nF_{2n+1}Si-$), and amines ($C_nF_{2n+1}-N-$). Examples of PFAS identified during NTA analysis include 40 novel classes of PFAS in AFFFs, all of which were ascribed new acronyms in the publication (Buck et al., 2011).

For some of the novel and emerging PFAS not included in Buck et al. (2011), it is challenging to formulate simple common terminology. For example, the per- and polyfluoroether alkyl acids often contain multiple ether linkages and sometimes chlorine atoms in the structures (e.g., $Cl-C_6F_{12}OCF_2CF_2SO_3K$, CAS No. 73606-19-6, or F53B). There is an ongoing international effort under the leadership of the OECD/UNEP Global PFC Group to categorize PFAS and provide a common terminology. In the absence of a common terminology, it is important that authors of scientific publications and reports unambiguously identify the substance in question providing as much information as possible. This may include documenting IUPAC names, CAS numbers, structures, structural formulas, SMILES, and InChI.

The OECD/UNEP Global PFC Group will soon publish their recommendation for a structural definition of PFAS. It is expected that the OECD will recommend that any chemical with at least a perfluorinated methyl group ($-CF_3$) or a perfluorinated methylene group ($-CF_2-$) should be defined a PFAS. This is purely a definition based on the chemical structure, and other definitions of PFAS (i.e., subgroupings) will need to be adopted for the purposes of regulation. Mapping the universe of PFAS is an important ongoing task being undertaken by the OECD, USEPA, ITRC, (2018), and other organizations. Mapping involves categorizing (assigning them to appropriate subcategories of PFAS) and providing them with unambiguous identifiers (i.e., IUPAC names, CAS numbers, structures and structural formulas, SMILES, and InChI).

PFAS polymers

How should fluoropolymers be classified? In both the Buck et al. (2011) and the OECD (2018) synthesis paper on PFAS, PFAS are differentiated initially on the basis of whether they are or are not polymers. Defining a polymer is beyond the scope of the present report. However, there are regulatory and nonregulatory definitions for polymer, depending on how many monomer units are needed to make a polymer (e.g., Buck et al., 2011; OECD, 1991) to which the reader may refer. Regardless of definition, the polymer or nonpolymer distinction is the first bifurcation in approaches to PFAS hierarchy and nomenclature. Being designated a polymer is not intended to imply hazard or lack thereof, although some regulatory schemes do exempt types of polymers from chemical notification requirements due to lack of hazards.

PFAS fluoropolymers, perfluoropolyethers, and side-chain fluorinated polymers. Proceeding through the PFAS polymer hierarchy/nomenclature, three types of PFAS polymers are identified: fluoropolymers, perfluoropolyethers, and side-chain fluorinated polymers. (See Buck et al., 2011 and OECD, 2018 for definitions of these three types of polymers.) These polymers are

not all the same. Some side-chain fluorinated polymers have been shown to be precursors to PFAAs because their ester linkages may be degraded to release their fluorinated side chains (Russell et al., 2008; Washington et al., 2015). Some fluoropolymer ionomers, like Nafion® are “functionalized” and degrade to release their sulfonic functional group. Some fluoropolymers, such as granular polytetrafluoroethylene (PTFE) or some fluorinated ethylene propylenes (FEPs) do not need a polymer polymerization aid (PPA) to be manufactured, whereas others, like fine powder or aqueous dispersion PTFE, do require a PPA to be polymerized.

Properties predicting polymer hazard

Additional discrimination among PFAS polymers is possible based on reports from the OECD Expert Group on Polymers (1993, 2009), which agreed that certain physical, chemical, and biological properties of any polymer were associated with “insignificant environmental and human health impacts” (OECD, 1993, 2009). These were designated “Polymers of Low Concern.” These criteria evolved from modelling the USEPA conducted under the original Toxic Substances Control Act. The USEPA reviewed thousands of polymers, leading to models that were then validated (Auer et al., 1990; USEPA, 2012b, 2017; Wagner et al., 1995). More recently, three reports on polymer registration commissioned by the European Commission confirmed these properties for assessing the safety of polymers (European Commission, 2012, 2020; BIO by Deloitte, 2015). Most recently, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 2019) published a Conceptual Framework for Polymer Safety also supporting these chemical, physical, and biological properties for predicting polymer safety. Therefore, PFAS polymers could be further segregated based on whether their chemical, physical, and biological properties are consistent with OECD criteria to differentiate substances of insignificant environmental and human health impacts. The PFAS polymers that meet these criteria would be demonstrably different from other PFAS, such as perfluoroalkyl acids (e.g., PFOA, PFOS, and PFHxS). A PFAS polymer that did not transform in the environment to a substance of concern would be very different from some side-chain fluorinated polymers that are PFAA precursors. A PFAS polymer that was not water soluble would be different from the highly soluble and mobile PFOA and PFOS. A PFAS polymer like a granular PTFE made without a polymerization aid (e.g., the long-chain PFOA or a short-chain HFPO-DA), would likely have a different hazard profile from an aqueous dispersion of PTFE with PFOA or other polymerization aids. All PFAS are not equal in human health or environmental impact, nor are all PFAS polymers. Therefore, using chemical, physical, and biological properties to categorize PFAS polymers according to relative risk for human and ecological receptors, as the USEPA and OECD and many others have concluded, may be prudent.

The data to address the polymer of low concern criteria should be generated for all PFAS polymers. A protocol to test PFAS polymers for environmental aging should be agreed on

and implemented to determine whether the PFAS polymers lack future degradation, potentially with chemical analysis and hazard assessment for leachable compounds, to address long-term exposure and toxicity issues.

PFAS GROUPINGS/CLASSIFICATION CONSIDERATIONS FOR RISK ASSESSMENT

PFAS are not a monolith in terms of environmental risk

The diversity of chemical structures and physicochemical properties in the PFAS universe (Supporting Information, Figure S1), as well as the differences in the uses and releases to the environment, results in a wide variety of PFAS behaviors in abiotic and biotic environmental compartments that preclude simple generalizations regarding environmental risk. Simply put, PFAS are not a monolith in terms of environmental risk.

Even within groups of PFAS with relatively similar chemical structures, hazard characteristics can span orders of magnitude in terms of risk. For example, widely different exposure and hazard profiles exist among the more commonly studied PFCAs and PFSAs. Among PFCAs and PFSAs, it is recognized that the bioaccumulation potential in animals increases with increasing perfluoroalkyl chain length, as evidenced by the bioconcentration factors for fish, pelagic invertebrates, and terrestrial invertebrates, which increase by up to seven orders of magnitude between perfluorobutanoic acid (PFBA; 3 perfluorocarbons) to perfluorotetradecanoic acid (PFTeDA; 13 perfluorocarbons; Conder et al., 2008, 2020).

Toxicity also varies with perfluoroalkyl chain length within the PFAAs (as measured on a daily ingested dose). An evaluation of mammalian ecological no-effect toxicity reference values (TRV) levels for growth, reproduction, and survival indicates differences in toxicity at the whole-organism level as a result of perfluoroalkyl chain length (Conder et al., 2020). For example, the TRV for PFHxA (five perfluorocarbons) is 100-fold higher (i.e., less toxic) than the longer chained perfluoro-n-undecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnDA; nine and 10 perfluorocarbons, respectively). Similarly, several reviews (Anderson, Luz, et al., 2019; Michigan Science Advisory Workgroup, 2019) have noted that human health reference doses for PFHxA are several orders of magnitude higher than those for PFOA (seven perfluorocarbons). Recently completed 28-d toxicity tests with rats indicated that higher doses of short-chain PFSAs and PFCAs were needed to achieve the same response as long-chained PFSAs and PFCAs (National Toxicology Program [NTP], 2019a, 2019b). Research by Gomis et al. (2018) may suggest that lower toxicity for some PFAAs was due to faster elimination and lower rates of accumulation in target tissues.

Beyond the intrinsic properties of PFCAs and PFSAs with regard to bioaccumulation potential and toxicity, differences in the environmental release or emission rates and occurrences at PFAS-impacted sites also contribute to extremely wide differences in risk among PFCAs and PFSAs. For example, PFSAs and PFCAs are common chemicals of potential concern at sites

impacted with AFFFs. Concentrations of PFCAs and PFSA in the abiotic media at many of these sites can vary by several orders of magnitude (Anderson et al., 2016), leading to wide ranges in exposure among PFAAs. Based on case studies and modeling of PFCAs and PFSA in aquatic ecosystems at several AFFF-impacted sites, Larson et al. (2018) found that dietary exposures of aquatic-dependent birds varied by orders of magnitude among individual PFAS within each site due to the concentration differences in abiotic media and bioaccumulation behaviors (Larson et al., 2018). Sites with other (non-AFFF) use and PFCA and PFSA release patterns would also likely result in considerable differences between the site-specific ecological and human health risks of PFCAs and PFSA. Simply put, individual PFAS observed or predicted to be among the most toxic and bioaccumulative via laboratory studies or by predictive approaches are not necessarily going to present the highest risk potential in the environment.

Using groups to prioritize data collection for informing risk paradigms

The need for scientifically sound data is acute, particularly the compound-by-compound information that is required for product registrations and product- and site-specific risk assessment. However, a compound-by-compound approach for generating these data is unfeasible given the hundreds to thousands of PFAS that may be environmentally relevant. Classifying and conceptualizing the environmental risk of subgroups of PFAS via paradigms similar to those currently used for multicomponent groupings of organic chemicals such as polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbon (PAHs), or polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) would streamline scientific and regulatory efforts to evaluate and manage risks (Ritscher et al., 2018).

Such a PFAS grouping or paradigm may not correspond to a PFAS hierarchy based on a chemical structure in the same simple manner as these non-PFAS chemical groupings because of the wide diversity of PFAS and the complexity of chemical-specific attributes that are important to such classifications. Building a PFAS grouping paradigm to facilitate risk assessment will not be easy because of the following general challenges:

- *“Read-across” approaches are unreliable for PFAS:* Risk assessors cannot necessarily attribute the same hazard potential (i.e., perform a “read across”) among all members of a PFAS chemical grouping. As mentioned in the previous section, *PFAS are not a monolith in terms of environmental risk*, there are large differences in hazard potential among compounds within the PFCAs and PFSA. This is not unlike the orders-of-magnitude differences among bioaccumulation potential of individual PCB congeners that are considered when one is evaluating the risk potential of PCBs as a group (Arblaster et al., 2015; Gobas & Arnot, 2010). Assuming the same behavior (e.g., bioaccumulation, toxicity) without quantitative understanding of potential differences among individual chemicals has the potential to mismanage the risk

of PFAS that share structural similarities (but not necessarily risk potential) with comparatively well-studied PFAS.

- *There are currently no PFAS quantitative structure–activity relationship (QSAR) models:* Simply counting the number of fluorine atoms or perfluorocarbons in a molecule will not provide a simple short cut to characterizing the risk of an individual PFAS. Such a QSAR may be useful within some or all of the PFCAs and PFSA, but outside these groups, the wide diversity of chemical structures and functional groups (Supporting Information, Figure S1) may be too great for a single QSAR to reliably predict inherent persistence, bioaccumulation, or toxicity. Multiple QSARs or new approaches are likely needed, and initial efforts show promise (see the challenge, *Development of QSARs* below).
- *There are currently no site-specific PFAS conceptual models:* Although analytical techniques are available to estimate the concentration of PFAS-derived fluorine atoms or perfluoroalkyl carbons from an abiotic or biotic sample, as previously noted, at a PFAS-impacted site, these techniques do not provide a short cut to quantifying site-specific PFAS risk. At best, it could be possible to use these tools to prioritize areas within a site if the composition of PFAS mixtures present is assumed to be relatively uniform among areas. It may be possible to develop a generic threshold below which the risk of adverse effects would be minimal. However, these approaches will be challenging, because the specific makeup of PFAS mixtures within and among sites may vary widely: dozens to hundreds of detectable PFAS are present at environmental sites beyond the typical PFCAs and PFSA (Barzen-Hanson et al., 2017). Relative toxicities remain unknown and, as already highlighted, read-across approaches and QSARs are currently under development (see the first challenge, *“Read-across” approaches are unreliable for PFAS*, as well as *Development of QSARs* below). Thus, given the complexity of PFAS mixtures in the environment and the wide variety of PFAS structures and risk profiles, concentrations of perfluoroalkyl carbons extracted from a particular environmental medium at any given site are likely to be poor predictors of risk and primarily useful only for screening or comparative approaches within a site. Empirical exposure and hazard characterization data from a wide variety of relevant PFAS chemical groups are needed to allow us to build scientifically sound risk paradigms. Such data will allow generalizations and extrapolations to untested PFAS, as well as groupings and classifications that help surmount the need for chemical-specific data for all PFAS. We suggest the following priority data needs and approaches for these initial data collection efforts:
 - *Elucidation of mode of toxic action:* Even on a suborganismal level, there is currently little or no consensus on the mode of toxic action for PFCAs and PFSA (USEPA, 2016a, 2016b). The verification of the same or a similar mode of toxic action is a key logical foundation for grouping compounds for risk assessment. For example, the binding of PCDD/Fs to the aryl hydrocarbon receptor (Van den Berg et al., 2006) is a foundational underpinning of grouping PCDD/Fs as a class. The current in vitro evaluation of 150 PFAS (USEPA, 2020c) being

conducted by the USEPA and the National Toxicology Program is a valuable step in *understanding mode of toxic action*. These assays are focused on *multiple endpoints*, including hepatotoxicity, immunotoxicity, developmental toxicity, mitochondrial toxicity, and developmental neurotoxicity, and will also provide information on toxicokinetics (Patlewicz et al., 2019). These data may be helpful to prioritize PFAS for subsequent *in vivo* testing.

- **Development of QSARs:** QSARs that would aid our understanding of water solubility, organic carbon or mineral solid phase binding capacity, toxicity, biotransformation potential, and bioaccumulation would greatly aid our ability in building a PFAS risk assessment paradigm. As noted above, the most important QSAR identified thus far is the number of perfluoroalkyl carbons within the PFAS molecule. As the number of perfluoroalkyl carbons increases, inherent toxicity tends to increase for PFCAs and PFSAAs based on the organisms and PFAS tested to date. As noted previously in the challenge, *There are currently no PFAS quantitative structure–activity relationship (QSAR) models*, this QSAR is unlikely to provide a simple holistic metric for all PFAS. However, for some persistent nonpolymeric perfluoroalkyl substances with different (noncarboxylate and nonsulfonate) functional groups or polyfluoroalkyl substances with other chain features (ether linkages, aliphatic linkages, etc.), there is tentative evidence that a fluorinated carbon-chain-length-based QSAR may be helpful in understanding some aspects of bioactivity. For example, as with PFCAs and PFSAAs, bioaccumulation in fish was found to be positively correlated with perfluoroalkyl chain length in perfluoroalkyl-phosphinic and -phosphonic acids (Liu & Liu, 2016). Cheng and Ng (2019) hypothesized that PFAS with perfluoroalkyl chain lengths of six–12 are likely to have high bioactivity, although the bioactivities of individual PFAS in this domain were not simply reflective of perfluoroalkyl chain length (Cheng & Ng, 2019). Ongoing research on protein binding of PFAS (Cheng & Ng, 2018; Ng & Hungerbuehler, 2015) and *in vitro* high-throughput toxicity testing (Patlewicz et al., 2019) efforts are likely to continue elucidating QSARs. As this research continues, nonpolymeric PFAS with longer perfluoroalkyl chain lengths (assuming other structural aspects are similar) should receive priority for empirical evaluation.
- **Understanding transformation pathways and kinetics of PFAS:** Additional work is needed to better understand the transformation pathways, kinetics, and products of PFAS that can undergo environmental or metabolic reactions. For example, whereas some PFAS are nonreactive or “inert” in the environment (e.g., PTFE), some other PFAS have the capability to abiotically or biotically transform into other substances (e.g., PFAAs). It should be noted, however, that it is incorrect to assume that PFAAs are always the terminal transformation products of those PFAS that can be transformed into other substances.
- **Considerations for molecular size:** Very large organic polymer compounds (e.g., thousands of atomic mass units/molecule) are generally considered to be unable to cross biological membranes and/or are of low biological activity (Boethling &

Nabholz, 1997; USEPA, 2013). Empirical data collection of nonpolymer PFAS should be a research priority. However, understanding the generation of PFAAs via transformation of polymer fluorinated side chains under environmentally relevant conditions should be a research priority for environmentally relevant PFAS polymers, as noted above (*PFAS fluoropolymers, perfluoropolyethers, and side-chain fluorinated polymers*).

- **Considerations of environmental releases and occurrences:** Intrinsic chemical properties such as persistence, bioaccumulation, and toxicity are a foundation for understanding overall chemical hazard, but the magnitude of expected or existing exposures is often overlooked in chemical evaluation programs (Arnot et al., 2006). When possible, prioritization of PFAS for empirical data collection should consider expected or observed exposures in the environment. This information can be quantified from production or release masses, as well as the frequencies and magnitude of detections in abiotic and biotic environmental media. Considerations for exposure scenarios should also be included, with high priority given to PFAS in products designed for or routinely used in open releases to the environment, such as in the case of AFFF or discharged waste streams, or in products that present key direct exposure routes (e.g., personal care products and other common consumer products).

Considering the above concepts, continuing evolution of data needs, and the improving understanding of PFAS, an initial streamlined approach to PFAS grouping, hazard assessment, and management has been proposed (Figure 2; Henry, 2020). In this approach, PFAS (polymers and nonpolymers) would be screened for various properties to ascertain where, on a relative risk spectrum, they fall so that risk-appropriate use and control measures may be assigned: physical (nine questions), chemical (four questions), and biological (11 questions), following initial suggestions by Henry (2020).

According to Figure 2, this screening for physical, chemical, and biological hazard should occur at each stage of the PFAS life cycle, along with consideration of potential uses and effective and efficient control measures. This is the first of four steps in the process for PFAS grouping:

- **Step 1:** Define health and environmental hazard posed by the PFAS by answering the chemical, physical, and biological properties questions predictive of human/environmental hazard.
- **Step 2:** Identify uses of the PFAS.
- **Step 3:** Identify effective control measure for the PFAS.
- **Step 4:** If the residual risk from Step 1 (hazard), Step 2 (uses), and Step 3 (control measures) is not sufficiently minimized, then consider further PFAS regulation and/or restriction. Group PFAS with the same hazard, uses, and control measures together for further regulation/restriction.

The chemical, physical, and biological questions outlined in the Supporting Information (Figure S2) would create health and

CHEMICAL ASSESSMENT / RISK MANAGEMENT PROCESS

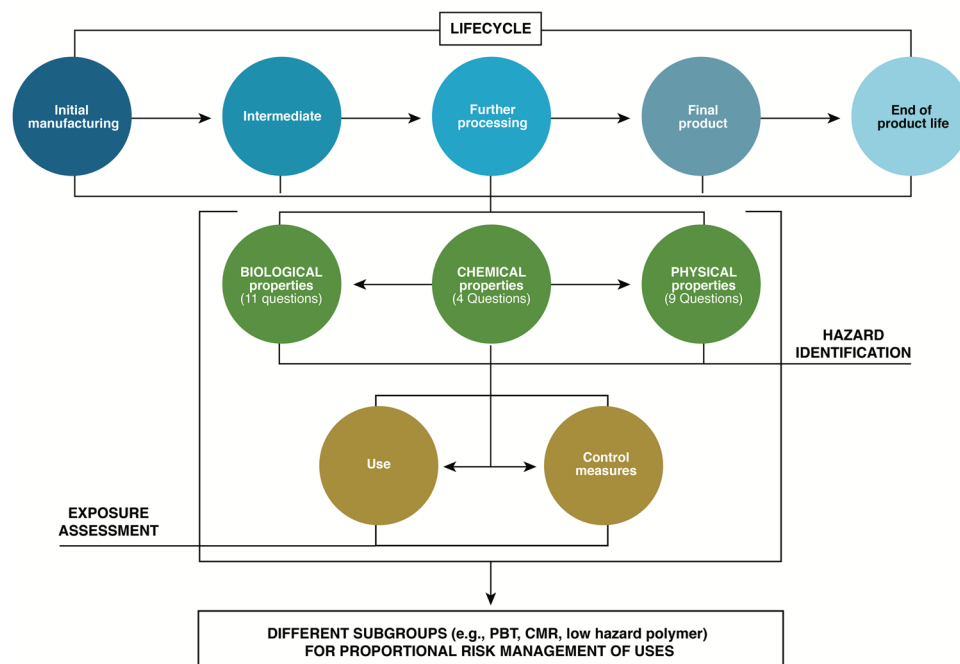


FIGURE 2: A streamlined approach for per- and polyfluoroalkyl substances (PFAS) grouping. PBT = persistent bioaccumulative toxic (substances); CMR = carcinogenic, mutagenic, or toxic to reproduction (substances).

environmental hazard categories in PFAS meeting the definition (e.g., health hazards: acute toxics, chronic toxics, carcinogens, mutagens, reproductive/developmental toxins, sensitizers, bioaccumulative; environmental hazards: acute or chronic aquatic toxins, persistent and water soluble, degrading into persistent and water-soluble substances, volatile or adsorbing to soil—mobile with air or soil in the environment, absorbed by plants consumed in the human food chain, etc.) These hazard identification questions rely on the UN Globally Harmonized System of Classification (GHS), the USEPA, the European Union Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) regulation, and UNEP Stockholm Convention definitions and principles for determining partitioning to air, water, and soil. In the absence of data to the contrary, these chemical, physical, and biological questions form the basis on which to segregate PFAS into hazard categories.

Next, in Step 2, the uses of the PFAS are identified. This provides insight into the exposure potential of the PFAS in its intended uses. Available and effective control measures (e.g., effective environmental controls/Best Available Techniques, occupational hygiene programs, recycling, reuse, buy/take back, incineration) should be identified in Step 3 of the process. In this four-step process, at each stage of the life cycle, the hazard(s) (biological, chemical, and physical properties), plus the use(s) and effective control measures (exposure potential), identify the risk of the PFAS to be appropriately and proportionally managed. This is consistent with the principle that risk is a function of hazard and exposure. For regulation/restriction/management purposes,

classes of PFAS with the same hazard and uses and control measures could be considered a “PFAS subgroup,” such as PFAAs or low hazard polymers, and so on.

In the absence of PFAS-specific fate, transport, and toxicity data to answer the chemical, physical, and biological property questions, the most conservative answer to each question should be used. To reduce residual risk in Step 4, data gaps may be filled to potentially reduce hazard, uses replaced with less dispersive options, and/or control measures strengthened to reduce exposure.

Some have suggested a one-property-only approach to PFAS regulation (e.g., Cousins et al., 2020). When a substance with one or more fully fluorinated carbons is determined to be persistent, questions on chemical, physical, and biological properties (hazard), use, and control measures (exposure) are not needed to regulate it with all other PFAS. More discussion of this alternative approach is found in Section S1 of the Supporting Information.

Challenges/key knowledge gaps/recommendations

Key challenges and recommendations for considering grouping of PFAS for risk assessment purposes include:

1. Realizing that PFAS exhibit very different environmental behaviors and toxicological potencies that prohibit treating them a single class of compounds in the context of risk assessment and environmental management (as for PCBs, PAHs, etc.).

2. Increasing our efforts to understand modes of toxic action and biological effects as a potential tool for characterizing risks of PFAS.
3. Evaluating and applying predictive approaches or general observations (e.g., QSARs, considerations for molecular size, use and release patterns, etc.) to extrapolate available empirical risk information to PFAS that have not been evaluated, and to prioritize additional evaluations.
4. Developing a streamlined approach for risk-based groupings—a paradigm that is not simply based on the presence of the perfluoroalkyl moiety, but considers a variety of additional considerations (biological, chemical, and physical properties) relevant to ecological and human health risks.

CONCLUSIONS AND IMPLICATIONS

As a result of unique chemical properties, widespread and diverse uses, complex fate and transport properties, and the need for validated analytical capabilities, PFAS environmental risk management presents an extreme challenge to the environmental community. A consistent theme encountered for PFAS across all technical areas is that our current knowledge base often limits extrapolation of information from site to site, scenario to scenario, and PFAS to PFAS.

In addition to the numerous technical challenges, PFAS regulations are currently evolving at the local, state, and federal levels. These changes are the result of interpretations of the developing exposure and risk science, industry innovation and product development, public and political awareness and involvement, various regulatory approaches, and in some cases, different legal actions.

Although the science is evolving, federal actions (e.g., Significant New Use Rules, Drinking Water Health Advisories, PFAS listing in the Toxics Release Inventory, proposed maximum contaminant levels [MCLs], UCMR testing) are being implemented and developed partly based on advances in government, academic, and industry efforts. The USEPA (2020d) continues to effectuate its PFAS Action Plan, focusing on collecting data to help inform future regulatory actions, researching analytical methods, developing information on remediation technologies, and conducting occurrence testing in various environmental media. In addition, several states in the United States have set guidance or promulgated standards for certain PFAS in drinking water, have required testing of water systems and/or environmental media, and have established remediation requirements for certain PFAS in groundwater and surface water (ITRC, 2020). As of May 30, 2020, 21 states have developed standards or guidance values for PFAS in drinking water and/or groundwater (ITRC, 2020). Of those, 11 are utilizing the USEPA's 2016 lifetime health advisory of 70 ppt (or ng/L) for PFOA and PFOS combined (for drinking water or groundwater; USEPA, 2016a, 2016b); however, six states have adopted more stringent values. Although PFOA and PFOS remain the primary focus for state agencies, nine states have values for other PFAS (e.g., New Jersey has an MCL

for PFNA; Minnesota has health-based guidance values for perfluorobutane sulfonic acid [PFBS] and PFHxS). Currently, there are different strategies for addressing multiple PFAS in drinking water or groundwater. Some states have values for individual PFAS, and others have a single value for a sum of concentrations for several PFAS.

For federal and industrial stakeholders that may have international footprints, the divergence between regulatory threshold levels in some other countries compared with US federal and state levels may be up to 2 orders of magnitude. For example, Health Canada has promulgated nationwide drinking water standards at 200 ng/L for PFOA and 600 ng/L for PFOS (individually, not combined), Sweden has recommended a limit of 90 ng/L for a sum of 11 PFAS in drinking water, and the European Union has a proposal to regulate the group of PFAS (as defined by the OECD) at a limit of 500 ng/L total. Different approaches across the United States and between the United States and other nations present a significant challenge for academia and industry to innovate and develop new formulations and chemistries to eliminate or minimize PFAS releases to the environment. In addition, as scientific and regulatory attention shifts toward nondrinking water exposure pathways, industry, regulators, and the public will be challenged to address PFAS in other media, including soil, surface water, effluent, and hazardous waste disposal.

Given the scientific uncertainties and policy differences among stakeholders, a consensus on how to adequately protect the environment and public from potential negative impacts from certain PFAS is difficult. Further advances in the areas of PFAS exposure, toxicology, and risk are needed to determine potentially problematic intrinsic properties and/or better understand potential risks to environmental and human health. For example, considerations to further break down the very large group of chemicals to groupings by class, structure, or behavior may help in better focusing the exposure and risk science in academia and government, industry innovation toward intrinsically safer products, and communicating risk to stakeholders. These decisions will likely vary between jurisdictions, and it is beyond the scope of the present report to provide general recommendations.

In conclusion, we hope that the synthesis of varying viewpoints and discussion of the current state of the science will facilitate assessment and management of this extremely diverse universe of compounds. As discussed, information regarding potential sources and how to best prioritize these sources for additional analysis and management is still in its infancy and is hampered by methodological and database limitations. More robust information, including source prioritization, predictive fate and transport models, and improved and standardized analytical methods is needed to produce safer products, manage legacy and contemporary PFAS risk, and make public health decisions. These decisions should be guided by the best available science at the present time and may require revisions as the science evolves. A PFAS risk paradigm can be built from the bottom up, taking advantage of our existing PFAS-specific knowledge and lessons learned from our understanding of other legacy environmental contaminants

during the past 4–5 decades of environmental risk assessment. This endeavor is and will continue to be challenging, and will require creative thinking, new ideas, dedication, and cooperation from all sides of the issue including industry, consumers, stakeholders, and regulators. However, the research and advances in science are necessary for addressing existing environments threatened by PFAS, evaluating the safety of continued uses of contemporary PFAS, and wisely evaluating substances being considered as PFAS alternatives.

Supporting Information—The Supporting Information is available on the Wiley Online Library at <https://doi.org/10.1002/etc.5182>.

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