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Food Packaging Forum

Dossier – Per- and polyfluoroalkyl substances (PFASs)

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1 Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFASs) are used in various consumer and industrial products, including food contact materials (FCMs) (Figure 1). Thousands of different PFASs have been synthesized in the past decades [1]. Their common properties include high water and oil repellency as well as thermal and chemical stability.

PFAS are fluorinated aliphatic substances in which the hydrogen substituents of at least one terminal carbon atom are completely replaced by fluorine atoms, i.e. all PFAS contain the moiety C_nF_{2n-1}- [2]. Substances where fluorine is substituted for *all* hydrogen atoms (except those belonging to functional groups) are designated as perfluoroalkyl substances. In contrast, polyfluoroalkyl substances contain not only fluorinated, but also (partially) hydrogenated carbon atoms [2-4].

Chemical bonds between carbon and fluorine are the strongest single bonds in organic chemistry [5]. Consequently, many perfluoroalkyl substances are highly persistent under abiotic and biotic conditions. Polyfluoroalkyl substances may be converted to a certain extent, but any perfluorinated parts of such molecules persist [2]. The extensive application and the high persistency of many PFASs contribute to their ubiquitous presence in biota and environmental samples. In wildlife and humans, high absorption and low elimination rates further increases the body burden of some PFASs. Although a high diversity of PFASs has been synthesized in the last decades, the level of available information varies strongly for the different PFASs: whereas few compounds have been thoroughly investigated, others are hardly characterized.

Fluorinated polymers form a second group of fluorinated organic molecules that are widely used in FCMs, e.g. as coating on cookware to provide non-stick properties.

2 Definition and nomenclature

PFASs are aliphatic substances containing, as a minimum requirement, one terminal carbon atom on which all hydrogen substituents have been replaced by fluorine atoms. As detailed above, PFASs can be divided into poly- and perfluoroalky substances. Many PFASs are used as surfactants or in the production of fluorinated polymers.

Fluorosurfactants form a heterogeneous group of PFASs that consist of a fluorinated carbon chain and a highly hydrophilic functional group or moiety and have a molecular weight below 1000 Da [4]. Many industrially used fluorosurfactants are mixtures of compounds with different chain lengths and of undefined purity [6, 7].

Fluorinated polymers containing a perfluoroalkyl moiety C_nF_{2n-1}- belong to the PFASs. However, the definition of fluorinated polymers includes also all other polymers containing fluorine in the backbone or side chain of at least one monomer. Fluoropolymers form a subgroup of fluorinated polymers with a backbone solely composed of carbon atoms and fluorine directly attached to it.

Further details about the terminology for PFASs was provided by Buck and colleagues with the aim to harmonize the chemical nomenclature for these substances and to avoid inconsistencies [2].

2.1 Examples of PFASs

Perfluoroalkane sulfonic acids (PFSA)

PFSAs belong to the group of perfluoroalkyl acids (PFAAs) and typically have linear perfluoroalkyl chains and a sulfonic acid or sulfonate group as functional group (**1**). PFSAs with 6 or more fluorinated C-atoms belong to the long-chain PFASs [2].

PFSAs are precursors of perfluoroalkane sulfonamides (**2**) that can carry a wide range of different side chains (e.g. R, R' = alkyl, alcohol, (meth)acrylates, phosphate).

The best investigated PFSAs are perfluorooctane sulfonic acid (PFOS, **3**, CAS 1763-23-1) and perfluorooctane sulfonates (CAS 45298-90-6), which have been used as surfactant in many different applications until the global voluntary phase-out by the main manufacturer 3M in 2002. Examples of PFSA derivatives that have been used in FCMs are e.g. perfluorooctane sulfonamidoethanol-based phosphate esters (SAmPAPs), and side-chain fluorinated polymers [2, 8, 9].

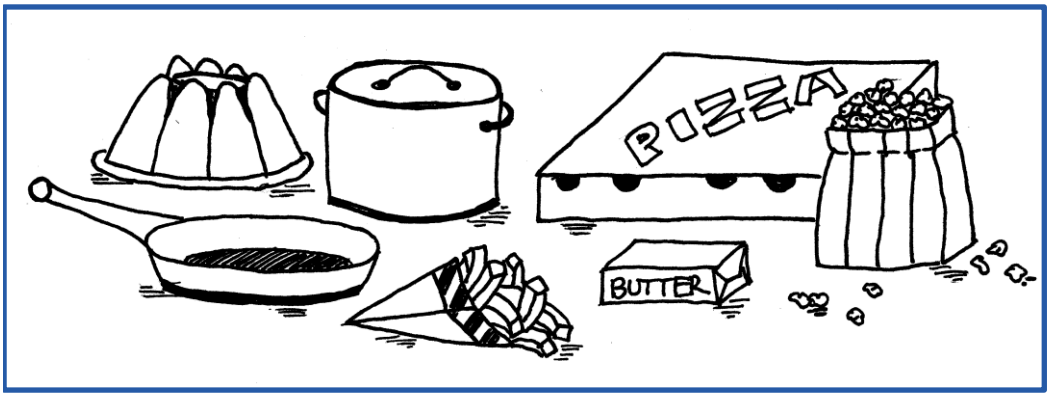
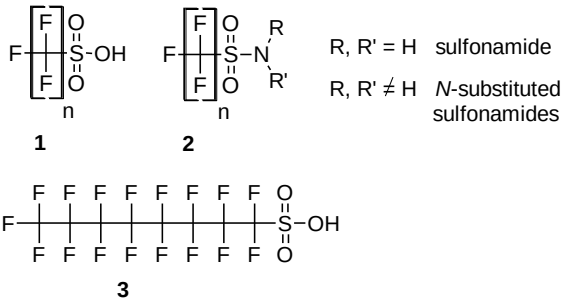


Figure 1. Examples of FCMs containing per- and polyfluoroalkyl substances (PFASs) and fluorinated polymers.



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Perfluoroalkyl carboxylic acids (PFCA)

PFCAs, another important group of PFAAs, have the general structure $CF_3(CF_2)_nCOOH$ (**4**). Perfluorooctanoic acid (PFOA, **5**, CAS 335-67-1) is the most prominent example of PFCAs. PFOA is available as free acid, various salts, and in functional derivatives. The ammonium salt of PFOA (APFO, CAS 3825-26-1) has been widely used as emulsion polymerization aid in the production of certain fluoropolymers. PFOA is also an unintended by-product in the production of fluorotelomers (see 2.3 and 4.2). PFCAs with 7 or more fluorinated C-atoms belong to the long-chain PFASs [2].

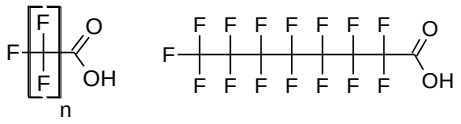

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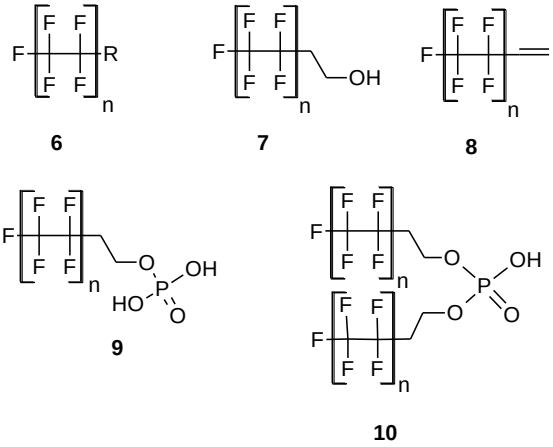
Table 1. Examples of PFASs belonging to the perfluoroalkane sulfonic acids (PFSAs), perfluorocarboxylic acids (PFCAs), and fluorotelomer alcohols (FTOHs). n = number of fluorinated carbon atoms.

Substance	n	CAS #
PFSAs (**1**)		
Perfluorobutane sulfonic acid (PFBS)	4	375-73-5
Perfluoropentane sulfonic acid (PFPeS)	5	2706-91-4
Perfluorohexane sulfonic acid (PFHxS)	6	355-46-4
Perfluoroheptane sulfonic acid (PFHpS)	7	375-92-8
Perfluorooctane sulfonic acid (PFOS) (**3**)	8	1763-23-1
PFCAs (**4**)		
Perfluorobutanoic acid (PFBA)	3	375-22-4
Perfluoropentanoic acid (PFPeA)	4	307-24-4
Perfluorohexanoic acid (PFHxA)	5	357-24-4
Perfluoroheptanoic acid (PFHpA)	6	375-85-9
Perfluorooctanoic acid (PFOA) (**5**)	7	335-67-1
Perfluorononanoic acid (PFNA)	8	375-95-1
FTOHs (**7**)		
6:2 Fluorotelomer alcohol (6:2 FTOH)	6	647-42-7
8:2 Fluorotelomer alcohol (8:2 FTOH)	8	678-39-7

Fluorotelomer-based substances

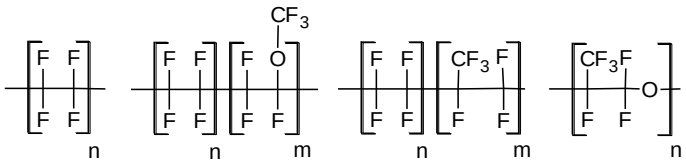
Fluorotelomers are molecules with straight, even-numbered fluorocarbon chains of limited lengths (n greater than 1 and often less than 10) (**6**). Perfluoroalkyl iodides (e.g. $F(CF_2CF_2)_nI$, Figure 3) are used to synthesize a variety of derivatives, such as fluorotelomer alcohols (FTOHs, **7**), fluorotelomer olefins (FTOs, **8**), polyfluoroalkyl phosphate monoesters (monoPAPs, **9**), and polyfluoroalkyl phosphate diesters (diPAPs, **10**). Fluorotelomer acrylates and methacrylates are major raw materials for fluorotelomer-based polymers.



6 **7** **8** **9** **10**

2.2 Examples of fluorinated polymers

Polytetrafluoroethylene (PTFE, **11**, CAS 9002-84-0) is a linear high-molecular weight polymer composed of tetrafluoroethylene units. PTFE consists only of fluorine and carbon atoms. It is sold under the trade name Teflon® and Dyneon PTFE.



11 **12** **13** **14**

Perfluoroalkoxy polymers (**12**) are related to PTFE, but have side chains connected by ether bonds. Fluorinated ethylenepropylene (FEP, **13**) is a copolymer of tetrafluoroethylene and hexafluoropropylene monomers. Perfluoropolyethers (PFPEs, **14**) are polymerized from hexafluoropropylene oxide and generally composed of 10-60 monomers**.** They are sold under the trade name Kryotox®.

3 Physical and chemical properties

The substitution of hydrogen by fluorine atoms in aliphatic molecules leads to a similar variety of substances as can be found in hydrocarbon chemistry [3]. Long perfluorinated carbon chains form a helical structure, in which the carbon skeleton is completely covered by fluorine atoms. This cover shields the molecule from most chemical attacks resulting in highly stable molecules. Additionally, the standard C-F bond is the strongest single bond known in organic chemistry and also the C-C bonds between two fluorinated carbons are stronger than between two hydrogenated carbons [5]. Thus, PFASs have high thermal stability, chemical resistance and general persistence [3, 10].

The fluorinated side chains of PFASs have a low surface energy leading to strong water and oil repellency of fluorinated chemicals with sufficient chain lengths [5, 11]. Furthermore, low intermolecular interactions between fluorinated side chains make PFASs relatively volatile, although they have a much higher molecular weight than their hydrocarbon analogues [5]. More details on the physicochemical properties of PFASs were recently summarized by Krafft and Riess [5].

4 Chemical synthesis

4.1 Electrochemical fluorination

A major production route of long-chain PFSAs and PFCAs has been electrochemical fluorination (ECF) [12]. Linear alkane sulfonyl fluorides ($C_nH_{2n+1}SO_2F$) and linear alkane acyl fluorides ($C_nH_{2n+1}COF$) are electrochemically fluorinated in hydrofluoric acid (HF) to perfluorinated sulfonyl fluorides ($C_nF_{2n+1}SO_2F$) and acyl fluorides ($C_nF_{2n+1}COF$), respectively (Figure 2A and B) [5, 13]. Due to the harsh and non-selective reaction conditions, the final products can be obtained at a low yield and accompanied by a mixture of linear chain, branched chain, and cyclic perfluorinated molecules. $C_nF_{2n+1}SO_2F$ is further converted into PFSA, the corresponding sulfonate salts, sulfonamides and sulfonamidoethanols (Figure 2A). This synthesis route has been mainly used for the production of PFOS from $C_8F_{17}SO_2F$ (perfluorooctane sulfonyl fluoride, POSF). $C_nF_{2n+1}COF$ species are the precursor molecules of PFCAs and their corresponding salts (Figure 2B).

A: $C_nH_{2n+1}SO_2F \xrightarrow{HF\ e^-} C_nF_{2n+1}SO_2F \longrightarrow C_nF_{2n+1}SO_3H$

B: $C_nH_{2n+1}COF \xrightarrow{HF\ e^-} C_nF_{2n+1}COF \longrightarrow C_nF_{2n+1}CO_2H$

($C_nF_{2n+1}SO_3H$), (**B**) synthesis of PFCAs ($C_nF_{2n+1}CO_2H$).

4.2 Telomerization

An alternative, more specific production route of PFASs is the telomerization process [2]. In a first step, tetrafluoroethylene (TFE, CAS 116-14-3) reacts with a perfluoroalkyl iodide yielding a distribution of linear perfluoroalkyl iodide telomers with a chain length that is divisible by 2 (Figure 3). Radical coupling of ethylene allows further derivatization of the resulting fluorotelomer iodides (FTIs) into e.g. FTOHs, fluorotelomer olefins and acrylates [5, 14, 15].

$F(CF_2CF_2)I + CF_2{=}CF_2 \rightarrow F(CF_2CF_2)_nI \xrightarrow{CH_2=CH_2} F(CF_2CF_2)_nCH_2CH_2I$

$\Rightarrow$ FTOHs, fluorotelomer olefins and acrylates

Figure 2. Telomerization of perfluoroalkyl iodide and TFE leads to a variety of per- and polyfluorinated compounds with n = 2,4,6,…

4.3 Polymerization

Fluorinated polymers, e.g. PTFE and PFPE, are produced by radical polymerization. These reactions are conducted in water yielding either a suspension of particles that are later milled into fine powders or a colloidal dispersion that can be directly used to coat articles. In these processes, fluorinated surfactants may be used as emulsifiers.

Box 1: History

- In 1938, PTFE was identified as the result of an unintentional polymerization reaction of TFE. In the 1940s, PTFE was patented by Kinetic Chemicals, a company founded by DuPont and General Motors, and the Teflon® trademark was registered.
- Since 1951, PFOA has been used in the production of PTFE at DuPont's Washington Works facilities near Parkersburg, WV [16].
- In the 1960s, the U.S. Food and Drug Administration (FDA) approved PTFE coated cookware and certain fluorosurfactants used in food packaging [14].
- In 1968, fluorinated organic compounds were measured in human serum [17] and eight years later tentatively identified as PFOA [18].
- In the 1980s and 1990s, exposure studies were conducted on PFASs by industry and academic laboratories: Elevated levels were reported in e.g. workers [19], in tap water close to a production site (internal study by DuPont, for more information refer to [20]) and in the general population [21].
- In the 1990s, analytical methods based on liquid chromatography-mass spectrometry allowed routine analyses of PFAS levels in biological and environmental samples [14].
- In May 2000, 3M decided to phase out its long-chain PFASs including PFOA, PFOS and PFOS-related substances and completed the phase-out in 2002 [22]. DuPont took over the production of PFOA in Fayetteville, North Carolina.
- In 2001, residents living near DuPont's Washington Works plant on the Ohio-West Virginia border sued the company in a class-action lawsuit for contaminating groundwater and air with PFOA over several decades [23]. According to the settlement agreement of the lawsuit, the court appointed three epidemiologists to study possible health effects of PFOA [24].
- In 2006, the U.S. Environmental Protection Agency (U.S. EPA) agreed with eight major fluoropolymer and telomer manufacturers on the 2010/2015 PFOA Stewardship Program which has the aim to strongly reduce the emissions and use of PFOA, its precursor chemicals and related higher homologues by 2010 [25]. A complete ban of these chemicals was envisioned by the end of 2015. Yearly reports show the progress which has been made in reaching this goal.
- In 2009, PFOS and related compounds were listed as persistent organic pollutants (POPs) under the Stockholm Convention [26]. The ratifying countries agreed to restrict the use of these chemicals to acceptable purposes and specific exemptions only.
- In 2013, DuPont's performance chemicals business including fluoroproducts spun off into a new company (Chemours).
- According to the 2014 progress report of the 2010/2015 PFOA Stewardship Program, the participating companies mainly fulfilled their 2010 obligations, but did not completely phase out these chemicals yet [25].
- In 2014, seven scientific experts on PFAS listed their concerns on the transition from long-chain PFAS to other fluorinated alternatives in the Helsingør Statement [27]. The lack of information on production volumes, uses, properties and biological effects of the alternatives in combination with their known persistence were claimed as highly problematic.
- In 2015, 14 scientists and other professionals in the field published the Madrid Statement on poly- and perfluorinated substances, which was additionally signed by 200 signatories [28]. The statement aims at limiting the production and use of PFAS and suggests specific actions for different stakeholders (e.g. scientists, governments, chemical and product manufacturers, retailers and consumers).
- In January 2016, FDA banned three long-chain PFASs that were regulated as indirect food additives [29].

5 Application and migration

At the turn of the millennium, manufacturers started to replace long chain PFCAs, PFSAs, and their precursors with alternatives such as shorter-chain homologues or other types of (non-)fluorinated substances [30]. As a consequence, the use pattern of PFASs has changed within the last years, but it is difficult to retrace it in detail due to the very high structural diversity of these substances. Thus, the studies cited here may only show a snapshot of selected PFASs used in FCMs in the last decades.

5.1 PFASs

Use in FCMs

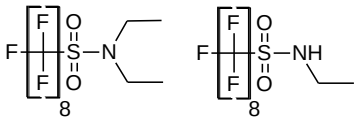
Since the early 1960s, non-polymeric PFASs have commonly been used to optimize the non-stick properties and oil, grease and water repellency of paper and board [4, 31]. During production of paper and board, fluorosurfactants are often directly added to the pulp leading to good coverage of the cellulose fibers [4].

- Between 1974 and 2002, SAmPAPs have been widely applied in food contact paper and packaging [8].
- After 2002, short- and medium-chain substances such as perfluorobutane sulfonate (PFBS) derivatives and 4:2/6:2 fluorotelomer derivatives have started to replace PFOS-based fluorosurfactants [4, 7].
- In the recent years, the use of fluorotelomer-based polymers and phosphate mono- and di-esters (monoPAPs, **8**, and diPAPs, **9**) has increased in food contact paper [4].
- In 2013, more than 115 PFASs were structurally identified from industrial blends of finishes used for FCMs [31].
- In the same year, a review paper reported on the use of fluorinated alternatives to long-chain PFCAs, PFSAs, and their derivatives [30]. Several 6:2 fluorotelomer-based polymers and PFPE-based products were used to treat the surface of FCMs.

Occurrence in FCMs and migration into food

A diverse range of PFASs is used in food contact paper and board. Popcorn bags, fast food wrappers, pizza boxes and other oil-repellent and heat-resistant types of packaging have been reported to contain and/or release PFASs (Table 2).

- Different popcorn bags contained between 6 and 290 ng PFOA per g, but PFOA concentrations in the food simulant Miglyol were below 1 ng/g after heating. Fluorotelomers were already present in the popcorn oil before heating (1400 ng/g or 4000 ng/dm^2 paper). After addition of fresh food simulant an additional 2100 $\pm$ 900 ng/g (or 7000 ng/dm^2 paper) of fluorotelomers migrated after heating [32].
- Low amounts of 8:2 FTOH were detected in the gas phase after the preparation of microwave popcorn. FTOHs belong to the volatile PFAS, which explains their presence in the gas phase [33].
- In 2007, PFOA was measured in the vapors of two different pre-packed popcorn bags after heating in the microwave (16-17 ng per bag) [34]. Additionally, one brand released 223 ng of 6:2 FTOH and 225 ng of 8:2 FTOH into the gas phase of the bag. Extraction experiments using the paper bag from the same brand revealed the presence of six further PFAS at ng/cm^2 concentrations.
- In 2009, the U.S. EPA detected PFHxA, PFHpA, and PFOA in food contact paper. PFOA concentrations reached levels between non-detectable and 4.64 x 10^3 ng/g [35].
- In 2011, migration of diPAPs (**9**) and their thioether analogues (S-diPAPs) was measured from microwave popcorn bags purchased in Denmark [31, 36]. Semi-quantitative levels of 200-700 ng/g food were analyzed.
- S-diPAP migration from microwave popcorn bags from the U.S. market reached levels up to 3900 ng/g food [37].
- In 2013, PFCA and FTOH levels were monitored in dairy products after processing and packaging [38]. Raw milk was already contaminated with these compounds, which were then enriched in the fatty dairy products after processing and separation. Additionally, coated packaging contributed to the levels of PFCAs and FTOHs in butter. Whereas migration of single PFCAs reached levels up to 0.5 ng/dm^2, levels of FTOH migration were 1000-fold higher.
- In 2014, PFBA, PFHxA, and PFHpA were measured in popcorn bags from the Greek market [39]. In the same study, PFCAs of very different chain lengths (C_4-C_{16}) were detected in fast food wrappers and paper boxes, but PFOA and PFSAs were not present in any sample. Migration of PFASs into food was not investigated.
- Three popcorn bags from the Spanish market were analyzed for seven PFASs [40]. At least five of the investigated PFASs were measured in all samples, reaching total concentrations up to 549 ng/g.
- Results from the Canadian Total Diet Study indicated that food packaging was a major source of the two PFOS-derivatives *N*,*N*-diethyl perfluorooctane sulfonamide (*N*,*N*-EtFOSA, **15**) and *N*-ethyl perfluorooctane sulfonamide (*N*-EtFOSA, **16**) [41]. Both substances were measured in different types of food collected between 1992 and 2004. Especially food with relatively high fat content, fast food and food to be prepared in the packaging exhibited the highest levels (up to 22.6 ng *N*-EtFOSA/g food), possibly because all these food types were stored in oil-resistant packaging. A clear decrease in the concentrations of *N*-EtPFOSA in fast foods was judged to be due to the cessation of PFOS production in 2000.



15 **16**

- Studies from Thailand and China indicated that PFOA and PFOS were still commonly used in FCMs in the years 2012 and 2009, respectively [42, 43].

5.2 Fluorinated polymers

Fluoropolymers such as PTFE are broadly used as non-stick surface on cookware. PTFE has a melting point of 327°C, which is very high in comparison with other polymers and allows its use at high temperatures. Other fluorinated polymers, e.g. acrylate polymers with fluorinated side chains, are used as coatings for paper and board to increase oil, grease, and water repellency [4]. PFPEs are used as lubricants during production, processing, and packaging of food. PTFE micropowders are added to a variety of materials (e.g. plastics, printing inks, lubricants, coatings) to enhance their chemical resistance and anti-friction properties [44].

- PFOA has been commonly used as polymerization aid in the production of PTFE and several studies investigated the presence of PFOA and related substances in PTFE-coated cookware. In 2005, residual PFOA was extracted from such cookware in the range of 4-75 ng/g [32]. Migration of PFOA was shown in experiments using spiked PTFE films, but migration from cookware was judged not to be a significant source of PFOA exposure under actual conditions of use [32].

- In 2007, PFOA, 6:2 FTOH, and 8:2 FTOH were measured in the headspace of nonstick cookware after heating [34]. Concentrations of these PFASs were in the range of several tens to few hundreds of ng released per pan. Repeated use measurements showed that the levels of PFOA decreased with each cycle for one pan, but another pan did not show a clear trend. FTOHs levels stayed under the level of quantification (LOQ) after the second test cycle at the latest. When water was boiled for 10 min in nonstick pans, the transfer of PFOA was only measured in 2 out of 6 cases (at 7.0 and 75 ng). Migration of 6:2 FTOH and 8:2 FTOH into these water samples was below the LOQ (2.5 ng) for any of the six pans.
- In contrast, another study from 2007 did not find evidence for the migration of fluorinated substances from coated cookware products at all [45].
- In 2013, a review paper listed fluorinated alternatives to previously used processing aids: Functionalized PFPEs, ammonium perfluorohexanoate, and 6:2 fluorotelomer carboxylic acid started to replace the ammonium or sodium salts of PFOA in the production of PTFE and other fluorinated polymers [30].
- In 2015, the release of PFASs from four PTFE coated pans and nine consumer products into the gas phase was monitored for normal conditions of use and overheating scenarios [13]. PFCAs of different chain lengths were frequently traced, but PFSAs were not detected. Total PFCAs emissions reached 4.75 and 12'190 ng PFCAs per hour under normal use and overheating conditions, respectively.

6 Market data

The historical global production volumes of POSF (a precursor of PFOS), PFOS, and PFOA have been estimated in different studies. These substances are currently being phased-out or produced in much lower quantities due to regulatory actions or self-regulation by industry.

- The total global production volume of POSF was estimated to be between 44'000 and 75'000 metric tons [12, 46, 47]. The production peaked at ≈4500 metric tons per year in the late 1990s [46]. Between 2000 and 2003, the phase-out of POSF by 3M resulted in a sharp decline in the production volume [46].
- In 2000, the global production volumes of PFOS-related chemicals were 2160, 1490 and 891 metric tons for surface treatment, paper protection and performance chemical applications, respectively (based on data from 3M) [48].
- It was estimated that 260 metric tons of the ammonium salt of PFOA were produced globally in 1999 [12]. The global historical emissions of total PFCAs from direct uses (e.g. manufacture, use, consumer products) and indirect sources (e.g. PFCA impurities and/or precursors) were estimated to be 3200-7300 metric tons [12]. Another source estimated that 150-200 metric tons PFOA-related substances are currently used for paper treatment within the EU each year [49].
- After the turn of the millennium, emissions of PFCAs in Japan, Western Europe, and the U.S. were estimated to drop sharply, whereas total levels in India, Poland, China, and Russia were likely to rise to a similar level, if not higher [50].
- Between the years 2001 and 2006, there was a steady increase in the PFOS production in China [51]. Starting at merely 30 metric tons per year in 2001, the production volume stayed at levels between 220 and 240 metric tons per year between 2008 and 2011. The cumulative production of PFOS-related compounds in China was estimated to be 1800 metric tons.
- In 2003, the global annual production volume of fluorotelomer alcohols was 5'000 metric tons [52]. It was estimated that 80% of the fluorotelomer-based substances were incorporated in polymers and 20% were used in non-polymeric applications.
- In 2014, a market research institute published a comprehensive market study on fluorotelomers [53-55]. A global fluorotelomer demand of 47'500 metric tons with a market value of 539 million USD was predicted by the year 2020. A compound annual growth rate of 12.5% was estimated in the same study. In 2013, FTOH was the leading product segment of all fluorotelomers with a market share of more than USD 95 million. Fluorotelomer-containing fire-fighting foams and food packaging created profits exceeding USD 130 million in 2013.

7 Exposure and biomonitoring

7.1 Exposure estimation

Human exposure to PFASs is a global phenomenon, because they are generally quantified in >95% of the samples [10, 56]. The most abundant PFSAs in human samples were generally PFOS, PFOA, and PFHxS [57]. Food and in some cases drinking water were identified as major exposure sources for the general population with indoor air and dust adding to the total PFASs exposure [56, 58]. For example, fish consumption can lead to high levels of PFOS and long-chain PFCAs [56]. Infants are exposed to PFASs via breast milk, infant formula or baby food [59]. FCMs contribute to the contamination of food with PFASs [31-33, 60].

Average daily intakes of single PFASs were estimated to be in the range between 0.14 and a few hundred ng/kg body weight (bw)/d for the general adult population [10, 56]. In 2012, the European Food Safety Authority (EFSA) assessed the exposure of adults to PFOS and PFOA and calculated daily intakes of 5-10 and 4-7 ng/kg bw/d, respectively (Table 2) [61].

7.2 Biomonitoring

General population

Biomonitoring studies of general populations from Europe, the U.S. and Australia have reported on a total of 23 PFASs, but only PFOS and PFOA were routinely measured in the majority of studies [62, 63]. In 2004, the analysis of 473 human blood samples from all over the world revealed that PFOS was found in all samples from Colombia, Brazil, Belgium, Italy, Poland, Malaysia, and Korea [64]. In India, only 51% of the samples contained PFOS at concentrations above 1 ng/ml. In human biomonitoring studies background levels of most short-chain PFASs are usually not targeted or below the quantitation limits [65]. Only PFHxS is regularly determined with typical medians of 0.5-1.5 ng/ml which are about ten times lower than the PFOS levels. diPAP congeners were monitored in human plasma samples collected in the years 2004-2005 and 2008 [60]. Concentrations of these compounds were in the low ng/ml range. Analyses of blood samples from the U.S. and Scandinavia revealed that levels of PFBS and PFHxS remained constant or were even increasing during the last years, while PFOS and PFOA levels were generally decreasing [60, 65-68].

PFASs manufacturing workers

Occupational exposure to PFASs leads to the highest observed levels in humans [14, 69]. PFAS levels in manufacturing workers were several orders of magnitude higher than in the general population (Table 2) [62]. Inhalation of PFOA is suggested to be a major route of exposure for this group [70].

Communities from environmentally contaminated regions

Population groups living in areas with contaminated drinking water are also at higher risk. Elevated serum concentrations of PFOA in such populations have been reported from e.g. Little Hocking, U.S. [71] and Arnsberg, Germany [72].

8 Toxicity

Adverse health effects of PFOA and PFOS have been reported for decades and were summarized in many peer-reviewed articles [14, 63, 73-75] and by different authorities [76-78] (Table 2). Thus, conclusions on the toxicity of PFOA and PFOS can be drawn on the basis of numerous *in vitro* and *in vivo* experiments and epidemiological studies, which also include data on occupational exposure. In contrast, the toxicological data for all other PFASs are less comprehensive.

8.1 Pharmacokinetics

In many animals, PFCAs and PFSAs are orally absorbed, but not metabolized *in vivo*. These chemicals are mostly distributed to the liver, kidney, and serum, rather than to other compartments such as fat tissue [10]. Long-chain PFAAs are not easily eliminated from the human body which leads to an elevated bioconcentration and bioaccumulation potential of these substances [10, 79, 80].

The elimination half-lives of PFAAs depend on the length of the perfluoroalkyl chain and the functional group of the substance as well as species and gender of the animal [30, 63, 88]. PFSAs commonly have longer half-lives and a higher bioaccumulation potential than their PFCA counterparts. In humans, PFOA, PFOS, and PFHxS were reported to have half-lives of several years [86, 89], whereas in most animals half-lives are in the range of hours and days [63, 79]. Elimination of PFASs is generally faster in females than in males, but exceptions are known (e.g. PFOA is faster eliminated in male monkeys and rabbits than in females). These strong differences in elimination led to the recommendation to evaluate toxicological effects based on the body burden rather than

Table 2. Key figures describing toxicity, exposure, distribution, and legislative measures concerning different PFASs (mainly PFOA and PFOS).

		Substance	Value	Comments	Ref.
Toxicity data	oral LD_{50}	PFOA	430-680 mg/kg bw	rodents	[81]
	chronic oral animal studies	PFASs	0.1-100 mg/kg bw/d		[10]
	NOAEL	PFOS	0.03 mg/kg bw/d	cynomolgus monkeys, alterations in lipids and thyroid hormones	[82]
	$BMDL_{10}$	PFOA	0.3 mg/kg bw/d	male rats, increased liver weight	[78]
Food/FCM	popcorn	fluorotelomers	2.1 mg/kg	migration into food simulant	[32]
	food contact paper	PFOA	4.6 mg/kg	concentration in the FCM	[35]
	popcorn bags	diPAPs and S-diPAPs	0.2-3.9 mg/kg food	migration into food	[31, 36, 37]
Drinking water	background levels	PFOA	1-10 x 10^{-6} mg/l water		[83, 84]
	contaminated sites	PFOA	50-3600 x 10^{-6} mg/l water		[58, 62, 71, 83]
Biomonitoring	occupationally exposed humans*	PFOS PFOS PFOA PFOA	10 mg/l serum 0.6 mg/l serum 4.4-5.7 mg/l serum 0.4 mg/l serum	median, in fishermen median, in retired workers median, in production workers median, in retired workers	[62, 85] [86] [62] [86]
	humans exposed through polluted drinking water	PFOA PFOA	0.30-0.37 mg/l serum 0.02-0.03 mg/l serum	median levels geometric mean	[2, 71] [72]
	background levels (NHANES)	PFOA (2000) PFOA (2010) PFOS (2000) PFOS (2010)	5.2 x 10^{-3} mg/l serum 3.1 x 10^{-3} mg/l serum 30.4 x 10^{-3} mg/l serum 9.3 x 10^{-3} mg/l serum	geometric mean	[67, 68]
Exposure estimates	daily dietary exposure	PFOA adults PFOA toddlers PFOS adults PFOS toddlers	0.08-4.3 x 10^{-6} mg/kg bw/d 0.2-17 x 10^{-6} mg/kg bw/d 0.27-5.2 x 10^{-6} mg/kg bw/d 0.58-14 x 10^{-6} mg/kg bw/d	mean values (lower bound - upper bound)	[61]
Legal recommen-dations & regulations	TDI (EFSA)	PFOA PFOS	1.5 x 10^{-3} mg/kg bw/d 0.15 x 10^{-3} mg/kg bw/d		[78]
	SMLs (Union list)	authorized PFASs	0.05-6 mg/kg food	see also Table 3	
	drinking water guidelines	PFOA PFOS	0.04-0.5 x 10^{-3} mg/l water 0.2-0.3 x 10^{-3} mg/l water		[87]

* PFOS and PFOA concentrations in some individuals reached levels exceeding the shown values by 2-3 orders of magnitude.

LD_{50} = lethal dose (50%); NOAEL = no observed adverse effect level; $BMDL_{10}$ = lower confidence limits of the benchmark dose for a 10% effect size; TDI = tolerable daily intake; NHANES = National Health and Nutrition Examination Survey, SML = specific migration limit

the administered doses [63]. PFOS and long-chain PFCAs concentrations increase within the food chain and with higher trophic levels [10]. PFOA crosses the human blood-placenta and blood-brain barriers and thus enters the fetus and the central nervous system, respectively [78].

8.2 PFOA

Oral LD_{50} values for PFOA were in the range of 250-1000 mg/kg bw in rats. Exposure to PFOA resulted in weight loss, increased liver weight, high levels of cholesterol and liver enzymes, peroxisome proliferation, and histopathological changes in the liver [76, 78]. PFOA is not genotoxic and not mutagenic. It induced liver tumors, Leydig cell tumors, and pancreatic acinar cell hyperplasia [78]. Data on the neurotoxicity of PFOA are limited. The impacts of PFOA on reproduction and development have been described in detail [76], and PFOA is known to be toxic to human reproduction and development [90-92]: Evidence exists that PFOA may reduce fecundity and fetal growth. In addition, it may increase neonatal mortality and affect mammary gland development. Exposure to PFOA affected the immune status of test animals by interfering with splenocyte and thymocyte precursor cells and their maturation [76] and by altering inflammatory responses [73].

PFOA belongs to the chemicals monitored under the National Health and Nutrition Examination Survey (NHANES) in the U.S. Associations were found between exposure to PFOA and e.g. thyroid disease [93], liver function [94], dyslipidemia [95], and hyperuricemia [96]. For many years PFOA was also subject of medical surveillance programs monitoring workers at plants that produce PFAS.

Members of the general population living nearby a PTFE production site were monitored in the “C8 Health Project”. The court decision of a class-action lawsuit against DuPont allowed epidemiologists to initiate a large study on the health effects of PFOA [24, 97]. In 2005 and 2006, almost 70’000 people living close to DuPont’s Washington Works plant participated in the baseline survey including blood analysis, medical interviews, and questionnaires. The panel of epidemiologists (“C8 Science Panel”) investigated 55 health outcomes. In 2011 and 2012, they published four reports concluding that PFOA was probably linked to six outcomes: kidney cancer, testicular cancer, ulcerative colitis, thyroid disease, hypercholesterolemia, and pregnancy-induced hypertension. Detailed results of their work have been and continue to be published in dozens of peer-reviewed research papers [24, 98].

Other epidemiological studies also mainly focused on PFOA and PFOS. In 2012, Grandjean and colleagues showed a negative association between cumulative exposure to five PFAS and antibody response to routine childhood vaccinations using a cohort of 587 participants [99]. In 2015, 14 scientific studies correlating exposure to PFOA and PFOS during pregnancy with weight at birth were systematically reviewed [100]. The authors concluded that most studies associated PFOA/PFOS exposure with lower birth weights, but not all results were statistically significant.

8.3 PFOS

In rats, an oral LD_{50} value of 250 mg PFOS per kg body weight was determined after a single dosing [78]. (Sub)chronic exposure to PFOS led to decreased body weight and increased liver weight and uric acid levels [63, 77, 78]. PFOS affected the lipid metabolism and the immune system and changed the homeostasis of thyroid hormones [63, 73, 78]. Further studies showed evidence of carcinogenicity inducing tumors of the liver and limited evidence for thyroid and mammary tumors in test animals [77, 78]. No indications were found for genotoxicity based on a large series of tests [78]. PFOS administration caused developmental toxicity in test animals, including effects on the fetal weight, cleft palates, edemas, delayed ossification of bones, and cardiac abnormalities [63, 78].

PFOS is routinely monitored in the U.S. population under NHANES. Epidemiological studies indicated that exposure to PFOS is associated with e.g. cholesterol levels [101], birth weight [100], liver function and uric acid levels [94].

8.4 Other PFASs

Although extensive toxicity data exist for PFOA and PFOS, information on the toxicity of most other PFASs is rather limited. However, evidence exists that 8:2 diPAP, 8:2 monoPAP, 6:2 FTOH, and 8:2 FTOH affect the synthesis of sex hormones *in vivo* and *in vitro* [102-106]. In other studies, 6:2 FTOH was judged not to be a reproductive or developmental toxicant [107] and a no observed adverse effect level (NOAEL) of 5 mg/kg bw/d was assigned [108]. Short-chain PFASs were judged to be less toxic than their long-chain homologues [109, 110]. In 2015, toxicological data on selected short-chain fluorinated substances were summarized [111]: Data on acute, subchronic, chronic, developmental, and reproductive toxicity were reviewed for 6:2 FTOH and PFHxA concluding that these compounds have more favorable biological properties than the long-chain PFASs, mainly due to their higher elimination rates.

Since 2000, industry has started to replace long-chain PFASs in FCMs by fluorinated alternatives. Between 2013 and 2015, it was stated by different authors that the publicly available information for most of these fluorinated alternatives is not sufficient for conducting realistic risk assessments [30, 65, 110]. Manufacturers of short-chain alternatives were encouraged to also publish the results of further studies.

8.5 Fluorinated polymers

Polymers are regarded as inert materials that are not absorbed by humans. Effects of low molecular weight processing aids used in the polymerization of fluorinated polymers are already covered in the previous sections. However, incorrect use of FCMs coated with fluorinated polymers or occupational exposure may also affect human health.

PTFE is a material that is often used at high temperatures (e.g. in PTFE-coated pans). Above 202°C it affects the lung of birds and may be fatal [112]. For rats, the critical temperature at which lethal amounts of PTFE degradation products are released is between 425-450°C [112]. In industrial settings, workers who are exposed to PTFE heated above 350°C can develop polymer fume fever, a condition with flu-like symptoms [113].

9 Environmental issues

9.1 Environmental occurrence

In 2001, PFOS was quantified in tissues of wild life from many different urbanized and remote areas demonstrating a global distribution of this chemical [114]. Since then, many more cases of PFAS contamination have been reported in various environments, including aquatic ecosystems [58, 115], soil [58], drinking water [83], sewage sludge [116], and air [117].

High environmental levels of PFASs were especially measured close to production sites and after improper handling of PFASs-containing waste, e.g. in contaminated ground, surface and/or drinking water in e.g. Hoosick Falls (NY) [118], nearby Parkersburg (WV) [97], and Arnsberg (Germany) [58, 72]. Depending on the site, the population and wildlife have been exposed to elevated PFOA levels for years or even decades.

9.2 Degradation

Many perfluorinated compounds are highly persistent in biota or under abiotic conditions [4, 119, 120]. By contrast, *poly*fluorinated compounds can be metabolized or converted [121]. However, they are not degraded completely, but mostly converted to persistent PFAAs. One prominent example is the conversion of FTOHs to PFCAs [117]. Similarly, most PFOS derivatives may be degraded to PFOS, which is persistent and remains in the environment [98]. Thus, degradation products of polyfluorinated compounds often contribute to the exposure of perfluorinated compounds. The length of the perfluorinated carbon chain does not influence the persistence of the molecule, i.e. also short-chain PFASs are as persistent as their long-chain homologues [30].

10 Legal limits of intake

In 2008, EFSA recommended tolerable daily intakes (TDIs) for PFOA and PFOS of 1.5 and 0.15 µg/kg bw/d, respectively [78]. The TDI for PFOA was calculated by using dose-response data on increased liver weight in male rats [122]: The lower confidence limits of the benchmark dose for a 10% effect size ($BMDL_{10}$) were modelled and a $BMDL_{10}$ of 0.3 mg/kg bw/d was derived [78]. The TDI for PFOS was based on a subchronic study with cynomolgus monkeys that showed alterations in lipids and thyroid hormones at 0.15 mg/kg bw/d and a NOAEL of 0.03 mg/kg bw/d [82]. An uncertainty factor (UF) of 200 was applied for both TDIs. It was based on inter and intra-species differences (UF 100) and internal dose kinetics. For PFOS the relatively short duration of the key study was considered as additional uncertainty. In the concluding risk characterization, EFSA assessed that human dietary exposure of PFOA is far well below the TDI, but highly exposed people may slightly exceed the TDI for PFOS.

In 2014, two draft documents on the health effect of PFOA and PFOS were published by the U.S. EPA [76, 77]. Reference doses (RfD) of 0.02 and 0.03 µg/kg bw/d were suggested for PFOS and PFOA, respectively. RfD values were based on increased liver weight [76] and developmental toxicity data [77]. PFOA and PFOS were both considered "suggestive of carcinogenicity". A quantification of the carcinogenic potential of PFOS to humans was judged to be currently impossible. The RfD value for PFOA was evaluated to be protective of Leydig cell tumors [76]. In 2016, U.S. EPA derived an RfD of 0.02 µg/kg bw/d for PFOA based on reduced ossification of the phalanges and accelerated puberty of male pups [123].

11 Current regulations

11.1 European regulation on FCMs

In Europe, organic fluorine compounds are authorized under Commission Regulation EU 10/2011, which regulates plastic FCMs. Eight monomers and nine additives were identified on Annex I of this regulation (Table 3). Monomers (e.g. TFE and hexafluoropropylene (CAS 116-15-4)) are mainly used for the production of fluoropolymers such as PTFE and FEP. The ammonium salt of PFOA (APFO; CAS 3825-26-1) and eight further fluorinated substances are authorized as additives in plastics. Most of the substances have either a specific migration limit (SML) in the range of 0.05-6 mg/kg or are only allowed to be used under certain restrictions.

A specific EU legislation for FCMs composed of paper and board does not exist. Thus, PFASs used in or on the surface of these materials do not have legally binding SMLs.

11.2 US legislation on FCMs

PFOA, PFOS and their salts are not regulated by the FDA. The inventory of indirect additives used in food contact substances published by the FDA lists 50 and 15 substances containing the search terms "fluor" and "perfluor", respectively. For example TFE is regulated to be used in perfluorocarbon resins (21 CFR 177.1550), fluorocarbon resins (21 CFR 177.1380), perfluorocarbon cured elastomers (21 CFR 177.2400), and rubber articles intended for repeated use (21 CFR 177.2600). Other PFASs are listed as components of paper and paperboard (21 CFR 176.170), components of resinous and polymeric coatings (21 CFR 175.300), and processing aids for polyolefins (21 CFR 1520).

In 2016, FDA prohibited the use of three PFASs as oil and water repellents for paper and paperboard in contact with food [29]. This decision was based on structural similarities with other long-chain PFASs, for which reproductive and developmental toxicity has been demonstrated, not on actual toxicological data for these three compounds.

11.3 Further legislations & recommendations

In 2015, a comprehensive summary on international risk reduction approaches for PFASs was published by the OECD [124]. Some important legal measures and recommendations are listed below:

Stockholm convention on POPs

In May 2009, PFOS, its salts and its precursor POSF were added to Annex B of the Stockholm convention on persistent organic pollutants (POPs) [26]. Accordingly, the ratifying countries shall restrict the production and use of PFOS, its salts and POSF.

Drinking water guidelines

International drinking water guidelines for PFOA and PFOS are in the ranges of 0.04-0.5 µg/L and 0.2-0.3 µg/L, respectively [87, 123].

European Chemicals Regulation (REACH)

Under REACH, PFOA and its ammonium salt and perfluorononanic acid (PFNA) were added to the Candidate List of substances of very high concern (SVHC) due to their toxicity for reproduction and their persistent, bioaccumulative and toxic (PBT) properties. PFCAs with a chain length of 11 to 14 carbon atoms are also listed as SVHCs because of their very persistent and very bioaccumulative properties (vPvB). In 2015, a restriction proposal for PFOA, its salts and related substances was submitted to the European Chemicals Agency (ECHA) [49].

FTOH and PFOS in Canada

Canada prohibited the manufacture, use, sale, offer for sale, and import of fluorotelomer-based compounds and PFOS in 2006 and 2009, respectively [125, 126].

PFASs under the Toxic Substances Control Act

In the past years U.S. EPA issued several Significant New Use Rules (SNURs), which request manufacturers and importers to notify U.S. EPA 90 days before the use of listed long-chain PFASs [127].

Table 3: Fluorinated organic molecules authorized for use in plastic FCMs according to Annex I of Commission Regulation EU 10/2011. SML = specific migration limit

CAS No.	Substance name		SML (mg/kg)	Restrictions and specifications
75-37-6	1,1-difluoroethane	additive		
75-38-7	vinylidene fluoride, 1,1-difluoroethylene	monomer	5	
75-45-6	chlorodifluoromethane	additive	6	content less than 1 mg/kg of the substance
79-38-9	chlorotrifluoroethylene	monomer		
116-14-3	tetrafluoroethylene	monomer	0.05	
116-15-4	hexafluoropropylene	monomer		
345-92-6	4,4'-difluorobenzophenone	monomer	0.05	
1187-93-5	perfluoromethyl perfluorovinyl ether	monomer	0.05	only to be used in anti-stick coatings
1623-05-8	perfluoropropylperfluorovinyl ether	monomer	0.05	
3825-26-1	perfluorooctanoic acid, ammonium salt (APFO)	additive		only to be used in repeated use articles, sintered at high temperatures
118337-09-0	2,2'-ethylidenebis(4,6-di-*tert*-butylphenyl) fluorophosphonite	additive	6	
329238-24-6	perfluoro acetic acid, α-substituted with the copolymer of perfluoro-1,2-propylene glycol and perfluoro-1,1-ethylene glycol, terminated with chlorohexafluoropropyloxy groups	additive		only to be used in concentrations up to 0,5 % w/w in the polymerization of fluoropolymers that are processed at temperatures at or above 340 °C and are intended for use in repeated use articles
51798-33-5	perfluoro[2-(poly(n-propoxy))propanoic acid]	additive		only to be used in the polymerization of fluoropolymers that are processed at temperatures at or above 265°C and are intended for use in repeated use articles
13252-13-6	perfluoro[2-(n-propoxy)propanoic acid]	additive		only to be used in the polymerization of fluoropolymers that are processed at temperatures at or above 265°C and are intended for use in repeated use articles
958445-44-8	3H-perfluoro-3-[(3-methoxy-propoxy)propanoic acid], ammonium salt	additive		only to be used in the polymerization of fluoropolymers when: processed at temperatures higher than 280°C for at least 10 minutes; processed at temperatures higher than 190°C up to 30% w/w for use in blends with polyoxymethylene polymers and intended for repeated use articles
908020-52-0	perfluoro[(2-ethyloxy-ethoxy)acetic acid], ammonium salt	additive		only to be used in the polymerization of fluoropolymers that are processed at temperatures higher than 300°C for at least 10 minutes.
19430-93-4	(perfluorobutyl)ethylene	monomer		only to be used as a co-monomer up to 0.1% w/w in the polymerization of fluoropolymers, sintered at high temperatures.

Abbreviations

APFO	Ammonium perfluorooctanoate
$BMDL_{10}$	Lower confidence limits of the benchmark dose for a 10% effect size
bw	Body weight
diPAP	Polyfluoroalkyl diesterphosphate
ECHA	European Chemicals Agency
ECF	Electrochemical fluorination process
EFSA	European Food Safety Authority
U.S. EPA	U.S. Environmental Protection Agency
FCM	Food contact material
FDA	U.S. Food and Drug Administration
FEP	Fluorinated ethylenepropylene
FTI	Fluorotelomer iodide
FTOH	Fluorotelomer alcohol
LD_{50}	Lethal dose, 50%
monoPAP	Polyfluoroalkyl monophosphates
N,*N*-EtPFOSA	*N*,*N*-Diethylperfluorooctanesulfonamide
N-EtPFOSA	*N*-Ethylperfluorooctanesulfonamide
NHANES	National Health and Nutrition Examination Survey
NOAEL	No observed adverse effect level
PBT	Persistent, bioaccumulative and toxic
PFAA	Perfluoroalkyl acid
PFAS	Perfluoroalkyl and polyfluoroalkyl substance
PFBS	Perfluorobutane sulfonic acid
PFCA	Perfluoroalkyl carboxylic acid
PFNA	Perfluorononanoic acid
PFPE	Perfluoropolyether
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFSA	Perfluoroalkane sulfonic acid/sulfonate
POP	Persistent organic pollutant
POSF	Perfluorooctane sulfonyl fluoride
PTFE	Polytetrafluoroethylene
REACH	European Chemicals Regulation
RfD	Reference dose
SAmPAP	Perfluorooctane sulfonamido ethanol-based phosphate
S-diPAP	Thioether analogue of diPAP
SML	Specific migration limit
SNUR	Significant new use rule
SVHC	Substance of very high concern
TDI	Tolerable daily intake
TFE	Tetrafluoroethylene
vPvB	Very persistent, very bioaccumulative

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- The market study to which these websites refer is not freely available. The information summarized in this dossier was obtained from press releases and published digests of the market study and refers to only limited data.