Potential Designated Chemicals:

Perfluoroalkyl and Polyfluoroalkyl Substances (PFASs)

March 13, 2015 Meeting of the Scientific Guidance Panel

Biomonitoring California[1]

Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are a class of fluorinated organic chemicals containing at least one fully fluorinated carbon atom.[2] The C-F bond is one of the strongest known covalent bonds, and the multiple C-F bonds in PFASs impart their chemical and thermal stability. The strength of the C-F bond arises, in part, from the electronegativity of the fluorine atom and from unique characteristics of the fluorine and carbon bonding orbitals (Kissa, 2001).

A chemical is a called a polyfluoroalkyl substance if hydrogen atoms on at least one of the carbon atoms have been replaced by fluorine atoms. If all of the hydrogen atoms attached to carbon atoms are replaced by fluorine atoms, the chemical is called a perfluoroalkyl substance.

PFASs are used to provide water, oil and stain repellency to textiles, carpets and leather, to create grease-proof and water-proof coatings for paper plates and food packaging, and as processing aids in fluoropolymer manufacturing. They are also used in chrome plating, in firefighting foams, and in many other applications (Trier et al., 2011; Z Wang et al., 2013).

After extensive industrial and consumer uses beginning in the late 1940s, perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) were found to be ubiquitous in the environment and in biota. PFOS, PFOA, perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS) have been detected in nearly all people tested (Calafat et al., 2007). PFOS, PFOA and several other long chain PFASs are now regulated by the European Union (EU) and Canada. Manufacturing of PFOS, PFOS-based and other perfluoroalkyl sulfonate-based chemicals with six or more carbon atoms was voluntarily phased-out in the U.S. during 2001 - 2002 (Buck et al., 2011). In 2006, the U.S. Environmental Protection Agency (U.S. EPA) and eight major manufacturers announced a voluntary PFOA phase-out, with a 95% use reduction by 2010 and elimination of all uses by 2015 (2010/2015 PFOA Stewardship Program) (U.S. EPA, 2009).

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[1] California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 et seq.

[2] Buck et al. (2011) defines the class of PFASs as “aliphatic substances containing one or more C atoms on which all the H substituents present in the nonfluorinated analogues from which they are notionally derived have been replaced by F atoms, in such a manner that PFASs contain the perfluoroalkyl moiety CnF2n+1 –.” For complete technical details on the class definition, see Buck et al.

The phase-outs of PFOS-related chemicals, PFOA and other long-chain PFASs have led to the development of a large number of replacement PFASs. Buck et al. (2011) lists 42 families and subfamilies of PFASs and 268 selected individual PFASs. Z Wang et al. (2013) discusses new PFASs being developed to replace phased-out compounds.

Twelve perfluorinated compounds are currently measured in Biomonitoring California studies (see Table 1 on page 4), including perfluorobutane sulfonic acid (PFBS), a PFOS replacement introduced in 2003. These chemicals were incorporated into the list of designated chemicals via their inclusion in the National Reports on Human Exposure to Environmental Chemicals program of the Centers for Disease Control and Prevention (CDC). At the July 2009 Scientific Guidance Panel (SGP) meeting, Panel members recommended that all twelve of the designated perfluorinated chemicals be named as priority chemicals (see Table 1).

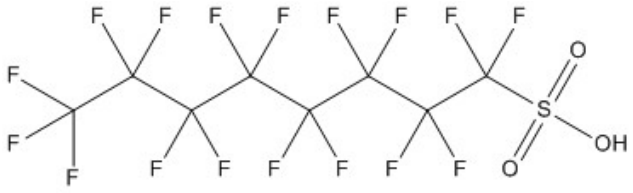
Recently, some PFASs that are not currently designated chemicals for Biomonitoring California have been detected in biomonitoring studies by other groups. For example, polyfluoroalkyl phosphate diesters (diPAPs), which are used in food packaging, have been detected in serum and breast milk (D'eon et al., 2009; Lee and Mabury, 2011; Kubwabo et al., 2013). Metabolites of a fluorotelomer alcohol (FTOH) were detected in a biomonitoring study of ski wax technicians in Sweden (Nilsson et al., 2013). Given the wide range of new PFASs, many more replacement chemicals, precursors, or breakdown products might also be detected in human blood or other biological samples.

This summary provides the Panel with information to consider recommending the addition of the entire class of PFASs to the list of designated chemicals for Biomonitoring California. If the Panel were to recommend adding the class of PFASs as designated chemicals, the Program could include any member of this class in future biomonitoring studies. Listing of this broad group would give the Program the flexibility to choose new PFASs of potential health concern that would be appropriate to measure in response to market shifts.

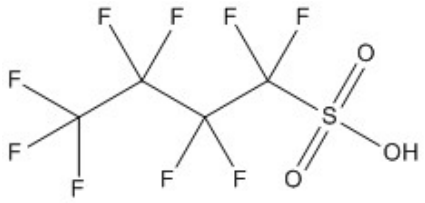
There is an extensive body of literature on PFASs. However, information is available primarily on PFOS, PFOA and other long chain perfluorinated compounds. Below we provide highlights from selected studies, with a focus on those that report findings on PFASs not currently included on the list of designated chemicals.

Chemical identity and example structures

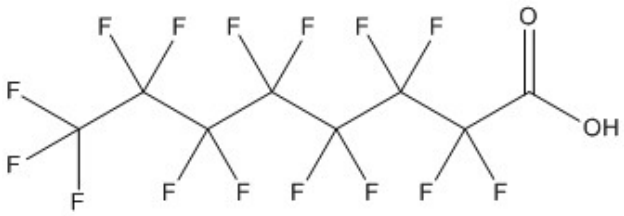
Table 1 (on page 4) summarizes some of the sub-types of PFASs, and provides the names and acronyms of substances mentioned in this document. PFASs already included as designated and priority chemicals for Biomonitoring California are indicated with an asterisk (*). Examples of PFAS structures, spanning several sub-types, are shown on the next page.



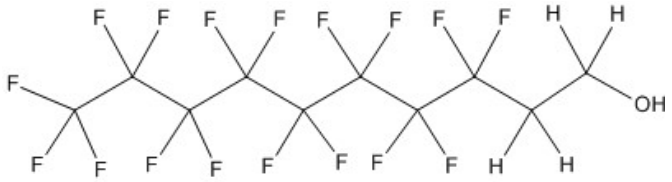
Perfluorooctane sulfonic acid (PFOS)



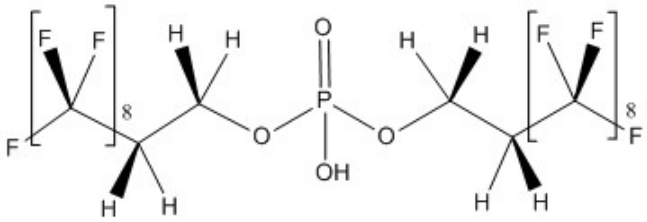
Perfluorobutane sulfonic acid (PFBS)



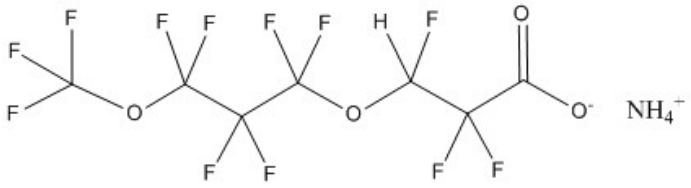
Perfluorooctanoic acid (PFOA)



8:2 Fluorotelomer alcohol (8:2 FTOH)
(or 2-perfluorooctylethanol)



8:2 Polyfluoroalkylphosphate diester



Ammonium 4,8-dioxa-3H-perfluorononanoate (ADONA)

Table 1. Example perfluoroalkyl and polyfluoroalkyl substances (PFASs)

Sub-type	Individual chemical name	Acronym
Perfluoroalkyl carboxylic acids (PFCAs)	Perfluorobutanoic acid	PFBA
	Perfluoropentanoic acid	PFPeA
	Perfluorohexanoic acid	PFHxA
	Perfluoroheptanoic acid*	PFHpA
	Perfluorooctanoic acid*	PFOA
	Perfluorononanoic acid*	PFNA
	Perfluorodecanoic acid*	PFDA
	Perfluorundecanoic acid*	PFUnA
	Perfluorododecanoic acid*	PFDoA
	Perfluorotridecanoic acid	PFTrDA
	Perfluorohexadecanoic acid	PFHxDA
	Perfluorooctadecanoic acid	PFOcDA
Perfluoroalkyl sulfonic acids (PFSAs)	Perfluorobutane sulfonic acid*	PFBS
	Perfluoropentane sulfonic acid	PFPeS
	Perfluorohexane sulfonic acid*	PFHxS
	Perfluoroheptane sulfonic acid	PFHpS
	Perfluorooctane sulfonic acid*	PFOS
	Perfluorononane sulfonic acid	PFNS
Perfluoroalkyl sulfamido substances	N-Ethyl-perfluorooctane sulfonamido ethanol	N-EtFOSE
	N-Methyl-perfluorooctane sulfonamido ethanol	N-MeFOSE
	N-Ethyl-perfluorooctane sulfonamido acetic acid*	N-Et-PFOSA-AcOH
	N-Methyl-perfluooctane sulfonamido acetic acid*	N-Me-PFOSA-AcOH
	Perfluorooctane sulfonamide*	PFOSA
Fluorotelomer alcohols (FTOHs)	6:2 Fluorotelomer alcohol	6:2 FTOH
	8:2 Fluorotelomer alcohol	8:2 FTOH
Polyfluoroalkyl phosphoric acid esters (PAPs)	6:2 Fluorotelomer phosphate diester	6:2 diPAP
	6:2/8:2 Fluorotelomer phosphate diester	6:2/8:2 diPAP
	8:2 Fluorotelomer phosphate diester	8:2 diPAP
Perfluoroalkyl phosphinic acids (PFPiAs)	C6/C6 Perfluorophosphinic acid	C6/C6 PFPiA
	C6/C8 Perfluorophosphinic acid	C6/C8 PFPiA
Fluorotelomer sulfonic acids (FTSs)	6:2 Fluorotelomer sulfonic acid	6:2 FTS
	6:2 Fluorotelomer sulfonic acid	8:2 FTS
Polyfluoropolyethers (PFPEs)	Ammonium 4,8-dioxa-3H-perfluorononanoate	ADONA

*Already included on the designated and priority chemical lists for Biomonitoring California.

Electrochemical fluorination (ECF) is one method for manufacturing perfluorinated chemicals. Historically in the U.S., the ECF method was used to produce perfluorooctylsulfonyl fluoride (or POSF), which was the starting material for PFOS and other perfluorinated chemicals used in the first stain and grease protection products, for carpets and textiles and for food packaging items. ECF was also used to produce PFOA (as ammonium perfluorooctanoate), which was used in the fluoropolymer manufacturing process. ECF manufacturing of chemicals with perfluoroalkyl chains of

six or more carbons was phased out by the major U.S. manufacturer by 2002. ECF is still being used to produce PFBS and related chemical products in the U.S. ECF may also be used in other countries to produce POSF-based and other perfluorinated chemicals.

Telomerization is the other major process used to manufacture PFASs (Buck et al., 2011; Prevedouros et al., 2006). It has been used to produce PFOA, which is currently being phased out in the U.S. Fluorotelomer alcohols (FTOHs), which are the starting materials for many polymers and surface coatings used in industry and in consumer products, are also manufactured via telomerization. These include, for example, fluorotelomer acrylates, olefins, and phosphates. The nomenclature for fluorotelomers indicates the number of fluorinated carbon atoms. For example, "8:2 FTOH" is a fluorotelomer alcohol with a ten carbon chain, in which eight of the carbons are fully fluorinated.

Some PFASs may be referred to as "precursors" of other PFASs. For example, FTOHs can break down to perfluorocarboxylic acids (PFCAs), such as PFOA and PFNA, so FTOHs would be considered "precursors" of these compounds. As a second example, chemicals derived from POSF-based compounds can break down to PFOS in the environment and in biota, and could be referred to as "PFOS precursors".

Exposure or potential exposure to the public or specific subgroups

PFASs have been detected in environmental media and wildlife worldwide (Lau et al., 2007), including in: outdoor air samples from population centers as well as remote regions such as the Arctic (Shoeib et al., 2006); soil, sediment, wasterwater and sludge (as reported in Lau et al., 2007; D'eon et al., 2009); indoor air (Shoeib et al., 2004; 2011); house dust (De Silva et al., 2012; Kato et al., 2009; Strynar and Lindstrom, 2008; Shoeib et al., 2005); wildlife (Hart et al., 2009; Kannan et al., 2006) and in food (Vestergren et al., 2012; Schecter et al., 2010; Zhang et al., 2010; Tittlemier et al., 2007).

PFASs in the diet: Dietary intake has been considered a major route of human exposure for perfluorinated compounds. Some studies in Europe and Asia have associated blood levels of PFOS, PFOA and a few other long chain compounds with fish and seafood consumption (Haug et al., 2010; Zhang et al., 2011). Tittlemier et al. (2007) and Schecter et al. (2010) estimated that beef was the greatest source of perfluorinated compounds in Canadian and U.S. diets. Their findings were based both on the measured blood levels of perfluorinated compounds in these populations (PFOA, PFOS and/or PFNA) and dietary consumption patterns.

A few studies were located on dietary sources of PFASs not currently on the designated chemical list, such as perfluorotridecanoic acid (PFTrDA) and perfluoropentanoic acid (PFPeA). In the Netherlands, Noorlander et al. (2011) detected PFASs in a number of foods. PFOS was detected at the highest levels in shellfish (582 pg/g) and in lean fish (308 pg/g), with PFTrDA at similar levels for these categories (268 pg/g in shellfish; 229 pg/g in lean fish). Vestergren et al. (2012) measured the highest concentration of

PFASs in “fish products” (PFOS, 1290 pg/g; PFUnDA, 316 pg/g; and PFTrDA, 123 pg/g) for samples collected in 2010 in Sweden. Llorca et al. (2009) found two short chain PFASs, PFPeA and PFBS, in samples of whole fish (striped mullet, anchovies and young hake), swordfish fillets and hake roe taken from fish markets in Spain.

PFASs used in food-contact materials, such as some paper plates, food wrappers, microwave containers, and pizza boxes have been shown to migrate into oily, greasy food (Begley et al., 2005; 2008; Trier et al., 2011). Starting in the 1970s, phosphate esters based on N-ethyl perfluorooctanesulfonamido ethanol (N-EtFOSE) were used in food contact material applications. These phosphate esters break down to N-EtFOSE which breaks down to PFOS and also to N-ethyl-perfluoooctane sulfonamido acetate (Xie et al., 2009). With the phase-out of PFOS-related products, other PFASs came into use for these applications. These include fluorotelomer polyfluroalkyl mono and di-ester phosphates esters (monoPAPs and diPAPs) (Trier et al., 2011). Recently, shorter chain PAPs have been replacing earlier products. Z Wang et al. (2013) reported that since 2008, seven 6:2 fluorotelomer-based side-chain fluorinated polymers had been registered with the U.S. Food and Drug Administration. Other products for food contact applications are based on perfluoropolyethers (PFPEs) (Z Wang et al., 2013).

PFASs in consumer products: PFASs are found in a wide variety of products including textiles, carpets, leather, liquid carpet and textile care treatments, floor waxes and sealants (Guo et al., 2009; Liu et al., 2014a,b). Unreacted, residual starting materials are thought to be present in these products and then released over time, leading to potential exposure (Dinglasan-Panlilio and Mabury, 2006). Degradation of the side-chains of fluorinated polymers is also considered to be a potential source of PFAS exposure (Z Wang et al., 2014b).

The first fluorinated polymer products used to impart stain resistance to carpets and textiles were derivatives of the ECF product, N-methyl-perfluorooctanesulfonamido ethanol (N-MeFOSE) (Buck et al., 2011; D’eon and Mabury, 2011). Since 2003, PFBS-related chemicals have been marketed for these applications. Fluorotelomer-based products are also used in these surface treatment products, with increasing use of shorter chain chemicals (Z Wang et al., 2013). PFPEs are used in these applications as well (Buck et al., 2011; Z Wang et al., 2013).

Liu et al. (2014a) analyzed levels of PFCAs in samples of household products purchased during 2007-2011 and reported an increase in shorter chain PFCAs (e.g., four carbon atoms) over this time period. These researchers also found PFBS in some products. In a follow-up study, Liu et al. (2014b) analyzed selected consumer products purchased during 2011-2013 for FTOH content. The highest levels found were in the category “treated floor waxes and stone/wood sealants.” All measured samples in this category (n=5) contained FTOHs in the µg/g range, with one sample containing 331 µg/g 6:2 FTOH and 92.4 µg/g 8:2 FTOH.

PFASs in indoor air and dust: Shoeib et al. (2011) found that FTOHs were the predominant PFASs of those measured in indoor air in homes in Vancouver, Canada (samples collected in 2007-2008). Median levels of 8:2 FTOH and 6:2 FTOH were 2.7

ng/m^3 and 1 ng/m^3, respectively. Fraser et al. (2012) found higher levels of FTOHs in indoor air in an office building constructed around 2008, with new carpeting and newly purchased furniture, compared to partially renovated and non-renovated office buildings. Of the FTOHs measured, 8:2 FTOH predominated in the new building (geometric mean >45 ng/m^3).

De Silva et al. (2012) detected some diPAPs in dust from households sampled in Vancouver (Canada) in 2007-2008. Levels of total diPAPs were 7637 ng/g (mean) and 2214 ng/g (median). De Silva et al. (2012) also detected low levels of perfluoroalkyl phosphonates (PFPAs) and perfluoroalkyl phosphinates (PFPIAs) in a subset of households.

PFASs in drinking water: Low levels of some PFASs have been detected in finished drinking water especially in areas near point sources (Post et al., 2009; Eschauzier et al., 2012). Although most studies have focused on measuring PFOS and PFOA in drinking water, PFASs with shorter carbon chains, such as PFBS, perfluorobutanoic acid (PFBA), PFPeA, and perfluorohexanoic acid (PFHxA) have been detected as well (Rahman et al., 2014). Quinones and Snyder (2009) reported that U.S. drinking water treatment facilities impacted by wastewater treatment plant (WWTP) effluents detected measured PFASs (chain length of C-6 or longer) at a frequency of almost 100%, with the exception of PFUnA and PFDoA. These authors noted that detection frequency and levels were generally higher for PFASs with eight or less carbons. In another U.S. study, Appleman et al. (2014), reported detection of PFASs in >70% of water source samples, including detections of shorter chain PFASs (PFBS, PFPeA and PFHxA). Levels of PFASs were generally in the low ng/L range in finished drinking water, with the exception of one detection of PFHxA at 62 ng/L in finished water at a single site. In a European study, PFASs with less than eight carbon atoms, such as PFBS and PFPeA, were the predominant PFASs in both tap and bottled water (Gellrich et al., 2013). Rahman et al. (2014) commented that the increasing content of shorter chain PFASs in water reflects both increased use of these PFASs as replacements for PFOS- and PFOA-related substances and the greater difficulty in removing them via water treatment processes.

PFASs in sewage sludge (biosolids) and reclaimed water: Sewage sludge applied to agricultural fields may be another route of PFAS exposure. Recent studies have shown that shorter chain PFASs are released more easily from sewage sludge than their longer chain homologues. A study that monitored the fate of PFASs in biosolids/soil mixtures over a three year period reported that the majority of short chain length compounds are lost from the soil within 100 days of biosolid application (Venkatesan and Halden, 2014). Higgins and Luthy (2006) showed that sorption of PFASs to sediment increased with increasing chain length.

Blaine et al. (2014) studied the uptake of perfluoroalkyl carboxylic and sulfonic acids (PFCAs and PFSAs) by lettuce and strawberries irrigated with reclaimed water. In experiments with wastewater effluent augmented with PFCAs and PFSAs, Blaine et al. found that uptake and accumulation decreased with increasing chain length. The

authors reported that the highest accumulation was found for PFBA and PFPeA, two short chain PFCAs.

Other potential sources of exposure: Other current and past uses of PFASs contribute to the presence of PFASs in the environment and to exposure in specific occupational settings. These include use in firefighting foam and in chrome plating (Z Wang et al., 2013).

The specific PFASs added to firefighting foams have changed in recent years. An analysis of contaminated water and fish after an accidental release of firefighting foam in 2000 (Toronto, Canada) found primarily PFOS, some PFHxS and a small amount of PFOA (Moody et al., 2002). More recently, Moe et al. (2012) identified a new firefighting foam that contains 6:2 fluorotelomer sulfonamide alkylbetaine.

In the chrome plating industry, salts of PFOS were used as wetting and mist suppressing agents (Z Wang et al., 2013). New fluorotelomer products (e.g., 6:2 fluorotelomer sulfonic acid) and PFBS-related chemicals are currently registered for use in this industry in Europe (as reported in Z Wang et al., 2013). In China, a chlorinated polyfluorinated ether sulfonate has been used in chrome plating as a PFOS alternative for more than 30 years (S Wang et al., 2013).

Known or suspected health effects

This section provides an overview of known or suspected health effects of PFASs. Other than PFOA and PFOS, the potential toxicity of PFASs has not been well characterized. The summary below briefly outlines information on well-studied PFASs, and some of the available information on the newer PFASs, including shorter chain compounds.

Many studies have documented toxicity associated with PFOS, PFOA or other long chain PFASs in animals and/or in *in vitro* systems. Observed effects include developmental toxicity (Lau et al., 2004; 2007); changes in brain function and behavior (Viberg et al., 2013; Johansson et al., 2008); altered mammary gland development (White et al., 2007; 2011); immune system effects (reviewed in Corsini et al., 2014 and DeWitt et al., 2012); altered weight gain after *in utero* exposure (Hines et al., 2009); thyroid hormone disruption (reviewed in Lau et al., 2007); and effects on steroidogenesis and reduced testosterone (as reported in Jensen and Leffers, 2008). Increases in the incidence of tumors of the liver, testes, and pancreas have been observed in animal studies of PFOA (as reported in Lau et al., 2007 and Jensen and Leffers, 2008). The International Agency for Research on Cancer (IARC) classified PFOA as possibly carcinogenic to humans (Group 2B) based on limited evidence in humans and animals (Benbrahim-Tallaa et al., 2014).

Epidemiological studies of PFASs are limited. Associations have been reported between exposure to certain perfluorinated compounds and lower birth weight (PFOA) (Fei et al., 2007), decreased fecundity (PFOS and PFOA) (Fei et al., 2009), and reduced semen quality (e.g., PFOS, PFOA, PFNA) (Joensen et al., 2009; Toft et al.,

2012; Louis et al., 2015). Several studies have found an association between levels of PFOS and PFOA and serum cholesterol (Nelson et al., 2010; Frisbee et al., 2010). Steenland et al. (2010) evaluated the epidemiological evidence on health effects of PFOA and concluded that the most consistent findings were those relating to increases in serum cholesterol. A study by Halldorsson et al. (2012) suggested that prenatal PFOA exposure might increase the risk of being overweight in females. A recent study of adults living near a chemical plant using PFOA found an association between PFOA blood levels and kidney and testicular cancer (Barry et al., 2013). Steenland and Woskie (2012) reported a positive exposure-response trend for kidney cancer in workers in a fluoropolymer production plant in West Virginia, but noted the results were limited by small numbers.

Multiple studies have indicated that toxicity of PFASs increases with increasing carbon chain length (Upham et al., 1998; Hu et al., 2002; Kudo et al., 2006; Kleszczyński and Skladanowski, 2009; Kleszczyński et al., 2009; Liao et al., 2009). Because of toxicity and bioaccumulation concerns for the longer chain PFASs, many of the new replacement PFASs have shorter carbon chain lengths. While limited data are available for shorter chain PFASs, some toxicity concerns have been identified.

Perfluorobutane sulfonic acid (PFBS) was developed as a PFOS replacement. In one study, PFBS suppressed neuronal cell differentiation in PC12 cells, a standard *in vitro* model for neuronal development (Slotkin et al., 2008). Another study found that PFBS inhibited CYP19 aromatase activity in a dose-dependent manner in JEG-3 human placental choriocarcinoma cells (Gorrochategui et al., 2014), suggesting that PFBS could potentially alter the equilibrium between androgens and estrogens. These researchers noted inhibition of aromatase activity by PFBS occurred in these cells at very low levels, as PFBS uptake by the cells was poor (below the limit of detection).

Some PFASs, including fluorotelomer alcohols (FTOHs) and polyfluorinated iodine alkanes (PFIs), have been reported to have estrogenic activity. Maras et al. (2006) reported the estrogenicity of 6:2 FTOH and 8:2 FTOH in a combination of *in vitro* assays in MCF-7 cells, such as E-screen assay, cell cycle analysis and estrogen-responsive gene expression analysis. Ishibashi et al. (2007) demonstrated estrogen receptor binding and activity of 6:2 FTOH and 8:2 FTOH in a yeast two-hybrid assay. Both research groups reported that 6:2 FTOH stimulated greater estrogenic effects compared to 8:2 FTOH. Wang et al. (2012) reported estrogenic activity of some PFIs, including fluorinated iodine alkanes (FIAs) and fluorinated diiodine alkanes (FDIAs), based on the E-screen and luciferase reporter gene assays and the increased expression of estrogen-response genes. Wang et al. (2012) found that, of the PFIs tested, those with six carbon atoms had the greatest estrogenic activity.

Rosenmai et al. (2013) investigated the effects of several polyfluoroalkyl phosphates (PAPs), 8:2 FTOH, and PFOA on steroidogenesis in H295R human adrenal cortico-carcinoma cells. Exposures to 8:2 diPAPs, 8:2 monoPAPs, and 8:2 FTOH led to significantly decreased levels of androgens and progestagens. Gene expression data showed that 8:2 monoPAP and 8:2 FTOH exposures led to a decrease in mRNA levels

of a gene (Bzrp) involved in the rate-limiting step of steroidogenesis. The study also found expression of CYP19 aromatase was significantly increased following 8:2 diPAP, 8:2 monoPAP, and 8:2 FTOH exposures.

FTOHs are metabolized to PFCAs, such as PFOA, and other shorter (or longer) carbon chain analogs. *In vitro* studies have found that metabolism of FTOHs leads to the formation of reactive intermediates that covalently bind to cell nucleophiles, including glutathione (GSH) and cellular proteins (Martin et al., 2005; 2009; Rand and Mabury 2013). An unsaturated fluorotelomer aldehyde has been identified as the reactive metabolic intermediate (Martin et al., 2005; Rand and Mabury, 2012). Martin et al. (2009) found that cytotoxicity was induced by 4:2 FTOH and 6:2 FTOH as well as 8:2 FTOH, in studies in isolated rat hepatocytes. An *in vivo* study reported that a GSH conjugate was a major metabolite of 8:2 FTOH in the rat (Fasano et al., 2006) and another *in vivo* study demonstrated covalent binding to plasma, liver and kidney proteins after exposure to 8:2 FTOH or 6:2 diPAP in rats (Rand and Mabury, 2014).

Wang et al. (2015) noted that two PFPE carboxylic acids have been shown to cause hepatic damage in laboratory animals with repeated low exposure (≤10 mg/kg/day). Wang et al. also commented that one of these compounds has been suggested to be classified under a European regulation as a chemical that causes "specific target organ toxicity."

Potential to biomonitor

Past biomonitoring studies: PFASs have been found in blood samples of nearly all people tested (CDC, 2015; Lau et al., 2007), in umbilical cord blood (Apelberg et al., 2007) and in breast milk (Tao et al., 2008a, 2008b; Kärrman et al., 2007). Levels of both PFOS and PFOA have steadily decreased in U.S. residents since 1999-2000 (CDC, 2015). However, many new PFASs have been developed and marketed, and recently some of these have been identified in biological matrices.

The summary below briefly describes biomonitoring studies of some of the subclasses of PFASs that are not yet included on the list of designated chemicals.

D'eon et al. (2009) analyzed pooled serum samples that were collected in 2004/2005 (n=10) and 2008 (n=10). Each pooled sample consisted of at least 10 individual donors. The samples were collected across the midwestern U.S. The study measured 4:2 through 10:2 diPAPs.

- 2004/2005 samples: All measured diPAPs were detected, with the exception of 8:2 diPAP. The 6:2 diPAP was found in all samples (mean, 1.9 ± 0.4 µg/L). The level of total diPAPs was 4.5 µg/L, comparable to PFOA (4.2 ± 0.3 µg/L). PFOS levels were 16 ± 1 µg/L.
- 2008 samples: The 6:2 diPAP was again detected most frequently, but at lower mean levels (0.63 ± 0.13 µg/L) than the 2004/2005 samples. Also, the 6:2/8:2 and 8:2 congeners were consistently observed, but at lower levels (0.15 ± 0.02 µg/L and 0.14 ± 0.02 µg/L, respectively). PFOS and PFOA levels were lower in

2008 samples (10 ± 1 µg/L and 1.7 ± 0.1 µg/L) but levels of PFNA, PFDA and PFUnA were higher.

Lee and Mabury (2011) analyzed serum samples collected in the U.S. in 2009. The samples consisted of 40 individual donor samples (20 male; 20 female) and 10 pooled samples, each of which contained at least 10 individual donors.

- diPAPs: The 6:2 diPAP was detected in approximately 80% of single donor samples (mean, 0.072 ± 0.015 µg/L) and in 100% of the pooled samples (mean, 0.13 ± 0.04 µg/L). The 6:2/8:2 and 8:2 diPAPs were also detected but less frequently (30-60%).
- PFPiAs: The C6/C6 and C6/C8 congeners were detected in >50% of the single donor samples, with mean levels of 3.65 ± 1.32 ng/L and 7.67± 1.91 ng/L, respectively.
- FTSs: The 8:2 FTS was detected in >95% of single donor samples (range, <LOD-231 ng/L), while 6:2 FTS was detected in 54% (range, <LOD-47 ng/L).
- PFCAs: PFBA (range, <LOD-228 ng/L), PFPeA (<LOD-502 ng/L) and PFHxA (<LOD – 718 ng/L) were detected in >55% of single donor samples. PFOA was detected in 100% of samples (range, 190-5164 ng/L).
- PFSAs: PFDS was detected in >60% of single donor samples (mean 39.9 ±6.4 ng/L). Mean PFOS was 12263.2 ± 3792.3 ng/L.

Kubwabo et al. (2013) analyzed breast milk samples (n=13) for diPAPs. The samples were collected in 2003-2004 in the Kingston region of Ontario, Canada. Four diPAPs were detected and quantified, and 10/13 samples contained one or more diPAP. The following diPAPs were detected:

- 4:2 diPAP in 8/13 samples (range, <0.01-0.26 ng/mL)
- 6:2 diPAP in 5/13 samples (range, <0.01-0.14 ng/mL
- 8:2 diPAP in 3/13 samples (0.21, 0.27, and 0.30 ng/mL)
- 10:2 diPAP in 7/13 samples (range, <0.01-0.83 ng/mL)

Nilsson et al. (2013) analyzed 94 whole blood samples collected from 2007-2011 from 11 ski wax technicans, who were exposed to high levels of 8:2 FTOH.

- PFCAs:
  - Median levels of PFBA, PFPeA and PFHxA were 0.51 µg/L, 0.14 µg/L, and 0.68 µg/L, respectively. Of the long chain PFCAs, median levels of PFTrDA, PFTDA (perfluorotetradecanoic acid), PFHxDA and PFOcDA were 0.39 µg/L, 1.2 µg/L, 1.2 µg/L, and 0.85 µg/L, respectively. The median level of PFOA was 110 µg/L.
- FTOH metabolites:
  - Three fluorotelomer unsaturated carboxylic acids (FTUCAs) (6:2, 8:2, and 10:2) were detected.
  - Two fluorotelomer carboxylic acids (FTCAs) (5:3 and 7:3) were detected. The authors noted the persistence of 5:3 FTCA (median, 1.7 µg/L) and 7:3 FTCA (median, 0.92 µg/L) that were still detected throughout collections

during the summer months even though technicians do not work with ski wax during the summer.

Rotander et al. (2015) analyzed serum samples collected in 2013 from Swedish firefighters (n=20) and compared them with a control group (samples from 19 university students and office workers), collected in 2011/2012. The study found certain PFASs exclusively or detected more frequently and at higher levels in firefighters compared to controls. These were:

- PFOS and PFHxS
- PFPeS
- PFHpS
- PFNS
- Four previously unknown metabolites, all derivatives of PFHxS or PFOS (tentatively identified as: Cl-PFOS, Cl-PFHxS, ketone-PFOS, ether-PFHxS)

Persistence and bioaccumulation: PFASs accumulate in protein-rich compartments such as blood, liver and kidney (Martin et al., 2003). Bioaccumulation of PFASs has been shown to depend on carbon chain length. Martin et al. (2003) found increases in bioconcentration factors and half-lives with increasing perfluoroalkyl chain length in rainbow trout.

Some PFASs are converted to perfluoroalkyl carboxylic and sulfonic acids (PFCAs and PFSAs), which are generally resistant to metabolism and environmental degradation. For example, FTOHs can be converted to persistent PFCAs. PFASs with short carbon chains have shorter elimination half-lives and do not appear to bioaccumulate. These PFASs are still persistent, however, due to the C-F bonds. Wang et al. (2015) discussed degradation of PFPE carboxylic and sulfonic acids and concluded that they are likely to be highly persistent in the environment and not easily metabolized in biota.

In humans, the half-life of PFOA has been estimated as 3.8 years, PFOS at 5.4 years and PFHxS at 8.5 years (Olsen et al., 2007). The half-life of PFBS was estimated to be much shorter, based on a study of six employees at a chemical plant producing K^+PFBS. In this small study, the geometric mean serum elimination half-life for PFBS was estimated as 25.8 days (Olsen et al., 2009).

Analytical considerations

The Environmental Chemistry Laboratory (ECL) currently has two LC-MS/MS instruments dedicated to measuring PFASs in various media. One instrument has online solid phase extraction (SPE), while the other requires offline sample preparation. The online SPE system enables rapid and simultaneous preparation and analysis of twelve PFASs in serum, with detection limits of 0.01-0.3 ng/mL PFASs in serum. Without making significant changes to the instrumentation or basic design of the SPE and LC methods, additional PFAS analytes could be added to the method easily, provided that they are present in serum or other biological material at concentrations roughly 0.05 ng/mL and higher. The method has not been tested for short chain

PFASs, such as those with perfluorinated groups of 6 carbons or less, and they may not be retained on the C18 SPE cartridges currently in use. Additionally, some analytes may not elute through SPE cartridges or the HPLC column with the current eluents and mobile phase solutions.

For the second LC-MS/MS system, an analytical method has been developed for measurement of a wide range of PFASs, including short chain PFASs and many polyfluorinated compounds, in groundwater and serum extracts reconstituted in methanol. The detection limits for these pre-prepared samples range between 0.01 and 0.1 ng/mL, depending on the analyte. Preliminary measurement of PFASs in serum has been conducted with this instrument using liquid-liquid extraction to partition PFASs out of the serum matrix. Some short chain analytes did not demonstrate good recovery, however their recoveries may be improved with additional optimization of the method. This analytical method can be easily applied to many types of biological samples provided that PFASs can be successfully extracted from those materials and can be concentrated or diluted within the range of the instrument calibration curve.

Adding additional analytes to either PFAS method would not require any major equipment purchases. Incremental costs include the purchase of additional native and labeled standards and the cost of labor and materials during method development and ongoing analysis.

Need to assess efficacy of public health action

Biomonitoring PFASs, including newly developed replacement chemicals, would help Biomonitoring California determine whether these chemicals are found in California residents and at what levels. Listing these chemicals as a class would be a resource-efficient approach. For example, it would facilitate the use of non-targeted laboratory screening methods, allowing the state to determine which PFASs pose the highest exposure concerns in California. Using this approach, the most important PFASs could be tracked over time to monitor levels in blood.

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