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Perfluorooctane sulfonate: A review of human exposure, biomonitoring and the environmental forensics utility of its chirality and isomer distribution

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Abstract

Perfluorooctane sulfonate (PFOS) found extensive use for over 60 years up until its restriction in the early 2000s, culiminating in its listing under the Stockholm Convention on Persistent Organic Pollutants (POPs) in 2009. Efforts to minimise human body burdens are hindered by uncertainty over their precise origins. While diet appears the principal source for the majority of western populations, with other pathways like dust ingestion, drinking water, and inhalation also important contributors; the role played by exposure to PFOS-precursor compounds followed by *in vivo* metabolism to PFOS as the ultimate highly stable end-product is unclear. Such PFOS-precursor compounds include perfluorooctane sulfonamide derivates, e.g. perfluorooctane sulfonamides (FOSAs) and sulfonamidoethanols (FOSEs). Understanding the indirect contribution of such precursors to human body burdens of PFOS is important as a significant contribution from this pathway would render the margin of safety between the current exposure limits and estimates of external exposure to PFOS alone, narrower than hitherto appreciated. Estimates derived from mathematical modelling studies,

put the contribution of so-called “precursor exposure” at between 10% and 40% of total PFOS body burdens. However, there are substantial uncertainties associated with such approaches. This paper reviews current understanding of human exposure to PFOS, with particular reference to recent research highlighting the potential of environmental forensics approaches based on the relative abundance and chiral signatures of branched chain PFOS isomers to provide definitive insights into the role played by “precursor exposure”.

Keywords

Perfluoroalkyl sulfonate, PFOS-precursors, perfluoroalkyl substances, biomonitoring, human exposure, chirality, isomer, body burdens

INTRODUCTION

Perfluoroalkyl substances (PFASs) are a family of synthetic compounds characterised by a fully fluorinated hydrophobic linear carbon chain, to which are attached different hydrophilic functional groups (Fromme et al., 2009). These chemicals have been manufactured since the late 1940s by 3M (3M, 1999) as well as other companies like Dupont, and have been produced and used in commercial products and industrial processes for over 60 years (Lindstrom et al., 2011). PFASs possess low molecular polarisability, short C–F bond length, and large C–F bond binding energy. Such characteristics govern the oil and water repellency, physical and chemical stability, and surfactant properties of PFASs (Zushi et al., 2012). These properties mean that PFASs have found wide use in a variety of applications, with historic production peaking at the end of the 20th century in North America and Europe (Paul et al., 2009). In an environmental context however, the strong C-F bond means that PFASs are resistant to thermal, chemical and biological degradation (Kissa, 2001) and are capable of bioaccumulation and long-range environmental transport, exemplified by their detection in the Arctic (Chaemfa et al., 2010; Sonne, 2010; Zhao et al., 2012). As a result, PFOS and its salts, as well as perfluorooctane sulfonyl fluoride (POSF) were in 2009 listed as persistent organic pollutants (POPs) under the Stockholm Convention (Geneva: Stockholm Convention Secretariat, 2009). POSF can degrade to PFOS directly or indirectly through chemical or enzymatic hydrolysis, and hence POSF-derived products can be degraded ultimately to PFOS (Zhao et al., 2012).

PFAS synthesis routes have been well described by Lehmler et al. (2005). The two main processes are electro-chemical fluorination (ECF) (3M, 1999), and telomerisation (Schultz et al., 2003), with PFOS, and PFOS salts synthesised via ECF. It is important to note here that a number of possible PFOS isomers exist in POSF based mixtures (in which process PFOS impurities are present between 0.1 and 5% (Paul et al., 2009) due to the nature of the ECF

process itself). The isomer composition of the commercial PFOS products can be up to 30% of total PFOS. Moreover, some of these isomers (specifically those that are branched chain) are chiral, with the result that the environmental fate and behaviour of PFOS may vary according to its isomeric and enantiomeric composition.

The main applications of PFOS and PFOS derivatives included uses in: inks, varnishes, waxes, fire-fighting foams, metal plating and cleaning products, coating formulations (for walls, furniture, carpeting, food packaging), lubricants, water and oil repellents for leather, paper and textiles (3M, 2000). Before 2003, POSF was used as a raw material for the synthesis of PFOS (among other perfluorooctane sulphonamide derivates) (Burk et al., 2011). However, 3M Company replaced PFOS with perfluorobutane sulfonate (PFBS) after 2003, because the former was considered harmful to the environment (Renner, 2006).

Over the last 15 years, a substantial weight of evidence has emerged concerning environmental contamination with PFOS, consequent human exposure, and its effects. This paper reviews this evidence, and summarises recent developments that exploit the chirality and relative abundance of branched chain PFOS isomers to provide valuable insights into the environmental fate and behaviour of PFOS and its precursors.

SOURCES, PRODUCTION AND APPLICATIONS

The history of PFAS production is difficult to portray accurately due to the proprietary nature of this information (Lindstrom et al., 2011), but the 3M Company was the first main producer of POSF (an intermediate product for the synthesis of PFOS) with the total cumulative production estimated to be approximately 96,000 t in the peak years between 1970 and 2002 (Paul et al., 2009). In 2002, the 3M Company discontinued its production; however other companies commenced manufacture at this point to meet existing market demands, with an

84 estimated 1,000 t being produced annually since 2002 (Paul et al., 2009). In addition to the
85 3M production facilities in the USA, another 6 plants were located in Europe (4 in EU
86 member states), 6 in Asia (of which 4 were in Japan) and one in South America (Paul et al.,
87 2009).

88 The main way of synthesising PFASs is ECF. In this process, a straight chain hydrocarbon is
89 reacted with H and F atoms and electricity to substitute all of the hydrogen atoms with
90 fluorine (Kissa, 2001). This constitutes the main process of POSF synthesis, generating about
91 70% of the straight chain product with the remainder comprised of branched and cyclic
92 isomers. POSF can then be used in a series of reactions via N-methyl and N-ethyl
93 perfluorooctane sulfonamide (N-MeFOSA and N-EtFOSA) to yield N-methyl and N-ethyl
94 perfluorooctane sulfonamidoethanols (N-MeFOSE and N-EtFOSE), which historically were
95 used to produce polymeric materials and phosphate esters respectively, and used on surface
96 coatings for textiles and paper products (Paul et al., 2009; Olsen et al., 2005, D'Eon and
97 Mabury, 2011).

98 The major applications of POSF derivatives have been: (1) in carpets to impart stain and dirt
99 repellence, (2) in apparel to provide water repellence, (3) in paper and packaging to afford oil
100 and grease repellence, (4) in performance chemicals such as hydraulic fluids for aviation, and
101 (5) in aqueous fire-fighting foams (AFFFs). AFFFs are perhaps the most prominent method
102 of widespread environmental dispersal, with use for oil drilling and military fire-fighting
103 practice (Paul et al., 2009).

104 All compounds produced from POSF are widely referred to as "PFOS equivalents" or just
105 "PFOS", due to their collective potential to degrade or transform into PFOS. In contrast,
106 PFOS itself is extraordinarily stable in the environment, with no known natural mechanism of
107 degradation. Hence, regulatory bodies have been working to reduce the production and use of
108 some PFASs (Zushi et al., 2012). The 3M company, together with the US Environmental

Protection Agency (USEPA) resolved to decrease the production of PFOS and related compounds between 2000 and 2002 (3M, 2008). At the same time, Significant New Use Rules (SNUR) were also put in place (2000, 2002, and 2007) in the US, designed to restrict the production and use of materials that contained PFOS or its various precursors. The EPA then worked with eight leading chemical companies in the 2010-2015 PFOA Stewardship Program to reduce emissions and residual content of PFOA and long-chain PFCAs by 95% by 2010, with the long-term goal to work towards elimination of long-chain PFCAs by 2015 (USEPA, 2010).

Within the EU, PFOS and its derivatives are regulated on the market or only used as a substance or constituent of preparations listed as permissible in the EU Directive (2006). Under this directive, PFOS may still be used in applications that are deemed un-substitutable, including photolithographic processes, photographic coatings, mist suppressants for non-decorative hard chromium (VI), plating/wetting agents in controlled electroplating systems (pollution prevention and control are required), and hydraulic fluids for aviation. Such regulation started within the EU in June 2008 (Zushi et al., 2012).

The presence of PFOS in the environment has been attributed to two major sources: direct and indirect (Armitage et al., 2009; Prevedouros et al., 2006; Paul et al., 2009). Direct sources are derived from the manufacture and application of PFOS and POSF (Paul et al., 2009). By comparison, indirect sources are a consequence of chemical reaction impurities or breakdown of so-called precursors such as N-Me-FOSE and N-Et-FOSE. It has been estimated that 85% of indirect emissions occur via release from consumer products during use and disposal (3M, 2000).

HEALTH CONCERNS

General toxicological findings associated with laboratory animals exposed to PFOS include hepatomegaly and hepatic peroxisome proliferation, liver, testicular (Leydig cell), and pancreatic (acinar cell) tumours, reproductive and developmental deficits, neurotoxicity, and immunotoxicity (DeWitt et al., 2012).

Most of the reported studies concerning PFOS toxicity have been conducted on mice, with subsequent extrapolation to humans of observed murine effects complicated by interspecies variability in toxicokinetics. Even gender and ethnic origin can play a role (Kato et al., 2011). Adverse effects attributed to PFOS in rodents include decreased body weight, increased liver weight, and a steep dose-response curve for mortality (Seacat et al., 2003), as well as an increase in hepatocellullar and follicular cell adenomas at high exposure levels (3M, 2002).

Human studies carried out on workers occupationally exposed to PFAS have generally yielded inconsistent results. While such workers have circulating blood levels of PFAS that are hundreds of times those of non-occupationally exposed individuals (Olsen et al., 2003; Steenland et al., 2010), it is difficult to determine conclusive results in these studies (either positive or negative) because sample populations are small, historical exposure levels are uncertain, individuals often have had simultaneous exposures to other compounds, and they may have pre-existing conditions that complicate evaluations (Fletcher et al., 2013). Compared to PFOS, studies of PFOA exposed workers are more numerous. Several studies have shown a positive association between PFOA exposure and cholesterol, which could have implications for the development of cardiovascular disease. PFOA has also been associated with elevated uric acid levels, which may in turn lead to hypertension and cerebrovascular disease (Lindstrom et al., 2011; Olsen et al., 2003; Costa et al., 2009; Sakr et al., 2007).

Based on the toxicological evidence available to date, chronic exposure guidelines are being developed for PFOS and PFOA by the USEPA and other jurisdictions for water and food, but

158 little has been done thus far for other PFASs. A review of current global guidelines and
159 regulations can be found in Zushi et al. (2012), and some especially pertinent illustrative
160 examples are discussed briefly here. The continuing uncertainty surrounding the human
161 health impacts of PFASs is reflected in the disparity between the values promulgated by
162 different jurisdictions. The risk from PFOS for human adults has been evaluated as low based
163 on the Margin of Exposure (MOE), derived from the ratio of the provisional tolerable daily
164 intakes (pTDI) and the level of intake (Zushi et al., 2012). Fromme et al. (2009) estimated the
165 average (and high end) daily intake of PFOS and PFOA, including the indirect contribution
166 from their precursors, as 1.6 (11.0) and 2.9 (12.7) ng/kg bw/day, respectively. These
167 exposures are comfortably lower than the pTDIs for the general adult population of 100 ng/kg
168 bw/day for PFOS and 3000 ng/kg bw/day for PFOA, promulgated by the German Federal
169 Institute for Risk Assessment (BfR) and the UK Committee on Toxicity of Chemicals in
170 Food, Consumer Products and the Environment (COT) respectively. Moreover, the USEPA
171 issued provisional short-term health advisories for PFOS (200 ng/L) and PFOA (400 ng/L) in
172 drinking water, on the assumption that short-term consumption below these levels will
173 safeguard public health (USEPA, 2009).

174 In a parallel approach to limit values for external exposure via ingestion of food and water,
175 the Biomonitoring Commission of the German Federal Environmental Agency used the 95th
176 percentile concentration values of two German studies (Midasch et al., 2006; Fromme et al.,
177 2007b), to establish reference values for PFOA and PFOS in plasma of children and adults.
178 These reference values specify a maximum permissible presence of PFOS of 10 µg/L for
179 children, 20 µg/L for adult females, and 25 µg/L for adult males (Wilhelm et al., 2009).

180

181 **HUMAN EXPOSURE**

The first report of the presence of PFOS, PFOA, and other PFASs in samples of human blood purchased from biological supply companies emerged in 2001 (Hansen et al., 2001), although the first paper regarding the presence of organofluorine compounds in biological samples dates from 1968 (Taves, 1968). Since then, a considerable database concerning human exposure to PFASs has emerged. The following section summarises current understanding of this topic with particular reference to PFOS.

Human Biomonitoring Data

With respect to human biomonitoring, concentrations of PFAS in human blood (whole blood, plasma and serum) in the general population have been reviewed recently (Angerer et al., 2011; Fromme et al., 2009) (*Table 1*). Most human biomonitoring studies are not carried out on whole blood, but on serum. The first reported concentrations of PFOS in blood were published by Hansen et al. (2001). This study showed 100% of the blood samples contained PFOS at concentrations ranging from 6.7 to 81.5 ng/mL. Following this seminal report, concern about how PFOS enters and remains in the human body increased, leading to the publication of a number of studies, each based on the analysis of a large number of blood samples. Amongst the most relevant of these are those of Calafat et al. and Kato et al. (Calafat et al., 2007a and 2007b; Kato et al., 2011) in the North American population, which each discuss results from the National Health and Nutrition Examination Surveys (NHANES) carried out by the US Center for Disease Control and Prevention, and published in the Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2009; CDC 2013). In these reports, the presence of a range of chemical contaminants is studied in blood and urine from the general population of the USA. The PFOS measurements reported in the two papers from Calafat et al. refer to the NHANES results from 1999-2000 and 2003-2004, and are based on 1,562 and 2,094 serum samples, with a detection frequency (DF) > 96% for PFOS in both studies, and geometric means of 21.1 and 20.7 ng/mL respectively. One of the

studies (Calafat et al., 2007b), also reported that geometric mean PFOS levels declined by 32% between 1999/2000 and 2003/2004. Moreover, the most recent (2007/2008) NHANES results (Kato et al., 2011), indicate that PFOS concentrations continue to decline (exemplified by a geometric mean of 13.2 ng/mL). This follows an earlier report (Olsen et al., 2007b) of a decrease on PFOS levels in human blood in the general American population, from a geometric mean of 33.1 ng/mL in samples collected in 2000, to 15.1 ng/mL in samples collected in 2005. A second study (Olsen et al., 2008) based on a large number of human blood samples (around 600), highlighted that the observed ~60% decline in PFOS was consistent with its elimination half-life and the time period since the phase-out of POSF by 3M in 2000-2002. Combined, these studies suggest that restrictions on the production and use of PFOS have led to reductions in human exposure in the US, although it remains in the environment, wildlife and the US population (CDC, 2009). Other US studies document similar PFOS concentrations in blood, but can not provide evidence of a temporal trend. Specifically, Hansen et al. (2001), as well as Olsen et al. (2005), published results in which median PFOS concentrations were 26.2 and 34.7 ng/mL for samples taken in the late 1990s/early 2000s (exact sampling dates not given) and 1974/1989 respectively. This apparent increase in human exposure in the immediate aftermath of the 2002 voluntary cessation of production by 3M, may be attributed to variation in the respective populations sampled in the two studies.

An important point is that – in line with Taniyasu et al., 2003 - the values in *Table 1* include data for both serum and whole blood. This approach is preferred here to the alternative format employed by others (e.g. Yeung et al. (2006) and Kannan et al. (2004)) whereby concentrations in whole blood were converted to concentrations in serum by multiplying whole blood concentrations by 2, to allow comparison across different studies. This conversion becomes even more sensitive when analysing PFOS precursors, due to their

different distribution between serum and blood (Martin et al., 2010). Notwithstanding the influence of serum versus whole blood basis concentrations, examination of the global database between 2004 and 2007, reveals some differences in both median and maximum PFOS concentrations in human blood recorded in different studies shown in *Table 1*. Likely causes of these between-study variations in the concentrations of PFOS include: international variations in use and exposure, as well as variations between sampled populations in lifestyle, age, ethnicity, and gender (Kato et al., 2011). While such differences in absolute concentrations of PFOS exist, they are not as marked as those observed for other halogenated persistent organic pollutants like polybrominated diphenyl ethers (Hites, 2004).

Table 2 reveals that, in addition to blood, human milk is being monitored increasingly. This shift towards monitoring milk may be attributed to its less invasive nature, greater sample availability and mass, recent improvements in the sensitivity and accuracy of ultra-trace analytical techniques (although these are likely still worse than for serum), and the dual role of human milk as an indicator of both the donor's body burden, and dietary intake of nursing infants. Of course, this is offset to some degree by the fact that human milk as a biomonitoring tool is restricted to a specific sector of the population. Moreover, comparing Tables 1 and 2, it is apparent that concentrations of PFOS in human blood exceed those in human milk. Several studies of human milk have been carried out since the first published reports. Most such studies show detection frequencies (DF) > 90%, except those of Bernsmann and Fürst (2008) (DF of 66% in Germany), and Guerranti et al. (2013), in which the detection frequency was below 50% (DF of 41% in Italy). Median concentrations range from 0.04 to 0.33 ng/mL, except for the study of Roosens et al. (2010) for the Flemish general population, who reported a median concentration an order of magnitude higher than other studies (2.9 ng/mL). Some of the samples reported by Roosens et al. (2010) were collected from donors living near a PFOS production facility, for which the authors also

reported high concentrations of PFOS in serum. Elevated concentrations of PFOS had also been reported previously in biota from the same location by Dauwe et al. (2007).

In contrast to blood and milk, only a small number of papers have reported concentrations of PFASs in other human matrices such as: liver, seminal plasma, and umbilical cord blood (Apelberg et al., 2007; Guruge et al., 2005; Inoue et al., 2004; Kärrman et al., 2007a; Kuklenyik et al., 2004; Midasch et al., 2007; Olsen et al., 2003; So et al., 2006).

Scientific understanding of the origins of and influences on the presence of PFOS in humans is complicated by a number of factors (Lindstrom et al., 2011). Just as environmental degradation of PFOS precursors constitutes an important indirect source of PFOS contamination of the ambient environment; external exposure to PFOS precursors followed by *in vivo* metabolism, has been identified as a potentially substantial indirect contributor to human body burdens of PFOS (Trudel et al., 2008; Vestergren et al., 2008). Such indirect pathways are distinct from direct exposure via human contact with and uptake of PFOS itself. Moreover, PFOS (as well as other long chain PFASs) tend to accumulate in the human body with an estimated half-life of around 5 years (Olsen et al., 2007a). This slow elimination from the human body hampers efforts to determine how changes in lifestyle, diet, or other exposure-related factors influence blood levels. Notwithstanding this, while age has been suggested to exert little influence on circulating PFAS concentrations, with inconsistent results in cross-sectional studies (Haug et al., 2009; Harada et al., 2007), age associations could be consistent with dietary exposure in a post phase out situation (Nøst et al., 2014). However, as highlighted above, gender and ethnicity do seem to influence the accumulation of some compounds. In a recent paper, Kato et al. (2011) attributed differences in human body burdens between ethnic groups to ethnic differences in exposure related to lifestyle, the use of products containing PFASs, and diet. Meanwhile, gender-related differences in body burden (lower concentrations in women than men) have been attributed to physiological

differences (i.e. accumulation and elimination), as well as pregnancy, lactation and menstruation (Harada et al., 2004).

Direct Pathways of Human Exposure to PFOS

Non-occupational exposure to PFOS is thought to occur via the ingestion of food and drinking water, as well via inhalation and contact with indoor dust.

Drinking water. Data concerning concentrations of PFOS in drinking water are rather limited, and all published studies report concentrations in the ng/L range (see *Table 3*). Initially, Saito et al. (2004) reported PFOS concentrations in tap water from Japan to fall between 0.1 and 12.0 ng/L. Later studies (Lange et al., 2007; Ericson et al., 2009; Skutlarek et al., 2006; Tanaka et al., 2008) have reported higher concentrations however; up to 58 ng/L and 143 ng/L PFOS in tap water from Spain (Ericson et al., 2009) and Japan (Tanaka et al., 2008) respectively. Overall, PFOS is one of the most frequently detected PFASs (together with PFOA) in drinking water, with detection frequencies varying between 40 and 100% in published papers. Reassuringly, maximum values reported in drinking water to date, fall below the USEPA's short term advisory limit concentration for drinking water of 200 ng/L PFOS.

Indoor air and dust. In addition to drinking water; recent investigations show the indoor environment is a potentially important contributor to human exposure to PFASs including PFOS (D'Hollander et al., 2010; Fromme et al., 2009; Goosey and Harrad, 2011; Haug et al., 2011a). The first paper concerning PFOS contamination of indoor dust was published in 2003, by Moriwaki et al. (*Table 4*). Sixteen samples of house dust were analysed, containing concentrations of PFOS between 11 and 2,500 ng/g. Since then, similar studies have been carried out in Canada, Japan, Sweden, USA, Australia, the UK, and Spain, with wide

306 variation in concentrations found. While Bjorklund et al. (2009) reported concentrations of
307 PFOS in dust from 10 houses in Sweden in 2009 to range between 15 and 120 ng/g, Strynar
308 et al. (2008) and Kato et al. (2009) reported substantially higher concentrations, ranging
309 between 8.9 and 12,100 ng/g in the USA, and 2.6 and 18,000 ng/g in Australia. Median
310 concentrations further reflect international variations, being 38 ng/g for the Swedish study,
311 and 201 ng/g and 480 ng/g for the Canadian and Australian surveys respectively. Moreover,
312 Goosey and Harrad (2011) also reported statistically significant differences ($p<0.05$) between
313 concentrations of PFOS in dust from different countries. Specifically, UK, Australia, Canada,
314 France, Germany, and US > Kazakhstan; and UK, Australia, Canada, and US > Thailand.
315 They attributed such differences to lower use of products containing PFAS in Kazahkstan and
316 Thailand compared to Europe, North America, and Australia.

317 Moreover, recent studies have reported concentrations of PFOS and other PFAS in indoor air
318 (principally vapour phase, but with some particulate phase compounds incorporated) (Ericson
319 Jogsten et al., 2012; Goosey and Harrad, 2012; Shoeib et al., 2011). In these, PFOS was the
320 most prevalent PFAS, with a wide range of concentrations between countries (for example,
321 lower values detected in Spain, higher in the UK). The frequency of detection for PFOS in
322 indoor air is more variable than for dust (in air the range is from 0% to 100% c.f. 60% to
323 100% for dust).

324 *Outdoor air.* Outdoor air has also been studied, sometimes in conjunction with indoor air.
325 Shoeib et al. (2005) reported PFAS concentrations in outdoor air were 1 or 2 orders of
326 magnitude lower than in indoor air, as data from more recent studies in *Table 5* corroborate.
327 This is consistent with the hypothesis that substantial indoor sources of PFOS exist, with the
328 result that indoor air likely exerts an appreciable influence on outdoor atmospheric
329 contamination. While this would logically lead to higher atmospheric concentrations of PFOS
330 in conurbations due to higher urban building densities; Barber et al. (2007) reported higher

detection frequencies of PFAS (including PFOS) than expected in outdoor air from rural areas. Such findings suggest the environmental distribution of PFAS is complex, and that indoor environments are not the only driver influencing outdoor contamination.

Diet. Overall, based on the exposure models and reviews published to date (D'Eon and Mabury 2011; Ericson-Jogsten et al, 2012; Fromme et al., 2009; Trudel et al., 2008; Vestergren et al., 2008); food contaminated via bioaccumulation, has been suggested by several authors as the principal pathway of direct human exposure to PFOS; (D'Hollander et al., 2010; Fromme et al., 2007a; Trudel et al., 2008; Kärrman et al., 2009; Vestergren et al., 2008; Fromme et al., 2009, Herzke et al., 2013).

In 2012, Ericson-Jogsten reported diet as the main pathway of PFOS exposure for adults and toddlers from Catalonia, Spain (constituting more than 70% of the daily total intake). Ingestion of water was identified as the second most important human exposure pathway, with inhalation of air and ingestion of dust considered negligible (< 0.5% of the total intake). An alternative Scenario-Based Risk Assessment approach (SceBRA) (Scheringer et al., 2001) was used in the studies of Trudel et al. (2008) and Vestergren et al. (2008). Both studies reported food ingestion as one of the most important pathways under three different exposure scenarios, although there was some divergence between the two studies about the absolute contribution of diet. Moreover, house dust ingestion was identified as a significant direct exposure pathway in both studies (though different absolute values of its proportional contribution to overall exposure were reported); while for some other pathways, e.g. direct hand contact with carpets treated with products containing PFOS and subsequent oral ingestion, assessment of their importance differs substantially between studies. Future evaluations of the relative contributions of different pathways to overall exposure to PFOS, will benefit from recent and on-going improvements in analytical techniques that permit detection of PFOS in foodstuffs and other exposure matrices at lower levels.

Indirect sources of human exposure to PFOS

As highlighted above, POSF-derived substances may be metabolised *in vivo* to PFOS, constituting a substantial indirect source of human exposure to PFOS. The POSF-derived substances in question represent a vast array of structures with the general formula $C_8F_{17}SO_2NRR'$, that are referred to generically as "PFOS-precursors" (or "PreFOS" in some literature, such as Asher et al., 2012). Consequently, as described by Prevedouros et al. (2006), and Ross et al. (2012), two general routes of exposure may occur: (1) direct exposure to PFOS, through diet, inhalation, and contact with contaminated settled dust (either by ingestion or dermal contact), and (2) exposure to PFOS-precursors, followed by their biotransformation in the body to PFOS. The main PFOS-precursor substances and its salts are listed in *Table 6*.

PFOS-precursors are mainly degraded to PFOS by *in vivo* metabolic processes (Martin et al., 2010; Xu et al., 2004). Some PFOS-precursors like N-Et-FOSA and N-Et-FOSE, have shown low conversion factors < 1% in rats and trout (Xu et al., 2004; Tomy et al., 2004) or have not yet been studied. However, in 2003, Seacat et al. reported a conversion factor to PFOS of up to 20% in a study where rats were exposed long term to N-Et-FOSE; an observation confirmed subsequently by Xie et al. (2009). Although the reported levels of PFOS-precursors are generally lower and their physicochemical properties differ from those of PFOS, a variety of them have been detected in water (Ahrens et al., 2009), in indoor and outdoor air (Shoeib et al., 2005; Jahnke et al., 2007), in packaged food (Tittlemier et al., 2006), and in live organisms (from mussels to bald eagles) and waterbird eggs (Kannan et al., 2005; Wang et al., 2008). One of the most measured PFOS-precursors is perfluorooctanesulfonamide (PFOSA), which is a stable intermediate in the pathway of PFOS-precursor degradation to PFOS, and whose structure is depicted in *Fig. 1*.

Perfluorinated sulfonamide based products (PFSAm) are also important, as their production is associated with the presence of FOSAs and FOSEs as degradation or residual products. Positive correlations between the concentrations of PFOSA and PFOS have been found in biological samples (e.g. Martin et al., 2004) suggesting that PFOSA, and maybe other PFOS-precursors, can be important contributors to body burdens of PFOS in animal species (Asher et al., 2012).

As mentioned above, recent papers have examined the utility of human exposure models to evaluate the contribution of indirect exposure pathways to human body burdens of PFOS (Vestergren et al., 2008; D'Eon and Mabury 2011; Fromme et al., 2009; Gebbink et al., 2015). Such studies are still quite limited in number, but their general consensus is that the significance of indirect sources in driving human body burdens of PFOS should be taken into account, or even had hitherto been underestimated (e.g. D'Eon and Mabury (2011)). This becomes even more important in the wake of the 3M phase out, as while direct sources of PFOS exposure are expected to decrease in the general population, indirect sources stemming from continued use of PFOS-precursors remain. Vestergren et al. (2008) suggested the relative contributions of direct and indirect exposure were dependent on the level of exposure. While under low and intermediate exposure scenarios, direct dietary exposure appeared the principal pathway, intake of PFOS under a high-end exposure scenario was dominated by indirect precursor exposure via indoor dust (41-68%), and indoor air (10-19%). The study of Gebbink et al. (2015) considered comparable pathways of exposure to those studied by Vestergren et al. However, total exposure in the Gebbink et al study was 1-2 orders of magnitude lower, with indirect exposure to PFOS making higher and lower contributions to overall exposure under low (11%) and high (33%) exposure scenarios respectively than estimated previously. Gebbink et al. attributed the differences between their observations and those of previous studies, to their use of recent data reporting lower levels

406 of PFOS and PFOS-precursors in human diet (Ullah et al., 2014). However, other reasons
407 such as the use of more recently published biotransformation factors describing the
408 conversion of precursors, as well as the development of more sensitive analytical methods
409 were identified as causes of the lower exposure estimates. Moreover, D'Eon and Mabury
410 (2011) critically reviewed the contribution of PFOS precursors to observed body burdens of
411 PFOS, and suggested that studies to date may underestimate the contribution of such indirect
412 exposure. This was principally due to the fact that such studies consider indirect exposure to
413 occur only as a result of exposure to PFOS precursors present as impurities or residual
414 products from the manufacture of PFOS, but do not include exposure arising from
415 manufacture and use of the precursors themselves.

416 In summary, studies to date suggest strongly that indirect exposure to PFOS makes an
417 important contribution to human body burdens. However, such studies are not yet conclusive.
418 For example, estimates of the contribution of such exposure varies between 10% and 70% of
419 the daily intake of PFOS in the studies of Verstergren et al. (2008) and Gebbink et al. (2015)
420 (based on the three different scenarios) and Fromme et al. (2009). Such variation is
421 attributable to inherent uncertainties in pivotal parameters such as the estimated efficiency of
422 precursor metabolism to PFOS. At the current time, efforts must focus on addressing: (1) the
423 lack of data on the toxicokinetics of various PFOS-precursor compounds in animals, (2) the
424 difficulty in extrapolating rodent data to humans, and (3) the fact that many commercially
425 relevant PFOS precursors have yet to be determined in any sample (Martin et al., 2010).
426 Overall, the uncertainties associated with studies to date, highlight a clear need for alternative
427 approaches, and a small but growing number of studies suggests that exploitation of the chiral
428 properties of some PFOS isomers and their precursors may constitute one such approach
429 (Wang et al., 2009; Liu et al., 2015).

430

Isomer patterns and chirality of PFOS and its precursors – environmental forensic tools?

Historically, ΣPFOS has been quantified together (*see Tables 1 to 5*). Recently however, new approaches (discussed further below) have been have been suggested as biomarkers of exposure and applied in efforts to differentiate between direct exposure to PFOS and PFOS-precursor exposure (Benskin et al., 2009; Martin et al., 2010).

Isomer profiles. As described above, the processes via which PFOS precursors (i.e. POSF) are manufactured, are expected to produce about 70% of the linear isomer, with the remaining 30% made up of a mixture of various branched chain isomers. In contrast, due to preferential retention of linear PFOS in humans and rats, PFOS isomer profiles in animal species are expected to comprise <30% branched chain isomers. While this holds true for species such as fish and gulls for which ≥90% of PFOS is the linear isomer (Asher et al., 2009; Gebbink and Letcher, 2010; Houde et al., 2008) (*Table 7)*; in some human samples, the proportion of branched chain isomers can be 40-50% (Kärrman et al., 2007b; Zhang et al., 2013; Beesoon et al., 2011, Liu et al., 2015). Moreover, an *in vitro* study using human microsomes has showed branched chain PFOSAs to be preferentially metabolised to PFOS relative to linear PFOSA (Benskin et al., 2009). This provides further evidence that precursor exposure may account for human PFOS isomer profiles that are enriched in branched chain isomers. This enriched profile in some human samples has been hypothesised as providing evidence of precursor exposure. Moreover, observed temporal and within-population variations in the relative abundance of branched chain PFOS isomers in humans (Kärrman et al., 2007a; Haug et al., 2009), may be at least partly attributable to concomitant variations in precursor exposure. In fact, the study of temporal trends by Liu et al. (2015), shows the percentage of branched isomers in the Swedish population has increased from 32 to 45% between 1996 and 2010, suggesting that exposure to PFOS precursors is becoming more

important compared to direct exposure, as predicted by the theoretical models discussed earlier.

Current evidence to support this hypothesis is not clear-cut however (Ross et al, 2012). While excretion in rats of branched chain PFOSAs exceeded that of the linear isomer; a corresponding increase in the relative abundance of the sum of branched chain PFOS isomers was not observed in the same animals. More detailed analysis of the relative abundance of individual branched chain isomers in this study suggests a more complex situation. While the relative abundance in the studied rats of one branched isomer (5m-PFOS), increased relative to its abundance in a commercial PFOS mixture; that of another (1m-PFOS) decreased (Ross et al., 2012). This may point to a need to monitor relative abundances of individual branched chain isomers rather than the sum of all such isomers, to provide more conclusive insights into the relative contribution of precursor exposure. This conclusion is supported by the study of Gebbink et al. (2015), where an estimated isomeric pattern of 84% linear PFOS was calculated for exposure via water, diet, air and dust, that contrasts with isomer patterns observed in human serum samples (Beesoon et al., 2011; Haug et al., 2009; Benskin et al., 2007; Zhang et al., 2013). The potential feasibility of such a detailed isomer-specific approach is demonstrated by a study of PFOS isomer distributions in gull eggs from spatially distinct breeding colonies throughout the Laurentian Great Lakes (Gebbink and Letcher, 2010). In this study, 8 individual branched chain PFOS isomers were detected in gull eggs, with spatial variations in the contribution of linear PFOS in eggs highlighted as potentially at least partly attributable to location-specific variations in the PFOS precursor exposure.

Chirality. One feature of many PFOS isomers is chirality, including the environmentally relevant monomethyl-branched isomers 1m-, 3m-, 4m-, and 5m- PFOS, represented in *Fig. 2*, where "#m-" refers to the carbon position of the branched CF_3 group (Asher et al., 2012). Chirality has environmental significance for several reasons. The enantiomers of a chiral

compound rotate polarised light in opposite directions, but otherwise exhibit identical physical and chemical properties. Consequently, environmental, physical, and chemical processes generally affect both enantiomers identically (Kallenborn et al., 2001). However, different enantiomers can interact differently with other chiral molecules (enzymes or biological receptors), leading to different biological and toxicological behaviour (Hühnerfuss et al., 2009). Moreover, unless production of a specific enantiomer is sought, the relative abundance of each enantiomer, or the enantiomer fraction (EF), (referred to thereafter as the chiral signature) is equal in commercially-produced chemicals. In such cases, the two enantiomers (A and B) exist in identical proportions (*eq 1*) and the chiral signature is said to be racemic (EF = 0.5). Consequently, observations of chiral signatures that deviate significantly from racemic in environmental or biological matrices are strong evidence of biodegradation or metabolism, and provide a powerful tool to enhance understanding of environmental processes (Lehmler et al., 2010). Specifically, in the context of elucidating the relative importance of precursor exposure, the EFs of chiral isomers such as 1m-PFOS in freshly-manufactured PFOS are 0.5. In contrast, a branched chain PFOS precursor (1m-PreFOS) was shown to be metabolised enantioselectively by human liver microsomes (Wang et al., 2009). As a result, the observation of non-racemic EFs in human serum of 1m-PFOS, combined with experimental evidence that 1m-PFOS itself is not excreted enantioselectively in rats (Wang et al., 2011) (see *Table 7*); represents strong evidence of a discernible influence of precursor exposure on human body burdens of PFOS. Recently, Liu et al. (2015) have also found non-racemic EFs in serum samples from Swedish and US population, supporting previous studies by Wang et al. (2009 and 2011). Furthermore, a significant correlation between %br-PFOS (i.e. the proportion of ΣPFOS that are branched chain isomers) and 1m-PFOS in samples from 1996-2000 has been also discussed there, but further studies are still

505 required in view of the fact that the observed changes in EF can explain only around 40% of
506 the increment in branched isomers (Liu et al., 2015).

507

508 $$EF=A/(A+B) \qquad (eq.\ 1)$$

509

510 The above are prime examples of how knowledge of chiral signatures of PFOS isomers in
511 various environmental compartments including those pertinent to human exposure, offer
512 potentially rich insights into various aspects of the environmental fate and behaviour of PFOS
513 and its precursors. As well as helping elucidate the relative influence on human body burdens
514 of direct exposure to PFOS compared to indirect exposure via metabolism of its precursors;
515 studies of chiral organochlorine compounds indicate wider insights may also be possible. For
516 example, measurement of the chiral signatures of polychlorinated biphenyls (PCBs) and
517 organochlorine pesticides in relevant environmental matrices has enhanced understanding of
518 issues such as: the relative contribution of primary versus secondary sources to outdoor air
519 (Bidleman et al., 1998; Robson and Harrad, 2004), and the role of volatilisation from soil as a
520 source of PCBs to grass (Desborough and Harrad, 2011). Moreover, tracking chiral
521 signatures of PFOS and its precursors could lead to better understanding of toxicological
522 effects on the human body, as enantioselective toxicity may exist (Loveless et al., 2006).

523

524 **Forward look**

525 PFOS is an environmental pollutant which has been widely studied. Significant manufacture
526 of both PFOS and PFOS precursors continues today; e.g. PFOS production has increased in
527 China since 2002 (with higher reported levels of PFOS in some regions of China than in the
528 US, despite the small production volumes in China compared to reported 3M production

529 (Olsen et al., 2012)), while PFOS and PFOS-precursors are still being manufactured in
530 Europe and Asia for certain applications (UNEP, 2010; Paul et al., 2009; Zhang et al., 2013).
531 This review has highlighted the potential insights into its environmental fate that may be
532 gained from better knowledge of the isomer and enantiomer-specific behaviour of both PFOS
533 and its precursors. Despite this, at the current time, only a few papers have been published
534 reporting the relative abundance of both linear and branched PFOS isomers in the
535 environment. Even fewer papers have been published that address the chirality of PFOS and
536 its precursors. In part, this is likely due to the fact that reference standards for branched chain
537 isomers and individual enantiomers have only recently become available, and to the
538 challenging nature of existing analytical methods for their measurement, exacerbated by the
539 usually very low concentrations of individual branched chain isomers in environmental and
540 biological samples. Moreover, as yet it has only proven possible to resolve the enantiomers of
541 1m-PFOS. As this represents only 2-3% of total PFOS and ~6-10% of Σbranched chain
542 isomers (Riddell et al., 2009), there are inherent uncertainties in extrapolating findings for
543 this one isomer to others. Furthermore, while variations in precursor exposure may explain
544 variations in PFOS isomer profiles; other factors such as gender and pregnancy may also be
545 influential. Despite these obstacles, exploiting the chirality and isomer patterns of PFOS and
546 its precursors offers new opportunities to gain insights into their environmental fate and
547 behaviour, as exemplified by previous studies of other chiral organohalogens like α-
548 hexachlorocyclohexane and PCBs. Given the potential rewards, further development,
549 validation, and carefully targeted application of analytical methods for the determination of
550 chiral signatures of PFOS isomers are necessary. They will not be a trivial task; but they
551 constitute urgent research priorities.

552

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Table 1. Comparison of reported PFOS concentrations and ranges in human blood or serum (ng/mL)

Authors	Year	Country	Matrix	n	% DF	Mean	Median[c]	Range
Ericson et al.	2007	Spain	Whole blood	48	100	7.64	7.6	0.76-16.2
Fromme et al. (b)	2007	Germany	Plasma	356	100	13.5	13.7	2.1-55.0
Hansen et al.	2001	USA	Serum	65	100	25.519	25.7	6.7-81.5
Haug et al. (b)	2011	Norway	Serum	41	100	6.9	NR	2.3-15.0
Hölzer et al.	2008	North Rhine	Plasma	80	NR	NR	4.3	1.5-26.2
Jin et al.	2007	China	Serum	119	NR	NR	22.4	0.2-145.0
Kannan et al.	2004	USA	Serum	46/29[d]	91/93[d]	32.5/32.9[d]	28.9/26.2[d]	<1.3-124
		USA	Whole blood	11/19[d]	100/100[d]	66/73.2[d]	81/72[d]	11-164
		USA	Plasma	70	100	42.8	42	16-83
		Colombia	Whole blood	25/31[d]	100/100[d]	8.0/8.5[d]	7.3/8.1[d]	4.6-14
		Brazil	Whole blood	17/10[d]	100/100[d]	10.7/13.5[d]	8.4/12.7[d]	4.3-35
		Italy	Serum	8/42[d]	87.5/90.5[d]	4.4/4.3[d]	3.5/4.2[d]	<1-10.3
		Poland	Whole blood	15/10[d]	100/100[d]	33.3/55.4[d]	33.8/40.9[d]	16.0-116
		Belgium	Plasma	4/16[d]	100/100[d]	11.1/16.8[d]	10.4/17.6[d]	4.5-27.0
		India	Serum	11/34[d]	55/50[d]	2.3/1.7[d]	2.5/1.3[d]	<1-3
		Malaysia	Whole blood	7/16[d]	100/100[d]	11.7/13.2[d]	12.7/13.1[d]	6.2-18.8
		Korea	Whole blood	25/25[d]	100/100[d]	15.1/27.1[d]	11.3/18.3[d]	3.0-92

		Japan	Serum	13/25[d]	100/100[d]	20.1/14.1[d]	18.3/12.4[d]	4.1-40.3
Kärrman et al. (a)	2006	Sweden	Whole blood	66	100	16	17.1	1.7-37.0
Kärrman et al. (b)	2006	Australia	Serum	40	NR	21.3	20.8	12.7-29.5
Kärrman et al. (a)	2007	Sweden	Serum	12	100	20.7	18.7	8.2-48.0
Kato et al.	2011	USA	Serum (years 99-00)	1562	100	30.4	NR	NR
(NHANES reports			Serum (years 03-04)	2094	99.9	20.7	NR	NR
overview). Calafat et			Serum (years 05-06)	2120	99.9	17.1	NR	NR
al. (2007) (a) (b)			Serum (years 07-08)	2100	99.8	13.2	NR	NR
Midash et al.	2006	Germany	Plasma	105	100	NR	22.3	6.2-131.0
Olsen et al.	2005	USA	Serum	178	NR	30.1	29.5	NR
			Plasma	178	NR	33.3	34.7	NR
Yeung et al.	2006	China	Serum	85	NR	NR	52.7	NR

c) For concentrations <LOQ, the value was assumed to = 1/2 LOQ. d) Separate female/male data reported for this study.

DF: Detection frequency. NR: Not reported.

Table 2. Comparison of reported PFOS concentrations and ranges in human breast milk (ng/mL)

Authors	Year	Country	n	% DF	Mean	Median[c]	Range
Antignac et al.	2013	France	48	90	0.092	0.075	<0.050-0.330
Bernsmann and Fürst	2008	Germany	203	66	NR	0.082	0.05-0.284
Fromme et al.	2010	Germany	201	72	NR	0.040	<0.030-0.110
Guerranti et al.	2013	Italy	49	41	0.85	NR	<1.020-4.280
Haug et al. (b)	2011	Norway	19	100	0.093	0.087	0.004-0.250
Kadar et al.	2011	France	30	100	NR	0.074	0.024-0.171
Kärrman et al. (a)	2007	Sweden	12	100	0.201	0.121	0.063-0.465
Kärrman et al.	2010	Spain	10	100	0.12	0.110	0.070-0.220
Kim et al. (b)	2011	Korea	17	100	0.061	NR	0.032-0.130
Liu et al.	2010	China	24	100	0.046	0.049	0.006-0.137
Llorca et al.	2010	Spain	20	95	0.071	0.084	0.028-0.865
Mosch et al.	2010	Germany	20	95	NR	0.049	<0.030-0.195
Nakata et al.	2007	Japan	51	100	NR	NR	0.008-0.401
Roosens et al.	2010	Belgium	22	NR	NR	2.900	<0.400-28.2
So et al.	2006	China	19	100	0.105	0.100	0.045-0.360
Sundstrom et al.	2011	Sweden	20[d]	100	0.156	0.206	0.088-0.151

Tao et al.	2008	USA	45	96	NR	0.106	<0.032-0.617
		Cambodia	24	100	0.067	0.040	0.017-0.327
		Vietnam	40	100	0.076	0.058	0.017-0.393
		Indonesia	20	100	0.084	0.067	0.025-0.256
		Philippines	24	100	0.098	0.104	0.027-0.208
		Malaysia	13	100	0.121	0.111	0.049-0.350
		India	39	85	0.046	0.039	<0.011-0.120
		Japan	24	100	0.232	0.196	0.140-0.523
Thomsen et al.	2010	Norway	68	NR	NR	0.110	0.028-0.36
Völkel et al.	2008	Germany	19	100	0.116	0.113	0.028-0.239
		Germany	38	100	0.126	0.123	0.033-0.309
		Hungary	13	100	0.317	0.330	0.096-0.639

c) For concentrations <LOQ, the value was assumed = 1/2 LOQ. d) 20 pools of human milk.

DF: Detection frequency. NR: Not reported.

Table 3. Comparison of reported PFOS concentrations and ranges (ng/L) in drinking water

Authors	Year	Country	n	% DF	A/GM	Median[c]	Range
Ericson et al.	2008	Spain	4	100	0.57[c] (GM)	0.59	0.39-0.87
Ericson et al.	2009	Spain	40	87	3.72 (GM)	0.51	<0.12-58.12
Kim et al.(a)	2011	Korea	15	NR	NR	NR	<0.33-11.00
Loos et al.	2007	Italy	6	100	8.1 (A)	NR	6.20-9.70
Saito et al.	2004	Japan	30	67	0.7-12.5[d] (GM)	0.65	<0.10-12.00
Skutlarek et al.	2006	Germany	37	35	2.09[c] (GM)	1.00	<1.00-22.00
Takagi et al.	2008	Japan	26	96	1.51 (GM)	1.90	<0.16-22.00
Tanaka et al.	2008	Japan	NR	NR	NR	NR	<0.01-143.0

c) For concentrations <LOQ, the value was assumed = 1/2 LOQ. b) Estimated in 6 different areas.

DF: Detection frequency. A: Average. GM: Geometric mean. NR: Not reported.

Table 4. Comparison of reported PFOS concentrations and ranges in indoor dust (ng/g)

Authors	Year	Country/Microenvironment Category	Source	n	% DF	Average	Median[c]	Range
Bjorklund et al.	2009	Sweden / Houses	Dust	10	100	49.0[d]	39.0	15-120
		Sweden / Apartments	Dust	38	79	175.0[d]	85.0	<8.0-1100
		Sweden / Offices	Dust	10	100	144.0[d]	110.0	29-490
		Sweden / Daycare centres	Dust	10	100	38.0[d]	31.0	23-65
		Sweden / Cars	Dust	5	60	18.0[d]	12.0	<8.0-33
Ericson Jogsten et al.	2012	Spain / Houses	Dust	10	100	2.1	2.2	0.13-12.0
Goosey and Harrad	2011	UK / Cars	Dust	20	100	132.0	97.0	20-1500
		UK / Classrooms	Dust	42	100	640.7	980.0	22-3700
		UK / Houses	Dust	45	100	144.7	450.0	3.5-7400
		UK / Offices	Dust	20	100	182.5	370.0	20-1000
		Australia / Houses	Dust	20	100	187.0	170.0	6.5-8100
		Canada / Houses	Dust	19	100	157.8	140.0	42-1300
		France / Houses	Dust	10	100	193.8	160.0	54-1700
		Germany / Houses	Dust	10	100	188.9	170.0	47-1000
		Kazahkstan / Houses	Dust	9	80	12.5	59.0	<0.03-130

		Thailand / Houses	Dust	20	100	19.5	16.0	3-130
		USA / Houses	Dust	10	100	318.1	310.0	110-930
Kato et al.	2009	Australia / Houses	Dust	39	74	NR	480.0	<2.6-18000
Kubwabo et al.	2005	Canada / Houses	Dust	67	67	443.7	37.8	2.3-5065
Moriwaki et al.	2003	Japan / Houses	Dust	16	100	39.5	25.0	15.0-2500
Strynar et al.	2008	USA / Houses (102) and child daycare centres (10)	Dust	112	95	761.0	201.0	<8.9-12100

c) For concentrations <LOQ, the value was assumed = 1/2 LOQ d) Arithmetic mean.

DF: Detection frequency. NR: Not reported.

Table 5. Comparison of reported PFOS concentrations and ranges in indoor and outdoor air (pg/m^3)

Authors	Year	Country	Source	n	% DF	Mean	Median[c]	Range
Barber et al.	2007	Norway	Indoor air	4	0	NR	NR	<47.4
Ericson Jogsten et al.	2012	Spain	Indoor air	10	33	0.3	0.1	<0.13-67.0
Goosey and Harrad	2012	UK	Indoor air	20	90	12.4	11.5	<1.0-400.0
		UK	Indoor air	12	100	49.4	55.0	12.0-89.0
Shoeib et al.	2011	Canada	Indoor air	39	0	<LOD	<LOD	<LOD
Barber et al.	2007	UK	Outdoor air	2	NR	NR	NR	46
		UK	Outdoor air	10	NR	NR	NR	1.6
Dreyer et al.	2009	Germany	Outdoor air	117	0	<LOD	<LOD	<LOD
		Germany	Outdoor air	121	0	<LOD	<LOD	<LOD
Genualdi et al.	2010	Diff. Countries	Outdoor air	20	50	NR	NR	2.03-149.5
Goosey and Harrad	2012	UK	Outdoor air	10	70	1.5	1.6	<0.1-6.1
Shoeib et al.	2011	Canada	Outdoor air	6	0	<LOD	<LOD	<LOD

c) For concentrations <LOQ, the value was assumed = 1/2 LOQ.

DF: Detection frequency. NR: Not reported.

Table 6. List of PFOS, its salts and its main precursors

CAS number	Common name	Systematic name	Molecular formula
N/A	PFOS anion	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonate	$C_8F_{17}SO_3^-$
1763-23-1	PFOS acid (perfluorooctanesulfonic acid)	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid	$C_8F_{17}SO_3H$
2795-39-3	PFOS potassium (K^+) salt	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid, otassium salt	$C_8F_{17}SO_3K$
29081-56-9	PFOS ammonium (NH_4^+) salt	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid, ammonium salt	$C_8F_{17}SO_3NH_4$
29457-72-5	PFOS lithium (Li^+) salt	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid, lithium salt	$C_8F_{17}SO_3Li$
70225-14-8	PFOS diethanolamine (DEA) salt	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonic acid,compd. with 2,2-iminobis[ethanol] (1:1)	$C_8F_{17}SO_3NH(CH_2CH_2OH)_2$
307-35-7	POSF	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonyl fluoride	$C_8F_{18}O_2S$
1691-99-2	N-EtFOSE alcohol	N-ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-(2-hydroxyethyl)-1-Octanesulfonamide	$C_{12}H_{10}F_{17}NO_3S$

4151-50-2	N-EtFOSA	N-ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-1-Octanesulfonamide	$C_{10}H_6F_{17}NO_2S$
24448-09-7	N-MeFOSE alcohol	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-(2-hydroxyethyl)-N-methyl-1-Octanesulfonamide	$C_{11}H_8F_{17}NO_3S$
31506-32-8	N-MeFOSA	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-methyl-1-Octanesulfonamide	$C_9H_4F_{17}NO_2S$
25268-77-3	N-MeFOSEA	2-Propenoic acid, 2-[[(heptadecafluorooctyl)sulfonyl]methylamino]ethyl ester	$C_{14}H_{10}F_{17}NO_4S$
423-82-5	N-EtFOSEA	2-Propenoic acid, 2-[ethyl[(heptadecafluorooctyl)sulfonyl]amino]ethyl ester	$C_{15}H_{12}F_{17}NO_4S$

Table 7. Linear versus branched chain composition profiles and enantiomer fractions (EFs) of PFOS and its precursors in various matrices

Authors	Year	Country	Study	Matrix	n	Analytes
Asher et al.	2012	Canada	Lake	Aquatic Species	67	PFOSA (≈57% linear)
						PFOS (>90% linear)
				Water	2	PFOS (70% linear)
				Sediment	3	PFOS (>90% linear)
Beesoon et al.	2011	Canada	Human	Dust	18	PFOS (≈70% linear)
				Serum	20	PFOS (≈64% linear)
				Cord serum	20	PFOS (≈54% linear)
Benskin et al.	2007	Canada	Human	Serum	14	PFOS (≈80% linear)
Haug et al.	2009	Norway	Human	Serum	57	PFOS (53-78 linear)
Houde et al.	2008	Canada	Niagara/Lake	Fish	22	PFOS (88-93% linear)
				Water	NR	PFOS (43-56 linear)
Kärrman et al. (b)	2007	Sweden	Human	Serum/blood	17	PFOS (68% linear)
		UK			13	PFOS (59% linear)
		Australia			40	PFOS (59% linear)
Ross et al.	2012	Canada	Animals	Blood	8	PFOSA (≈78% linear)
				Blood	8	PFOS (≈77% linear)

				Heart	8	PFOSA (≈93% linear)
				Fat	8	PFOSA (≈86% linear)
Sharpe et al.	2010	Canada	-	Fish	NR	PFOS (>70% linear)
Wang et al.	2011	Canada	Animals	Rats	3	1m-PFOS (EF≈0.5)
			Human	Serum	8	1m-PFOS (EF=0.43)
			Human	Serum	7	1m-PFOS (EF=0.35-0.43)
Zhang et al.	2013	China	Human	Serum	129	PFOS (48% linear)

NR: Not reported.

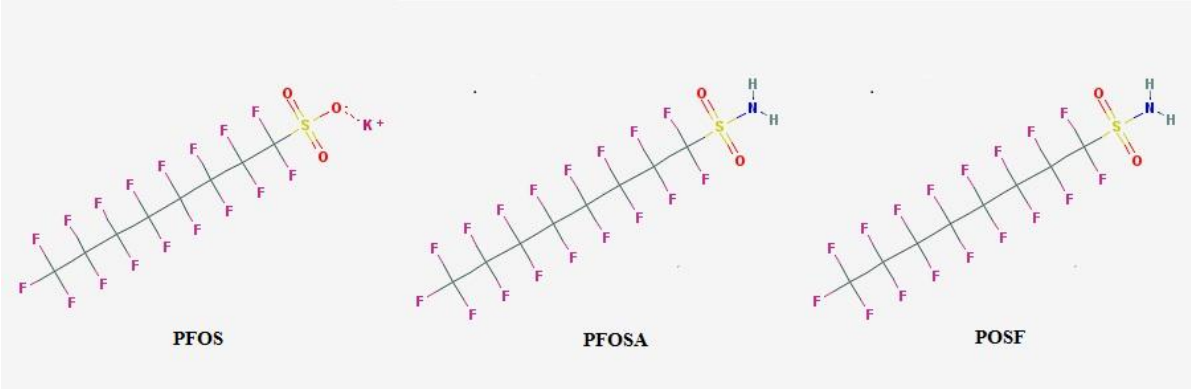

Fig. 1. PFOS K salt, PFOSA, and POSF structures

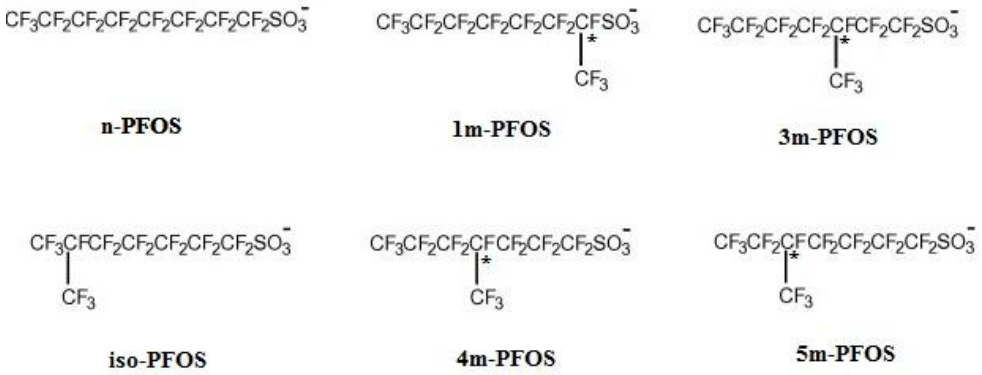

Fig 2. Linear PFOS structure (named as n-PFOS) and monomethylated PFOS branched isomers, where the chiral carbon is represented by *. Each isomer containing a chiral centre has 2 enantiomers (R and S)