A Critical Review of a Recommended Analytical and Classification Approach for Organic Fluorinated Compounds with an Emphasis on Per- and Polyfluoroalkyl Substances

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ABSTRACT

Organic fluorinated compounds have been detected in various environmental media and biota. Some of these compounds are regulated locally (e.g., perfluorononanoic acid maximum contaminant level in drinking water by the New Jersey Dept. of Environmental Protection), nationally (e.g., perfluorooctanoic acid maximum acceptable concentration in drinking water by Health Canada), or internationally (e.g., Stockholm Convention on Persistent Organic Pollutants). Globally, regulators and researchers seek to identify the organic fluorinated compounds associated with potential adverse effects, bioaccumulation, mobility, and persistence to manage their risks, and, to understand the beneficial attributes they bring to products such as first responder gear, etc. Clarity is needed to determine the best analytical method for the goal of the analyses (e.g., pure research or analysis to determine the extent of an accidental release, monitoring groundwater for specific compounds to determine regulatory compliance, and establish baseline levels in a river of organic fluorinated substances associated with human health risk prior to a clean-up effort). Analytical techniques that identify organic fluorine coupled together with targeted chemical analysis will yield information sufficient to identify public health or environmental hazards. Integr Environ Assess Manag 2021;17:331–351. © 2020. W.L. Gore & Associates Inc. Integrated Environmental Assessment and Management published by Wiley Periodicals LLC on behalf of Society of Environmental Toxicology & Chemistry (SETAC).

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INTRODUCTION

In the area of the environmental chemistry of fluorinated substances, and particularly as it applies to setting limits supporting environmental and health and safety regulations, clarity is needed to match the appropriate laboratory analytical method to the stated goal(s) for such analyses. For example, an adequate limit of detection varies depending on the matrix, the compounds of interest, and the intended regulatory purpose or aim of the study. Monitoring for specific purposes, such as emissions from a manufacturing facility or to obtain certain environmental permits, may impact sampling and testing procedures. The capabilities of an analytical chemistry laboratory to measure fluorinated substances in a particular matrix can drive regulatory decision making. On the other hand, regulatory decision making determines how compliance is achieved analytically (i.e., the requirements of an analytical method).

With respect to analytical techniques applied to identify fluorinated compounds, the use of properly validated analytical chemistry measurements is critical to determining the identity and concentration of fluorinated substances. The presence of certain per- and polyfluoroalkyl substances (PFAS) in the environment, for example, has become of concern to the regulatory community globally. This paper discusses fluorinated compounds, briefly addressing inorganic fluorine and inorganic fluorinated compounds, then generally focusing on organic fluorinated compounds and more specifically, per- and polyfluoroalkyl substances. Fluorinated compounds regulated under the Montreal and Kyoto protocols will be mentioned, as will fluorine-containing pesticides, pharmaceuticals, and veterinary drugs.

THE UNIVERSE OF FLUORINE-CONTAINING COMPOUNDS

Inorganic fluorinated compounds

Elemental fluorine, the thirteenth most abundant element in the earth’s crust (Jaccaud et al. 2000), almost never occurs in nature except in its inorganic form, fluoride. Fluoride can...
be released to the environment through natural activities such as volcanic emissions, weathering of minerals, and dissolution mainly due to groundwater and marine aerosols. Some anthropogenic sources of fluorine are the manufacture and use of hydrofluoric acid, and the production of Al, steel, and oil. Historical production or application sites may be sources of fluorine (or the inorganic form fluoride) in the environment.

Common inorganic fluorine compounds include hydrogen fluoride (HF), sodium fluoride (NaF), and naturally occurring minerals such as fluorite (CaF₂) (see Table 1). Hydrogen fluoride is an acid used to make refrigerants, pharmaceutical intermediates, fluoropolymers, and metals (Speight 2017). Calcium fluoride is used in the purification of Si, the manufacture of glass, the removal of Pb in flotation waste, the manufacture of clean steel, as pigment for paper with titanium dioxide (TiO₂), as a solid lubricant for hot rolling, and to strengthen cement (Kirk et al. 1991). Inorganic fluorine compounds will not be discussed further other than to mention the analytical methods that can detect them.

**Organic fluorinated compounds**

There are thousands of organic fluorinated compounds, mostly synthetic, which differ in chemical class, uses, and physical, chemical, and toxicological properties. Organic fluorinated compounds include industrial chemicals (e.g., haloalkane refrigerant R-134a also called 1,1,1,2-tetrafluoroethane); pesticides (e.g., pyrazifluidum, fluopyram, broflanilide); pharmaceuticals (e.g., Lipitor, Prozac, Celebrex, isoflurane); and veterinary drugs (e.g., florfenicol, isoflurane) (Cormier et al. 2009). The addition of fluorine stabilizes an agrochemical and can modify bioactivity through binding to a target site or enzyme, transporting the bioactive molecule from application site to target site, or blocking metabolic activation (Theodoridis 2006; Fujiwara and O’Hagan 2014). The addition of multiple fluoride atoms to pharmaceuticals and veterinary drugs increases lipophilicity and bioavailability of the molecule and can increase its therapeutic index and help optimize pharmacokinetic properties (O’Hagan 2010; Fujiwara and O’Hagan 2014).

To highlight the variety and utility of fluorinated chemicals, Table 1 provides examples of different types of fluorinated chemicals including their names, uses, whether organic or inorganic, and chemical structures. Chemically, these organic fluorinated compounds contrast with the PFAS in that they may have only a few fluorine atoms in their structures, such as terminal CF₃. Fluorine has also been found in many industrial or consumer products (e.g., fluorine in liquid crystal displays [LCD], and flat panel televisions, halon fire extinguishers, refrigerants like Freon 12) (Dolbier 2005). Historical production and application sites of fluorinated compounds and products containing them may be sources of fluorine (or the inorganic form fluoride) in the environment.

**Per- and polyfluoroalkyl substances.** Differentiation of organic fluorinated compounds by characterization of functional groups is useful for discussion of analytical methods and interpretation of results. In this paper, PFAS are aliphatic substances for which all or most H atoms have been replaced with fluorine atoms and contain the perfluoralkyl moiety (CₙF₂ₙ₊₁-R) (Buck et al. 2011; OECD 2018). Broadly, PFAS are either polymers or nonpolymers.

**Nonpolymer per- and polyfluoroalkyl substances.** There are 2 types of nonpolymer PFAS: perfluoroalkyl substances and polyfluoroalkyl substances. Perfluoroalkyl substances are those aliphatic substances for which all of the H atoms attached to C atoms (in the nonfluorinated substance from which they are notionally derived) have been replaced by fluorine atoms (except those H atoms whose substitution would modify the nature of any functional groups present). The polyfluoroalkyl substances are similar to perfluoroalkyl substances with the exception that not all H atoms attached to C atoms have been replaced with fluorine atoms (Buck et al. 2011). Table 2 provides a more detailed comparison of the toxicological, chemical, and physical characteristics of some of the nonpolymer perfluoroalkyl substances (note that this paper will not address the nonpolymer PFAS, such as chlorofluorocarbons [CFCs] and hydrofluorocarbons [HFCs] that are subject to the Montreal and Kyoto Protocols).

Nonpolymer perfluoroalkyl substances, such as perfluoroalkyl acids (PFAAs), include examples as the C₈ carboxylic or sulfonic acids perfluorooctanoic acid (PFOA) or perfluorooctane sulfonic acid (PFOS), respectively; the C₆ carboxylic or sulfonic acids perfluorohexanoic acid (PFHxA) or perfluorohexane sulfonic acid (PFHxS), respectively; and the C₄ carboxylic or sulfonic acids perfluorobutanoic acid (PFBA) or perfluorobutane sulfonic acid (PFBS), respectively. See Table 2 for a comparison of some chemical, physical, toxicological, and environmental fate endpoints for nonpolymer PFAS. Table 2 presents 3 examples of the perfluoroalkyl carboxylic acids (C₈, C₆, C₄), 2 examples of perfluoroalkyl sulfonic acids (C₈, C₆), 1 per- and 1 polyfluoropolyether carboxylic acids (NH₄⁺ salt of hexafluoropropylene oxide dimer acid, and 2,2,3-trifluoro-3-(1,2,3,3-hexafluoro-3-(trifluoromethoxy) propoxy)propionic acid, respectively), and 2 fluorotelomer alcohols (C₆ and C₈). All of these have relatively low molecular weights (<500 Da). The C₄ carboxylic and C₈ sulfonic acids appear to be more potent in toxicity and have longer half-lives, based on the data in Table 2. The PFAAs tend to be water soluble. Stability data are less readily available. In water, PFAAs dissociate into their anions that are highly persistent and a cation such as K⁺, Li⁺, and NH₄⁺. Their global distribution may be through atmospheric transport of acids and/or transport of anions in water (Vierke et al. 2013). Atmospheric transport and transformation of volatile precursors, such as fluorotelomer compounds that degrade to PFAAs, may also be an important mechanism of global distribution (Prevedouros et al. 2006; Wang et al. 2014a, 2014b).

The perfluorinated polyether surfactants, such as hexafluoropropylene oxide dimer acid (HFPO-DA), are nonpolymer perfluoroalkyl substances, more specifically
| Type                        | Organic/inorganic | Name                  | Use                                                                                           | Structure         |
|-----------------------------|-------------------|-----------------------|------------------------------------------------------------------------------------------------|-------------------|
| Industrial chemical         | Inorganic         | NaF                   | Prevent dental caries, insecticide, wood preservative, cleaning compound, glass making        | Na–F              |
| Industrial chemical         | Inorganic         | HF                    | Making of refrigerants, pharmaceutical intermediates, fluoropolymers, metals, glass etching and polishing, gasoline production, semiconductor preparation | H–F              |
| Industrial chemical         | Inorganic         | CaF₂                  | Purification of Si, glass manufacture, removal of Pb in flotation waste, manufacture of clean steel, pigment for paper with TiO₂, solid lubricant for hot rollers, to strengthen cement | CaF₂              |
| Industrial chemical         | Organic           | R₁₃₄a (1,1,1,2-tetrafluoroethane) | Refrigerant, organic extraction solvent                                                  |                   |
| Industrial chemical         | Organic           | Perfluorooctanoic acid (PFOA) | Surfactant, fluoropolymer polymerization aid                                             |                   |
| Industrial chemical         | Organic           | Krytox (FG26)         | Lubricant                                                                                   |                   |
| Industrial chemical         | Organic           | Pyrazilumid           | Fungicide                                                                                   |                   |

(Continued)
| Type      | Organic/inorganic | Name              | Use                      | Structure |
|-----------|-------------------|-------------------|--------------------------|-----------|
| Pesticide | Organic           | Fluopyram         | Fungicide                |           |
| Pesticide | Organic           | Broflanilide      | Insecticide              |           |
| Pesticide | Organic           | Fipronil          | Insecticide              |           |
| Pharmaceutical | Organic       | Lipitor (atorvastatin) | Cholesterol lowering drug |           |
| Pharmaceutical | Organic    | Prozac (fluoxetine) | Antidepressant, antianxiety drug |           |
| Type                    | Organic/inorganic | Name               | Use                               | Structure |
|------------------------|-------------------|--------------------|-----------------------------------|-----------|
| Pharmaceutical         | Organic           | Celebrex (celecoxib) | Nonsteroidal anti-inflammatory drug (NSAID) | [Structure image] |
| Veterinary drug         | Organic           | Florfenicol        | Veterinary antibiotic              | [Structure image] |
| Veterinary drug,       | Organic           | Isoflurane         | Anesthetic                         | [Structure image] |
| medicinal              | Organic           |                    |                                   |            |

PFOA = perfluorooctanoic acid; WHO = World Health Organization.
* For more organic fluorinated compounds used in pharmaceuticals, pesticides, and veterinary drugs, see Cormier et al. (2009).
Table 2. Nonpolymer PFAS toxicity, physical, and chemical properties

| Substance | PFBA | PFHxA | PFOA | PFBS | PFOS | Hexafluoropropylene oxide (HFPO) dimer acid, ammonium salt | 2,2,3-trifluoro-1,1,2,3,3-pentafluoropropane (trifluoromethoxy) propanoic acid | 6:2 FTOH | 8:2 FTOH |
|-----------|------|-------|------|------|------|----------------------------------------------------------|----------------------------------------------------------|---------|---------|
| CAS number | 375-22-4 | 307-24-4 | 335-67-1 | 375-73-5 | 1763-23-1 | 62037-80-3 | 919005-14-4 | 647-42-7 | 678-39-7 |
| Structure | ![Structure](image1) | ![Structure](image2) | ![Structure](image3) | ![Structure](image4) | ![Structure](image5) | ![Structure](image6) | ![Structure](image7) | ![Structure](image8) | ![Structure](image9) |
| Chain length | Short | Short | Long | Short | Long | Short | Short | Short | Long |
| Molecular weight | 214.0384 | 314.0534 | 414.069 Da | 300.11 | 500.13 | 347.084 | 378.07 | 364.1 | 464.12 |
| Physical state, description | Liquid | Colorless liquid | White to off-white powder | Colorless liquid | Liquid | Clear, colorless liquid | Clear, colorless liquid | Clear, colorless to pale yellow liquid | Waxy solid |
| Boiling point | 120 to 121 °C | 157 °C | 192 °C | 210 to 212 °C | 249 °C | 108 °C | 183 °C | 171 °C | NDA |
| Melting point | −17.5 °C | NDA | 54.3 °C | NDA | NDA | 183 to 184 °C | NDA | 78 °C | NDA |
| Vapor pressure | 5866 Pa at 56 °C | 263.9 Pa at 25 °C (est) | 4.21 Pa at 25 °C | 3.57 Pa at 25 °C (est) | 0.2667 Pa at 25 °C | 2910 Pa at 20 °C | 32 Pa at 20 °C | 26.6645 Pa at 25 °C | 31 Pa at 25 °C |
| Stability (hydrolysis, photolysis, oxidation, thermal, biological) | Stable | Concentrations decreased by 0.8% after 106 d of solar irradiation; no other data | Stable | NDA | NDA | Stable | Stable | NDA | NDA |
| Water solubility (USP 2011) | 2.14 x 10^5 mg L^{-1} at 25 °C | In water, 1.570 mg L^{-1} at ambient temperature | 9.50 x 10^{-1} mg L^{-1} at 25 °C | In water, 3.2 x 10^{-3} mg L^{-1} at 25 °C (est) | >1000 g L^{-1} at 20 °C | 100% Soluble in water | “insoluble” 18.8 mg L^{-1} | 140 µg L^{-1} at 25 °C | |
| Log K_{OW} | Not applicable | 3.48 (est) | 4.81 (est) | 1.82 (est) | 4.49 (est) | NDA | 1.89 | 4.54 | NDA |
| Particle size µm | NDA | NDA | NDA | NDA | Dried solid 76% >105 microns; 24% < 105 microns | NDA | NDA | NDA | NDA |

(Continued)
Table 2. (Continued)

| Substance | PFBA | PFHxA | PFOA | PFBS | PFOS | Hexafluoropropylene oxide (HFPO) dimer acid, ammonium salt | 2,2,3-trifluoro-3-[1,1,2,2,3,3-hexafluoro-3-(trifluoromethoxy) propanoyl] propanoic acid | Acute Dermal LD50 | Skin irritant, Y or N | Eye irritant, Y or N | Skin sensitizer, Y or N | 90-d animal feeding study (no effect dose) | Mutagen, Y or N | Caused tumors in lab rats, Y or N | Half-life in humans | References |
|-----------|------|-------|------|------|------|-----------------------------------------------------------|---------------------------------------------------------------------------------|----------------|----------------------|----------------------|----------------------|---------------------|------------------------|------------------------|------------------|
| Nonpolymer PFAS | | | | | | | | | | | | | | | | |
| Perfluoroalkyl substances | | | | | | | | | | | | | | | | |
| Perfluoroalkyl acids (PFAA) | | | | | | | | | | | | | | | | |
| Polyfluoroalkyl substances | | | | | | | | | | | | | | | | |
| Fluorotelomer alcohols | | | | | | | | | | | | | | | | |
| Description | PFBA | PFHxA | PFOA | PFBS | PFOS | Hexafluoropropylene oxide (HFPO) dimer acid, ammonium salt | 2,2,3-trifluoro-3-[1,1,2,2,3,3-hexafluoro-3-(trifluoromethoxy) propanoyl] propanoic acid | Acute Dermal LD50 | Skin irritant, Y or N | Eye irritant, Y or N | Skin sensitizer, Y or N | 90-d animal feeding study (no effect dose) | Mutagen, Y or N | Caused tumors in lab rats, Y or N | Half-life in humans | References |
| Acute Dermal LD50 | NDA | Low (>2000 mg/kg) | Low (>2000 mg/kg) | Low (>2000 mg/kg) | NDA | Low (5000 mg/kg) | Low (5000 mg/kg) | NDA | Low (5000 mg/kg) | Low (5000 mg/kg) | NDA | Low (5000 mg/kg) | Low (5000 mg/kg) | NDA | NDA |
| Skin irritant, Y or N | Y, corrosive | Y | N | N | Y | Y | Y | Y | Y | Y | NDA | NDA | NDA | NDA | NDA |
| Eye irritant, Y or N | Y (serious damage) | Y | Y | Y | Y | Y | Y | Y | Y | Y | NDA | NDA | NDA | NDA | NDA |
| Skin sensitizer, Y or N | NDA | N | N | N | NDA | N | N | Y | N | N | NDA | NDA | NDA | NDA | NDA |
| 90-d animal feeding study (no effect dose) | 6 mg/kg-day | 50 mg/kg-day | 0.06 mg/kg-day | 200 mg/kg-day | 0.4 mg/kg-day | 0.1 mg/kg-day | 10 and 100 mg/kg-day for males, females | 5 mg/kg-day | 5 mg/kg-day |
| Mutagen, Y or N | NDA | N | N | N | N | N | N | N | N | N | NDA | NDA | NDA | NDA | NDA |
| Caused tumors in lab rats, Y or N | NDA | N | Y | NDA | Y | Y | NDA | NDA | NDA |
| Half-life in humans | 69 to 87 h | <28 d | 3.3 to 3.8 y | 24 to 46 d | 5.4 to 5.9 y | 2.3 h | 23 ± 11 d | NDA | NDA |
| References | (Ding and Peijnenburg 2013; NICNAS 2015; ChemSpider 2018; Sigma Aldrich 2018a; ATSDR 2018) | (Savu 1994; USEPA 2012; Environ 2014; Zhao L et al. 2014; ChemSpider 2014; ChemSpider 2016; Luz et al. 2019) | (Kennedy et al. 2004; Buhrenhoff et al. 2004; Yalkowsky et al. 2010; Bihatarei and Granata 2011; USEPA 2012; Aldrich 2015) | (Kosswig 2000; Lewis 2012; USEPA 2012; Sigma Aldrich 2015) | (Ashford 1994; Lewis 2012; USEPA 2012) | (Biegel et al. 2001; Caverly Rae et al. 2015; Beelerman et al. 2016; Hoke et al. 2016; ECHA 2019b; PubChem. 2019) | (Gordon 2011; Wang et al. 2013; ECHA 2020) | (Beekman et al. 2004; Yalkowsky et al. 2010; Bihatarei and Granata 2011; USEPA 2012; Aldrich 2015) | (Daikin 2007, 2009a, 2009b) | (Ladics et al. 2008; Climate and Pollution Agency, Norway 2010) |

PFAS = per- and polyfluoroalkyl substances; PFAA = perfluoroalkyl acids; PFBA = perfluorobutanoic acid; PFHxA = perfluorohexanoic acid; PFOA = perfluorooctanoic acid; PFBS = perfluorobutane sulfonic acid; HFPO = hexafluoropropylene oxide; FTOH = fluorotelomer alcohol; NDA = no data available.
perfluoroether carboxylic acids (PFECA) (see Table 2). Additional perfluoroalkyl substances include perfluorooctane sulfonic acid (PFOSI) and bis(perfluoroctyl) phosphonic acid, perfluoroalkane sulfonyl fluorides and sulfonamides, perfluoroalkanoyl fluorides, and perfluoroalkyl iodides and aldehydes (Buck et al. 2011). Refer to Table 2 for more comparisons of the toxicological, chemical, and physical properties of perfluoroalkyl substances.

Table 2 also compares the toxicological, chemical, and physical characteristics of some of the nonpolymer polyfluoroalkyl PFAS. Nonpolymer polyfluoroalkyl substances comprise a large number of compounds including semi-fluorinated n-alkanes and alkenes, fluorotelomer-based compounds (e.g., 6:2 fluorotelomer sulfonamide alkylation, 6:2 fluorotelomer sulfonate, 6:2 fluorotelomer sulfonamide amine, 6:2 fluorotelomer alcohol, 8:2 fluorotelomer alcohol, fluorotelomer iodides, fluorotelomer olefins, fluorotelomer aldehydes) (Moe et al. 2012; D’Agostino and Mabury 2014), polyfluoroalkyl phosphate surfactants (commonly referred to as PAPS), and their thioether derivatives (Trier et al. 2011). Many polyfluoroalkyl substances have the potential to be transformed in the environment into perfluoroalkyl substances (Prevedouros et al. 2006; Wang et al. 2014a, 2014b; Mejia-Avendaño et al. 2016; D’Agostino and Mabury 2017) and as such can be PFAA precursors.

Pesticides, pharmaceuticals, and veterinary drugs. As previously mentioned, many pesticides, pharmaceuticals, and veterinary drugs contain at least 1 fluorine atom with some containing more (see Table 1). These chemicals represent the many fluorinated chemicals that are beneficial to society that are not typically considered as PFAS as defined by Buck et al. (2011) or OECD (2018) but may be detected by nontargeted methods of analysis.

Polymer per- and polyfluoroalkyl substances. There are 3 types of PFAS polymers: fluoropolymers, perfluoropolyethers, and side-chain fluorinated polymers. The properties of fluoropolymers, such as polytetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), ethylene tetrafluoroethylene (ETFE), and perfluoroalkoxy (PFA), were extensively discussed by Henry et al. (2018). Fluoropolymers are characterized by very high molecular weights (>100 000 Da), insolubility in water and most organic solvents. See Table 3 for the toxicological, physical, and chemical properties of examples of the polymer PFAS.

Perfluoropolyethers span a broad range of molecular weight from <500 Da to greater than 10 000 Da (Sianesi et al. 1994). They exist as liquids or greases, and are sold commonly under the trade names of Krytox™, Fomblin®, and Galden® (see Table 3).

Side-chain fluorinated polymers constitute a diverse type of polymer substances. The fluorinated side-chain moieties of these materials can be produced by the telomerization or electrochemical fluorination process. Fluorinated side-chains are attached to the polymer backbone by a “spacer moiety” and a linking group, as shown in Figure 1.

Environmental occurrence of PFAS

Matrices

Some PFAS, mostly PFAAs, certain precursors, PFCAs, or perfluoroether sulfonic acids (PFESAs), are quite mobile and have been reported in multiple environmental and biotic matrices (e.g., drinking water, soil, air, surface or groundwater, precipitation, sediment, human blood, human breast milk, urine, aquatic and terrestrial organisms, plants) (Giesy and Kannan 2001; Ahrens and Bundschuh 2014; Wang et al. 2015; Chen et al. 2018; Macheda-Tsendengu et al. 2018; Gewurtz et al. 2019). The widespread occurrence of nonpolymer PFAS is due to their diverse chemical and physical properties (see above), which determine their environmental fate and transport.

Due in part to their lower molecular weight, nonpolymer PFAS are more likely to occur in water and air, which leads to their mobility and distribution distant from their point of manufacture, use, or disposal. For example, some of the nonpolymer perfluoroalkyl substances, like PFAAs, exist in their anionic form in water under environmental conditions, making them soluble and mobile in that matrix as demonstrated by their detection in surface water, groundwater, and drinking water (Ahrens and Bundschuh 2014; Chen et al. 2018; Crone et al. 2019; Gewurtz et al. 2019). In addition, per- and polyfluorinated substances, especially acids, telomers (acids and alcohols), amides, and amidoethanols, have been measured in the air where they are primarily associated with particles and aerosols (Barton et al. 2006; Chen et al. 2018; Wang et al. 2018; Han et al. 2019). In the atmosphere, some nonpolymer polyfluorinated PFAS, such as fluorotelomer alcohols (FTOAs), can be transformed to PFAAs (Ellis et al. 2004; Styrler et al. 2013), and then undergo global transport. Thus, the ability of some nonpolymer PFAS to dissolve in water or enter the atmosphere enables their long-range transport and global distribution (Dreyer et al. 2009; Cai et al. 2012a, 2012b; Vierke et al. 2013).

Water solubility and low molecular weight of the PFAA anions render them more likely to bioaccumulate (Conder et al. 2008; Liu et al. 2011).

The fluoropolymers and perfluoropolyethers generally display a high molecular weight, show no degradation under environmental conditions, little to no water solubility...
Table 3. Polymer PFAS toxicity, physical, and chemical properties

| Description | Side-chain fluorinated polymers | Fluoropolymer | Perfluoropolyether |
|-------------|---------------------------------|---------------|--------------------|
| Substance   | 6:2 Fluorotelomer acrylate*     | 6:2 Fluorotelomer methacrylate* | 1H,1H-perfluorooctyl methacrylate* | Polytetrafluoroethylene (PTFE) | 1,1,2,2,3,3,3-heptafluoro-3-(1,1,2,2,2-pentafluorooxy) propane |
| CAS number  | 17527-29-6                     | 2144-53-8     | 3934-23-4          | 9002-84-0                      | 60164-51-4                           |
| Structure   | ![Structure](image)             |               |                    |                               |                                   |
| Chain length| Short                           | Short         | Long               | N/A                            | N/A                                |
| Molecular weight | 418.15                        | 432.18        | 468.16             | 389 000–45 000 000             | NDA                                |
| Physical state/description | Colorless liquid            | Yellow liquid | Liquid             | Solid                          | Colorless, viscous liquid        |
| Boiling point | 210.2 °C                       | 210 °C        | 70 °C              | Not applicable                 | NDA                                |
| Melting point | Not applicable                  | Not applicable for liquids | Not applicable for liquids | 326 °C                        | NDA                                |
| Vapor pressure | 259 Pa at 25 °C                | 8.6 Pa at 25 °C | NDA                | NDA                            | NDA                                |
| Stability (hydrolysis, photolysis, oxidation, thermal, biological) | Unstable                     | Unstable       | NDA                | Stable                         | Stable                             |
| Water solubility (USP 2011) | 0.185 mg L⁻¹ at 25 °C           | 0.042 mg L⁻¹ at 20 °C | NDA                | Practically insoluble or insoluble (1 x 10⁻⁵ mg L⁻¹) | Insoluble                          |
| Log Kow     | NDA                            | 5.2 at 23 °C   | NDA                | NDA                            | NDA                                |
| Particle size µm | Not applicable for liquids | Not applicable for liquids | Not applicable for liquids | 100 to 500 µm (powders) | Not applicable for liquids |
| Acute dermal LD₅₀ | NDA                            | >5000 mg/kg    | NDA                | NDA                            | >17 000 mg/kg                        |
| Skin irritant, Y or N | N                              | N             | Y                  | N                              | N                                  |
| Eye irritant, Y or N | N                              | N             | Y                  | N                              | N                                  |
| Skin sensitizer, Y or N | N                              | N             | NDA                | N                              | N                                  |

(Continued)
or volatility, and therefore pose a low risk of mobility (note there are some lower molecular weight perfluoropolyethers (<1000 Da) with appreciable vapor pressures at ambient temperatures) (Sianesi et al. 1994). These polymer PFAS types would not be expected to be found in water or air or distant from their point of use or disposal, nor would they be expected to degrade to lower molecular weight PFAS.

The side-chain fluorinated polymers have high molecular weights, which makes them relatively nonmobile. The polymers themselves would not be expected to be found in water and air or distant from their point of use or disposal. However, unlike other polymer PFAS, they can degrade under environmental conditions to nonpolymer PFAS, which themselves can be mobile and undergo long-range transport (Prevedouros et al. 2006; Wang et al. 2014a, 2014b).

As discussed previously, water is one of the primary matrices by which the mobile PFAS are transported and how humans are exposed. For this reason, this paper will focus on drinking water and the various regulatory limits for PFAS in this matrix (see Table 4).

**REGULATION OF PFAS**

Globally regulators seek to identify, quantify, and characterize the organic fluorinated compounds in various media (e.g., drinking, surface, and groundwater; soil; sediment; air) to facilitate risk management. Regulations currently address only mobile PFAS, not polymeric PFAS. Some organic fluorinated compounds are regulated locally (e.g., perfluorononanoic acid maximum contaminant level [MCL] in drinking water by the New Jersey Dept. of Environmental Protection), nationally (e.g., perfluorooctanoic acid in drinking water maximum acceptable concentration by Health Canada), or internationally (e.g., Stockholm Convention on Persistent Organic Pollutants).

Currently, the most “horizontal” and widest legally binding regulation of PFAS are the listings in the Stockholm Convention on Persistent Organic Pollutants (POPs) with the aim of elimination of production and use of these chemicals: PFOS, its salts, and PFOSF in annex B (UNEP 2009, 2019a); PFOA, its salts, and PFOA-related compounds in annex A.
Table 4. Standards and guidance values for PFAS in drinking water; PFAS analyte concentration (µg/L)

| Location          | Agency and/or dept. | Standard and/or guidance | Type      | PFBA | PFHxA | PFOA | PFBS | PFOS | HFPO | NH₄⁺ |
|-------------------|---------------------|--------------------------|-----------|------|-------|------|------|------|------|------|
| CAS number        | 375-22-4            | 307-24-4                 | 335-67-1  | 375-73-5 | 1763-23-1 | 3252-13-6 |
| US Environmental Protection Agency |                  |                          |           |      |       |      |      |      |      |      |
| USEPA             | Office of Water     | HA                       | DW        | 0.070| 0.070 |
| US states         |                      |                          |           |      |       |      |      |      |      |      |
| Alaska (AK)       | DEC                 | Action level             | DW/GW/SW  | 0.070| 0.070 |
| California (CA)   | SWRCB               | NL                       | DW        | 0.0051| 0.0065 |
|                   | SWRCB               | RL (CA)                  | DW        | 0.0100| 0.0400 |
| Connecticut (CT)  | DPH                 | AL                       | DW/GW     | 0.070| 0.070 |
| Massachusetts (MA)| DEP                 | Drinking water values    | DW        | 0.020| 0.020 |
| Michigan (MI)     | DEQ                 | GCC                      | DW/GW     | 0.070| 0.070 |
|                   | DHHS                | Screening levels         | DW        | 0.009| 1     | 0.008 |
| Minnesota (MN)    | MDH                 | HRL-subchronic           | DW/GW     | 7    | 0.035 | 9    |
|                   | MDH                 | HRL-chronic              | DW/GW     | 7    | 0.035 | 7    | 0.300 |
|                   | MDH                 | HBV-subchronic           | DW/GW     | 3    | 0.015 |
|                   | MDH                 | HBV-chronic              | DW/GW     | 2    | 0.015 |
| Nevada (NV)       | DEP                 | BCL                      | DW        | 0.667| 0.667 | 0.667 |
| New Jersey (NJ)   | DEP                 | MCL                      | DW        |      |      |      |      |      |      |
|                   | DWQI                | MCL                      | DW        | 0.014|      |      |      |      |      |
|                   | DWQI                | MCL                      | DW        |      |      |      |      |      |      |
| Location                | Agency and/or dept. | Standard and/or guidance | Type         | PFBA | PFHxA | PFOA | PFBS | PFOS | HFPO NH₄⁺ |
|-------------------------|---------------------|--------------------------|--------------|------|-------|------|------|------|-----------|
| North Carolina (NC)     | DHHS                | Health goal              | DW           |      |       |      |      |      | 0.140     |
| Ohio (OH)               | ODH                 | Action level             | DW           | 0.070| 140   | 0.070| 0.700|      |           |
| Rhode Island            | DEM                 | GWQS                     | DW/GW        | 0.070|       | 0.070|      |      |           |
| Vermont (VT)            | DEC/DOH             | MCL                      | DW/GW        | 0.020|       | 0.020|      |      |           |
|                         | DEC/DOH             | HA                       | DW/GW        | 0.020|       | 0.020|      |      |           |
| International           |                     |                          |              |      |       |      |      |      |           |
| Australia               | DOH                 | Health-based             | DW           | 0.560|       | 0.070|      |      |           |
| British Columbia, Canada|                     | Water standard           | DW/GW        | 0.200| 80    | 0.300|      |      |           |
| Canada                  | HC                  | DWSV                     | DW           | 30   | 0.200 | 0.200| 15   | 0.600   |
|                         | HC                  | DWSV                     | DW           |      |       |      |      |      |           |
|                         | HC                  | MAC                      | DW           | 0.200|       | 0.600|      |      |           |
| Denmark                 | EPA                 | Health-based             | DW/GW        | 0.100| 0.100 | 0.100| 0.100| 0.100  |
| Germany                 | GMH                 | Health-based             | DW           | 0.300|       | 0.300|      |      |           |
|                         | Administrative      | DW                        |              | 0.100|       | 0.100|      |      |           |
| Italy                   |                     | Health-based             | DW           | 7    | 1     | 0.500| 3    | 0.030   |
| Netherlands             | EPA                 | Health-based             | DW           |      |       | 0.530|      |      |           |
|                         | Administrative      | DW                        |              |      |       | 0.0053|      |      |           |
| Sweden                  |                     | Health-based             | DW           | 0.090| 0.090 | 0.090|      |      |           |
|                         | Administrative      | DW                        |              | 0.090| 0.090 | 0.090|      |      |           |

(Continued)
Table 4. (Continued)

| Location | Agency and/or dept. | Standard and/or guidance | Type | PFBA | PFHxA | PFOS | PFBS | PFAS | HFPO NH₄⁺ |
|----------|---------------------|--------------------------|------|------|-------|------|------|------|-----------|
| USA      | Admin. level 1      | DW                        | PFAS | 10   | 0.300 | 0.300 |      |      | 1         |
| USA      | Admin. level 2      | DW                        | PFAS | 10   | 0.300 | 0.300 |      |      | 1         |
| USA      | Admin. level 3      | DW                        | PFAS | 90   | 0.300 | 0.300 |      |      | 9         |

Note: The values for these nonpolymer PFAS vary across programs (recommended for listing) in annex A (UNEP 2019b); and PFHxS, its salts, and PFHxS-related compounds (recommended for listing) also in annex A (UNEP 2019c). No other PFAS are under consideration for the Stockholm Convention currently. Note that the POPs definition does not include limit values for any matrix and often is not correct as to terminology although CAS numbers are provided. To establish trends over time using ambient air, surface water, or human milk as core matrices, all POPs listed in the Convention (e.g., PFOS, PFOA) including certain transformation products or precursors shall be included in environmental and human monitoring plans (UNEP 2019d).

The World Health Organization (WHO), in accordance with the WHO Framework for safe drinking water, has included PFOS and PFOA, due to their widespread occurrence and respective health concerns (WHO 2017). The report recommends that the guideline values (GVs) for drinking water are 0.4 μg·L⁻¹ (ppb) for PFOS and 4.0 μg·L⁻¹ (ppb) for PFOA (note that these GVs were derived on the basis tolerable daily intake [TDI] values of the European Food Safety Authority [EFSA] report as of 2008, which stipulated TDIs of 0.15 μg per kg bodyweight per day for PFOS and 1.5 μg per kg body weight and day) (EFSA 2008). The EFSA recommended much lower tolerable intake values in 2018 expressed as tolerable weekly intakes (TWI) of 13 ng per kg bodyweight per week and TWI of 6 ng per kg bodyweight per week for PFOS and PFOA, respectively (EFSA 2018a). A group value TWI of 4.4 ng per kg bodyweight per week was proposed by EFSA in 2020 for PFOA, PFOS, PFHxS, and PFNA (EFSA CONTAM Panel 2020). In contrast to limits set for water, air, or soil, which reflect the concentration of the above mentioned PFAS in that medium, the TDI or TWI is the mass of the PFAS that can be safely consumed in the diet per kilogram of human body weight per day or week; it is a dose. The EFSA used the upper bound 95th percentile human consumption for these limits imparting a high degree of conservatism because 95% of the population will consume this amount or less of these specific PFAS per day or week.

Regarding drinking water intended for human consumption in Europe, the EC modified the 2017 WHO values and recommends sum parameters by including 11 PFAS (PFBS, PFHxS, PFOS, 6:2 fluorotelomer sulfonic acid [6:2 FTSA], PFBA, perfluorooctanoic acid, [PFPeA], PFHxA, perfluorohexanoic acid [PFHpA], PFOA, perfluorononanoic acid [PFNA], and perfluorodecanoic acid [PFDA]) and recommends values of 0.1 μg L⁻¹ (ppb) for individual PFAS and 0.5 μg L⁻¹ (ppb) for PFAS as the sum (EC 2017).

In the United States, regulatory human health-based guidance values (HBVs) and/or standards have been derived for 16 PFAAs, and/or including 2 polyfluoroalkyl precursors, and 1 fluorinated ether carboxylate (Feca) by state and/or federal agencies in the United States, as of September 2019 (see Table 4 for US and international standards and HBVs for drinking water for a subset of these perfluorocarboxylic acids [PFCA], PFSAs, and a PFNA). The values for these nonpolymer PFAS vary across programs. Differences can be attributed to selection and interpretation of different key toxicity studies, choice of
uncertainty factors, approaches used for animal-to-human extrapolation, the life stage and the percentage of exposure assumed to come from nondrinking water sources, and so forth. The vast majority of regulatory guidance and/or standards available are for PFOA and PFOS (ITRC 2020).

The US Environmental Protection Agency (USEPA) and the Food and Drug Administration (FDA) are the 2 US federal agencies that have the legal authority to regulate PFAS. Currently, both agencies have regulatory or guidance initiatives for PFAs.

The only USEPA “limit” for a PFAS that exists is the USEPA lifetime health advisory (LHA) of 70 ng/L−1 for PFOA and PFOS (individually or in combination if both are present) in drinking water, which is advisory in nature, not legally enforceable, and is subject to change (USEPA 2016a, 2016b). But, since 2002, the USEPA has utilized use and import regulations under Section 5 of the Toxic Substance Control Act (TSCA) to monitor PFAS through multiple final Significant New Use Rules (SNURs) covering over 250 fluorinated organic substances (polymeric and nonpolymeric) and an SNUR for PFOA and PFOS. The USEPA established an action plan for PFAS in 2019 (USEPA 2019c), while US regulatory HBVs and standards have been primarily focused on PFCAs, PFASs, and precursors to them, in early 2020, a SNUR and Premanufacture Notice was issued for a fluoropolymer (P-17-0400; SNUR 40 CFR 721.11414) involving any new use of a terpolymer of vinylidene fluoride, tetrafluoroethylene, and 2,3,3,3-tetrafluoropropene, that results in inhalation exposure.

The USEPA has generated data around PFAS in public drinking water through the Unregulated Contaminant Monitoring Rule (UCMR), which included 6 PFAs in the most recent round of monitoring efforts: PFOA, PFOS, PFNA, PFHxS, PFHpA, and PFBS. The UCMR3 reported limits of between 10 and 90 ng/L depending on the specific PFAs (USEPA 2017).

To the inexperienced, these limits can appear to be an almost random assortment of numerical values. In actuality, each limit is based in part on definitions, statutes, and risk assessment processes that vary between laws and across regulatory authorities, jurisdictions, and media being regulated (e.g., surface, ground, or drinking water) (see Table 4). The end result is widely varying regulatory limits for the same chemical often in the same matrix. Thus, caution must be used when comparing and interpreting analytical results to different limits across regulatory jurisdictions.

Robust, reproducible, and validated methods to differentiate organic from inorganic fluorinated compounds, as well as between the many types of organic fluorinated compounds, are needed for regulatory purposes. The next section will present some analytical approaches for various types of fluorine and the importance of interlaboratory assessment.

**ANALYTICAL METHODS TO IDENTIFY ORGANIC FLUORINATED COMPOUNDS**

In this section, we will focus on the organic per- and poly-fluoroalkyl substances, especially the sulfonic and carboxylic acids, but not on pesticides, pharmaceuticals, or veterinary drugs. The analytical methods discussed here will start with the determination of all fluorine in a sample, briefly cover some parameters, and finish with confirmatory analysis of specific PFAS including identification of certain isomers. This compilation is primarily created to support regulations or controls for the various jurisdictions or attempt to create a common basis for harmonizing reporting of results. Table 5 provides a graphical sketch to categorize fluorine in the different types as they can be determined analytically. Some fluorine-containing compounds, such as nonpolymer PFAS, can be detected by multiple method types, while others, such as CaF₂, can only be detected by total fluorine methods (Koch et al. 2020).

The ability of PFAS to respond in a method depends on the specific PFAS, extraction method, sample matrix, chromatography conditions (if applicable), and instrument settings. The table also indicates which types of methods are unable to differentiate between PFAS. For example, many approaches only detect fluorine and may not be able to differentiate between nonpolymer and polymer PFAS. By application of certain extraction solvents as used in extractable organic fluorine (EOF), some specification can be obtained. Only after extraction and purification can neutral PFAS be differentiated from ionic forms and specific PFAS be determined (e.g., identified by CAS numbers).

Total fluorine

Total fluorine (TF) in chemical compounds can be defined as the sum of inorganic fluorine (IF) and organic fluorine (OF). Total fluorine in biota, especially blood, can be determined by total mineralization in O or H atmospheres and subsequent absorption of the fluoride in water and detection with fluoride ion-selective electrodes, such as in the Wickbold Torch method (Čapka et al. 2004). Total fluorine can also be analytically determined by proton induced gamma emission (PIGE), which measures gamma ray emissions from fluorine atoms in a sample in response to an ion beam. The PIGE has been applied to determine the total fluorine in paper and textiles (Robel et al. 2017). Another approach uses inductively coupled plasma mass spectrometer (ICP MS/MS) through the formation of the polyatomic ion BaF⁺ to enable fluorine analysis (Jamari et al. 2017; Feldmann et al. 2018). While, theoretically, all fluorine, organic and inorganic, can be determined with these methods, the ability to detect polymer PFAS, for example, will depend on sample preparation and material properties. Most fluoropolymers have limited, if any, solubility. Inorganic fluorine, such as sodium fluoride, and fluorinated pharmaceuticals and pesticides, are expected to respond in this ICP MS/MS method.

Total organic fluorine (TOF) or total extractable organic fluorine

In total extractable organic fluorine (TEOF) analysis, the sample is divided whereby the first portion undergoes
Table 5. Analytical approaches for PFAS within determination of fluorine

| PFAS | Total fluorine | IF | OF | Nonextractable fluorine | Extractable fluorine | Quantifiable | Unquantifiable | Identifiable | Unknown |
|------|----------------|----|----|--------------------------|----------------------|--------------|---------------|--------------|---------|
|      |                |    |    |                          |                      |              |               |              |         |
| Nonpolymer - perfluoroalkyl substances | | | | | | | | | |
| Perfluoroalkyl acids | + | − | − | + | + | ? |
| Perfluoropolyether carboxylic acids | + | − | − | + | + | ? |
| Perfluoroalkyl sulfonic acids | + | − | − | + | + | ? |
| Perfluoroalkyl phosphinic acids | + | − | − | + | + | ? |
| Perfluoroalkyl sulfonyl fluorides | + | − | − | + | + | ? |
| Perfluoroalkyl sulfonamides | + | − | − | + | + | ? |
| Perfluoroalkyl iodides | + | − | − | + | + | ? |
| Nonpolymer - polyfluoroalkyl substances | | | | | | | | | |
| Fluorotelomer alcohols | + | − | − | + | + | ? |
| Fluorotelomer sulfonamides and derivatives | + | − | − | + | + | ? |
| Fluorotelomer sulfonates | + | − | − | + | + | ? |
| Fluorotelomer iodides | + | − | − | + | + | ? |
| Fluorotelomer olefins and aldehydes | + | − | − | + | + | ? |
| Fluorinated pharmaceuticals and pesticides | + | − | − | + | + | ? |
| Polyfluoralkyl phosphate surfactants | + | − | − | + | + | ? |
| Semifluorinated n-alkanes and alkenes | + | − | − | + | + | ? |
| Polymer - fluoropolymers | | | | | | | | | |
| PTFE, FEP | + | − | + | − | − | − |
| Fluoroelastomers | + | − | + | − | − | − |
| Polymer − perfluoropolyethers | | | | | | | | | |
| Fomblin or Galden materials | + | − | + | − | − | − |
| Polymer - side-chain fluorinated polymers | | | | | | | | | |
| Fluorinated acrylate and methacrylate polymers | | | | | | | | | |
| Fluorinated urethane polymers | + | − | + | − | − | − |

PFAS = per- and polyfluoroalkyl substances; IF = inorganic F; OF = organic F; TOF = total organic fluorine; PTFE = polytetrafluoroethylene; FEP = fluorinated ethylene propylene.

+ = a PFAS is detectable by the type of analytical method.
− = a PFAS is not detectable by the type of analytical method.
? = substances under this definition can be detected with a given analytical method as unknowns.

Footnotes:

1 Lower molecular weight species (<1000 Da) may be quantifiable, unquantifiable yet identifiable, or unknowns.
2 Transformation can create other PFAS that are quantifiable, unquantifiable yet identifiable, or unknowns.

Numeric footnotes provide common types of instrumentation used for targeted quantitative analysis.

References:

1 LC-MS – (Jahnke & Berger 2009; D’eon et al. 2009; Sun et al. 2011; Lee and Mabury 2017; Robel et al. 2017; ISO 2019; USEPA 2019a; USEPA 2020; Pan et al. 2020).
2 GC-MS – (Alzaga & Bayona 2004; Jahnke & Berger 2009; Orata et al. 2009; Bach et al. 2016; Robel et al. 2017).
3 GC-ECD (Plaschmann et al. 2010).
targeted or confirmatory analysis according to one of the approaches discussed in the Targeted Analysis section. Combustion ion chromatography (CIC) is used on the second portion to determine TF and EOF. It uses an automated combustion unit and an ion chromatography system (Yeung et al. 2009). The ability to detect nonpolymer PFAS, including fluorinated pharmaceuticals and pesticides, will be affected by the extraction conditions, the nature of the sample matrix, and the specific nonpolymer PFAS. The ability to detect polymer PFAS will depend on sample preparation and material properties. In most applications, there was a large amount of fluorine that could not be assigned to any type of fluorinated organic substance; thus, often leaving up to 92% of the fluorine unknown (Kärrman et al. 2019; Koch et al. 2019).

Total oxidizable precursor

Total oxidizable precursor (TOP) analysis uses hydroxyl radicals where all polyfluorinated precursors are oxidized into PFCAs, the final “dead end” oxidation products (Houtz and Sedlak 2012; Houtz et al. 2013). This procedure involves chemical and thermal treatment of the samples and is restricted to aqueous extracts or water samples. Water soluble nonpolymer PFAS are expected to respond in this method. Nonpolymer PFAS with few fluorine atoms, such as a single CF$_3$ group, are expected to have a poor response. Polymer PFAS, such as fluoropolymers and perfluropolymers, will not be detected in these methods because of their insolvency in aqueous solvents.

It shall be noted that all of the above-mentioned approaches can be used for mass balance purposes to quantify fluorine in samples of interest. The approaches are destructive to the organic molecule and do not allow a retrospective identification of specific organic fluorinated compounds. Both the TOF and the TOP approaches are typically complemented by a second chromatographic separation and determination, the targeted analysis to identify the known and often restricted substances.

Nontargeted and targeted analysis for nonpolymer PFAS

Nontargeted analysis explores unknown compounds using mass spectrometry by identifying a peak in a chromatogram. Today, time-of-flight (ToF) or Orbitrap instruments are used for nontargeted analysis. In a typical approach, one would be looking at protonated molecules using MS/MS spectra for identification. A nontargeted method would allow detection of both known and unknown chemicals; however, not all peaks are identified and only a limited number of the most abundant ions (50–100) will be monitored over the entire time of the experiment. The largest problem in nontargeted analysis is the data processing. Since the chemicals present in the (injected) sample depend on extraction and purification methods, in practice it is not possible to see all chemicals in a sample (even the unknowns). A recent paper provides an example for the determination of 24 PFAS in firefighting foams using LC/qToF instrumentation (Dubocq et al. 2020).

Targeted analysis means that the analyst is looking for specific chemicals only. For such confirmatory analysis, typically mass spectrometry on selected reaction monitoring (SRM) and the fragmentation profile based on retention time of compounds compared with internal standards are used. The mass spectra and retention times for each compound are known and all targeted chemicals above the noise level will be detected by this approach. The determination is typically optimized for sensitivity and selectivity, and subsequently reduced by limiting the number of analytes. Other chemicals present in the sample will not be seen. Berger et al. (2004) and Liu et al. (2019) provide good reviews of targeted methods for nonpolymer PFAS.

Nonpolymer PFAS can be identified after either gas chromatographic or liquid chromatographic separation followed by mass selective determination. The most used instrumentation for the determination of nonpolymer ionic PFAS is a combination of liquid chromatography (LC) using either HPLC or UPLC columns (high performance or ultrahigh performance liquid chromatography) coupled to a mass selective detector (LC/MS). The most commonly used detector is a triple quadrupole MS (MS/MS) detector in negative ion mode. Time-of-flight detectors or Orbitrap, can be used as well; however, the large datasets generated may pose a problem due to limitations in storage size. The LC MS/MS approaches are commonly used for the determination of ionic PFAS in ambient or indoor air. Gas chromatography is used for the neutral volatile PFAS such as certain PFOS precursors such as the perfluorooctane sulfonamides (FOSAs) and the perfluorooctane sulfonamide ethanols (FOSEs), or FTOHs, which are determined with chemical ionization (CI) GC/MS. Fluoroalkyl acids can be analyzed by GC/MS (with negative chemical ionization, GC-NCI-MS) approaches after derivatization, thus requiring much greater effort in sample preparation; for examples, see Alzaga and Bayona (2004) and Orata et al. (2009).

Applications of either LC MS/MS or GC/MS instrumentation include the analysis of ambient or indoor air collected with polyurethane foam (PUF), XAD$^\text{®}$ or solvent impregnated PUFs (SIPs), and solid-phase cartridges (SPE) or grab samples (Jahnke et al. 2007; Wang et al. 2018). Analyses of aqueous matrices include drinking water, ground or surface waters, as well as waste waters. The most commonly used methods are either ISO or EPA methods or variations thereof (ISO 2019; USEPA 2019b; Shoemaker and Tettenhorst 2020). Ionic and neutral PFAS have also been determined after Soxhlet, pressurized liquid or solid liquid extraction followed by ENVI-Carb or SPE clean-up in abiotic solid matrices like sediments, soils, or sludges (Ahrens 2011; Ahrens et al. 2016) as well as in foods of animal or plant origin (Chu et al. 2016; EFSA 2018b, 2020; Sadia et al. 2020). Reviews by various authors or institutions provide examples of approaches of analysis of perfluoroalkyl and PFASs in different sample matrices (Jahnke and Berger 2009; Berger et al. 2011; Liu et al. 2019; USEPA 2019b; Pan et al. 2020; USEPA et al. 2020).
Quality assurance and quality control

Today, commercial suppliers provide a wide spectrum of native and isotopically labeled internal standards for PFAS used at different steps of the analysis (extraction, recovery, quantification). The availability of such standards steadily increases and include: PFCA, PFSA, FOSA, FOS, FOSA, FTOHs, fluorotelomer acids (FTAs), fluorotelomer sulfonates (FTSs), perfluoroalkylphosphonic acids (PFAPAs), and perfluoroalkylphosphinic acids (PFPPs). There are not yet internationally agreed mixtures of PFAS available since the scope of many monitoring and other projects vary. Most research groups prepare their own standard solutions as a mixture of individual compounds to meet the purpose of the investigation.

For quality control purposes, standard reference materials (SRM) are available (for serum and human milk by the US National Institute of Standards and Technology (NIST) (Schantz et al. 2013), and international intercalibration assessments are undertaken (Fiedler et al. 2017; Fiedler et al. 2020) coordinated by UNEP or Quasimeme (Weiss et al. 2013). In the UNEP-coordinated interlaboratory assessments, between 20 and 30 laboratories participate in these studies. In comparison with the analysis of organochlorine pesticides, these LC MS/MS laboratories generally have better performances. In the UNEP-coordinated interlaboratory assessments, satisfactory performance is granted to a laboratory’s value that is 25% above or below the assigned value (satisfactory results with <2 z-scores corresponding to ±25% deviation from assigned value); others use ±40%. In general, the more sophisticated laboratories (e.g., having MS detection and isotopically labelled internal standards) perform better than the laboratories with simple instrumentation, for example, electron capture detection (Fiedler et al. 2020). The results have shown that dioxin and PFAS laboratories have higher percentages of satisfactory results than laboratories analyzing organochlorine pesticides. However, it also has to be noted that due to the lack of harmonized regulation, the spectrum of PFAS analyzed and the types of matrices are many, so that often the number of participating laboratories is too small for a statistical evaluation to be performed.

As discussed previously, TOF, TOP, or PIGE spectroscopy methods can be applied to polymer PFAS. Response will depend on sample preparation and material properties. It also shall be noted that on the basis of these sum parameters, environmental fate, transformation and/or metabolism, or toxicity cannot be determined.

It is critically important to remember that chemical bonds that can be broken in an analytical lab do not automatically reflect real world environmental transformations. For example, combustion ion chromatography subjects samples to extreme temperatures not reflective of actual environmental scenarios. In addition, some testing is intended to be destructive to the sample while other testing is not. Finally, since robust analytical data can be the basis for regulation, be mindful of whether the method is analyzing a parent compound or something created or manipulated in the laboratory analysis.

DISCUSSION

In this paper, we summarized a broad spectrum of inorganic and organic fluorinated substances and matched them with analytical approaches and subsequent application in regulatory context. We found widely accepted methods only for a limited number of organic fluorinated substances such as the PFAAs in drinking water while those for other environmental matrices are not yet defined.

In order to address the above mentioned gap, clarity is needed to match the analytical method to the goal of the analyses. Is the analysis to advance pure research or pragmatically to determine the extent of a reported accidental release to a river? Is it monitoring for specific substances in the emissions at a manufacturing facility to determine environmental permit compliance? Is it a survey to determine if organic fluorinated substances are present and then to identify and quantify baseline levels of specific compounds? Knowing the purpose of the analysis and how the results are intended to be interpreted and used (e.g., identify what was released into the river; confirm the facility is in compliance with the permit; no organic fluorine is present) will inform analytical decision making. Analytical techniques that identify organic fluorine coupled together with targeted chemical analysis will yield information sufficient to identify public health or environmental hazards.

Valid analytical chemistry measurements provide critical information on the presence of PFAS in the environment, but cannot by themselves determine sources of PFAS because the measured analyte itself can have multiple sources (e.g., itself as a product, transformation product from nonpolymer PFAS, and degradation from side-chain fluorinated polymers). In other cases, the analytical method (e.g., PIGE, T(E)OF) does not provide sufficient specificity for PFAS identification, which limits the utility of the measurement in determining sources. Proper source attribution requires an understanding of the method specificity, the environmental fate, transport, and possible precursors of the analyte, as well as location-specific information on historical use and possible sources. Misattribution of sources may result in undue public alarm, ineffective regulation, and wasted regulatory resources. Similarly, incorrect comparisons between analytical measurements and regulatory limits (e.g., ocean water measurements compared to drinking water standards) can mislead the public as to whether a PFAS in a particular environmental matrix should be a concern. This paper provides guidance on an approach to analyses of drinking water for the presence of organic fluorinated compounds as well as which analytical method is optimal.

Before a regulatory authority sets a limit for a PFAS substance, some clear, unambiguous criteria, usually hazard-based, should be established. Definitions of hazard differ across and within jurisdictions for different statutes, law, conventions, and so forth, leading to variations in
limits for the same substance in the same media (e.g., food, drinking water, soil). The objectives of various laws, conventions, and other regulatory authorities may also vary impacting how limits are set and for which substances. Differences in limits for the same PFAS in the same media across jurisdictions can be attributed to selection and interpretation of different key toxicity studies, choice of uncertainty factors, approaches used for animal-to-human extrapolation, the life stage assessed, and the percentage of exposure assumed to come from non-drinking water sources, and so forth. Matrices for PFAS limits differ for water between surface, ground, and drinking water. Some limits are advisory in nature while others are legally enforceable. Even within a jurisdiction, differences in limits for the same substance may be attributed to differing exposure or risk assessment processes using the same scientific data. In the USEPA alone there are MCLs under the Safe Drinking Water Act, water quality standards under the Clean Water Act, the Clean Air Act’s technology-based “maximum achievable control technology” air quality criteria to avoid emission that “may reasonably be anticipated to endanger public health or welfare,” or site cleanup standards under the Superfund Amendments and Reauthorization Act. Some laws are set to protect environmental quality and others human health. Because these different regulatory objectives, endpoints, processes, matrices, and units vary, one must be cautious in interpreting analytical results in terms of specific regulatory values.

CONCLUSIONS

There are many organic fluorinated compounds of varying physical, chemical, and toxicological properties. Some of these compounds are PFAS, but there are other fluorinated organic compounds that do not have the C\(_2\)F\(_n\)(CF\(_2\))\(_n\) moiety. Whether they are PFAS or not, they can be persistent, widespread in the environment, or toxic. To effectively protect public health and the environment, efforts must focus on those fluorinated compounds that pose the greatest risk, which necessitates an understanding of exposure pathways and determination of the concentration of the hazardous substance therein. Adequate samples from potential exposure media must be taken and analyzed appropriately per national and internationally accepted methods. Since these methods do not always exist, this paper addressed analytical approaches so that fluorinated organic compounds can be identified and quantified appropriately. This paper provided an overview of fluoride-containing compounds, their uses, their toxicological, chemical, and physical properties in relation to environmental occurrence, their analysis, and how the interpretation of the analytical data is critical to effective regulation.

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