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REVIEW Open Access

Toxicology of perfluorinated compounds

Thorsten Stahl[1*], Daniela Mattern[2] and Hubertus Brunn[2]

Abstract

Perfluorinated compounds [PFCs] have found a wide use in industrial products and processes and in a vast array of consumer products. PFCs are molecules made up of carbon chains to which fluorine atoms are bound. Due to the strength of the carbon/fluorine bond, the molecules are chemically very stable and are highly resistant to biological degradation; therefore, they belong to a class of compounds that tend to persist in the environment. These compounds can bioaccumulate and also undergo biomagnification. Within the class of PFC chemicals, perfluorooctanoic acid and perfluorosulphonic acid are generally considered reference substances. Meanwhile, PFCs can be detected almost ubiquitously, e.g., in water, plants, different kinds of foodstuffs, in animals such as fish, birds, in mammals, as well as in human breast milk and blood. PFCs are proposed as a new class of 'persistent organic pollutants'. Numerous publications allude to the negative effects of PFCs on human health. The following review describes both external and internal exposures to PFCs, the toxicokinetics (uptake, distribution, metabolism, excretion), and the toxicodynamics (acute toxicity, subacute and subchronic toxicities, chronic toxicity including carcinogenesis, genotoxicity and epigenetic effects, reproductive and developmental toxicities, neurotoxicity, effects on the endocrine system, immunotoxicity and potential modes of action, combinational effects, and epidemiological studies on perfluorinated compounds).

Keywords: PFCs, PFOA, PFOS, toxicology

Introduction

Perfluorinated compounds [PFCs] are organic substances in which all of the hydrogens of the hydrocarbon backbones are substituted with fluorine atoms. The fluorine-carbon bonds are extremely stabile conferring these substances with very high thermal and chemical stability. PFCs are persistent, and some of the substances bioaccumulate in the environment.

They can be divided into the groups of perfluorinated sulfonic acids, perfluorinated carboxylic acids [PFCA], fluorotelomer alcohols, high-molecular weight fluoropolymers and low-molecular weight perfluoroalkanamides. Perfluorooctanesulfonic acid [PFOS] and perfluorooctanoic acid [PFOA], often referred to as reference or key substances for the first two groups, have been most intensively studied from a toxicological standpoint.

PFCs have been synthesized for more than 50 years and are used in numerous industrial and consumer products. These compounds are intermediates or additives in the synthesis of certain fluorine compounds or their decomposition products. These fluorine compounds are commonly used in consumer products as stain/water/grease repellents in carpets and clothing or in cooking utensils as nonstick coatings [1,2].

The potentially toxic effects of these substances are presently being studied with increasing intensity. The relevance of this topic is also clearly reflected by the number of publications that have appeared in recent years. This increasing interest is the result of reports of toxic effects of PFCs in connection with the ubiquitous detection of this substance in the environment and in sundry matrices, i.e., bodies of water, wild animals, human blood, and breast milk samples, all of which have come to the attention of the public.

An estimate was published in 2008 by the German Federal Institute for Risk Assessment [BfR] and the European Food Safety Authority [EFSA] regarding the potential risks of PFCs in food stuffs for human health. In this document, it was reasoned that adverse effects for the general population were unlikely, based on the known PFC concentrations in food stuffs and serum samples and the present state of scientific knowledge. However, uncertainty was noted in the risk evaluation, and available data are inadequate in regard to the

* Correspondence: thorsten.stahl@lhl.hessen.de
[1]Hessian State Laboratory, Glarusstr. 6, Wiesbaden, D-65203, Germany
Full list of author information is available at the end of the article

diversity of foodstuffs. In addition, only PFOS and PFOA were considered in the risk evaluation, but according to the Organisation for Economic Co-operation and Development [OECD], 853 different poly- and perfluorinated compounds exist [3,4].

In a European Union [EU]-supported research project, which began in August 2009 and was called Perfluorinated Organic compounds in our Food [PERFOOD], efforts are being made to estimate the dietary exposure to PFCs. The present review summarizes current data on exposure and provides an overview of the present toxicological evaluation of PFOS and PFOA, as well as other PFCs.

Exposure to polyfluorinated compounds

Exposure via the food chain

Dietary uptake

One of the pathways by which PFCs can be taken up is through the ingestion of contaminated foodstuffs and/or drinking water. PFCs have been detected in fish, meat, milk products, and plants, e.g., grains. Plants can apparently take up PFCs from contaminated soil. This hypothesis was examined by Weinfurtner et al. [5], showing that the transfer of PFCs from the soil to the plants for potatoes, silage corn, and wheat was so marginal that no health danger for humans would be expected by this path of uptake.

Stahl et al. [6] described for the first time a significant, concentration-dependent transfer ('carry over') of PFCs from the soil to the plant. The higher the concentration of PFOA and PFOS in the soil, the higher the concentration that could be detected in the plants. The uptake and storage of these substances in the vegetative parts of the plants appear to be more significant than the transfer to the storage organs within the plants. In this study, the uptake, distribution, and storage of PFOA and PFOS were seen to be dependent upon the type of plant. The uptake of PFOA and PFOS from contaminated soil by plants enables the entrance of PFCs into the food chain of humans and may provide an explanation for the presence of these compounds in, for example, foodstuffs of animal origin, human blood samples, and human breast milk [6].

Trudel et al. [7] reported that oral ingestion of contaminated foodstuffs and drinking water accounts for the largest proportion of PFOA and PFOS exposures for adults. Tittlemier et al. [8] and Haug et al. [9,10] also expressed the opinion that foodstuffs are the most important uptake path. Within the framework of the 'Canadian Total Diet Study, ' the authors calculated that Canadians ingest on an average of 250 ng of PFCA and PFOS per day. Scheringer et al. [11] also had come to the conclusion that 90% of all PFOS and PFOA exposures is derived from food. Similarly, Vestergren and Cousins [12] are convinced that the main exposure of humans to PFOA is through dietary uptake.

Fromme et al. [13] quantified PFC dietary exposure in Germany. The authors collected and analyzed 214 duplicate meals and beverages from 31 volunteers aged 16 to 45 years old on 7 days in a row. The samples were tested for content of numerous PFCs. The results for PFOS and PFOA uptake of the general population are presented in Table 1.

Perfluorohexane sulfonate [PFHxS] and perfluorohexane acid [PFHxA] levels above the limit of detection [LOD] of 0.1 or 0.2 μg/kg fresh weight, respectively, were detected in only a few samples (3% and 9% of the 214 samples, respectively), whereas perfluorooctane sulfonamide FOSA] was not detected (LOD = 0.2 μg/kg fresh weight). These authors also assume that dietary uptake represents the main source of PFC exposure for humans [13].

Numerous foodstuffs were tested for the presence of PFOS, PFOA, and other PFCs within the framework of the 'UK Total Diet Study' in 2004. PFOS concentrations above the LOD[a] were detected in potatoes, canned vegetables, eggs, sugar, and preserves. Particularly striking was the group of potato products, where in addition to PFOD, PFOA and 10 other PFCs were detected. The upper and lower bounds of total PFOS and PFOA uptake from foodstuffs are estimated in Table 2[14,15].

Inhabitants of reputedly remote regions are by no means exempt from the uptake of PFCs in their food. In a recent study, Ostertag et al. [16] examined the dietary exposure of Inuit in Nunavut (Canada) to these substances. The authors calculated an average daily exposure of 210 to 610 ng/person. The traditional foods such as caribou meat contributed to a higher PFC exposure for this population group. Caribou meat contributed 43% to 75% of the daily exposure [16].

In 2008, an exposure assessment was made on dietary uptake of PFOS and PFOA in connection with possible health effects. The report was based on published data concerning concentrations of PFOS and PFOA in various foods in Europe and on the amount of the individual foods consumed according to the 'Concise European Food Consumption Database' [15]. Since the data for other foods were inadequate to make an exposure assessment, it was based solely on the presence of PFOS and PFOA in fish and drinking water. The results

Table 1 Dietary uptake of PFOS and PFOA (ng/kg BW/day) by adults in Germany

Substance	Range	Mean	Average	90th percentile
PFOS	0.6 to 4.4	1.4	1.8	3.8
PFOA	1.1 to 11.6	2.9	3.9	8.4

Adapted from Fromme et al. [13]; n = 214.

Table 2 PFOS and PFOA uptake (ng/kg BW/day) from UK Total Diet Study of adults and children

Substance	Average consumption		Heavy consumption	
	Adults	Children[a]	Adults	Children[a]
PFOS	10 to 100	50 to 300	30 to 200	100 to 500
PFOA	1 to 70	4 to 200	3 to 100	10 to 300

[a]In each case, the age group with the highest estimated uptake is listed.
Adapted from UK FSA [14]; EFSA [15].

of the exposure assessment for PFOS suggest a daily exposure of 60 ng/kg body weight [BW] for persons who consume average amounts of fish or 200 ng/kg BW those who consume large amounts of fish. For PFOA, the daily uptake was estimated at 2 ng/kg BW/day, and for those who eat larger amounts of fish and fish products, the estimate was 6 ng/kg BW/day [15].

The estimated consumption of drinking water was 2 L/person/day. The uptake from drinking water of PFOS and PFOA were *ca*. 0.5% and 18%, respectively, of the average amount taken up by consumption of fish and fish products. For further details, see Table 3.

The German BfR [17] also undertook an assessment of dietary exposure of the general population to PFOS and PFOA. As a basis for the calculations, the Federal Office of Consumer Protection and Food Safety provided data on PFC concentrations in foods from 2006 to 2008. The data were, for the most part, derived from the Federal Control Plan (2007) 'Perfluorinated surfactants in specific foods' and encompassed 3, 983 test results on contents of PFOS (1993 data sets) and PFOA (1990 data sets) in foodstuffs. Concentrations of the substances were measured in chicken eggs, beef and poultry liver, pork, game and fish offal, poultry and game meat, salt water and fresh water fish, French fries, honey, and drinking water. In addition, the records contained data on the consumption of food and food products by the German population derived from a survey made in 1998. Since one must assume that for over a longer period of time, some foods that have a higher PFC concentration and others with a lower concentration will be consumed, the statistical calculations were made using an average[b] value. In addition, the possibility had to be considered that foods that have exceptionally high concentrations may be consumed perhaps because of unusual local paths of entry. Therefore, exposure through particularly heavily contaminated foods was quantified for both average and above average consumers. The following scenarios were assumed for exposure assessment:

- Average concentration of PFOS and/or PFOA and average amounts consumed
- High concentration of PFOS and/or PFOA and average amounts consumed
- Average concentration of PFOS and/or PFOA and large amounts consumed
- High concentrations of PFOS and/or PFOA and large amounts consumed (worst case).

The PFOS and PFOA dietary uptake of the general population, divided into the four scenarios described above, can be seen in Table 4. In addition, the table shows the percentage of the EFSA-derived tolerable daily intake [TDI] calculated for PFOS and PFOA uptake.

In this exposure assessment, drinking water played a relatively small role in the total exposure to PFOS. The average PFOS uptake from drinking water by an average consumer amounted from 0.02 to 0.08 ng/kg BW/day. The average PFOA uptake from drinking water, however, amounted from 0.32 to 0.40 ng/kg BW/day. Thus, the total PFOA uptake, including drinking water, amounted from 1.03 to 1.34 ng/kg BW/day for an average consumer [17]. If, however, the water is contaminated by an unusual source of PFCs, the role of drinking water in exposure to these substances may be considerable. This was the case, for example, in Arnsberg, Germany where the source of drinking water in 2006 was the PFC-contaminated river, Möhne [18]. Hölzer et al. [19] measured a PFOA concentration 4.5 to 8.3 times higher in the blood plasma of residents than in the plasma of a reference population from the neighboring towns, Siegen and Brilon. The mean concentrations of PFOA in the blood are shown in Table 5. The highest PFC concentration detected in the contaminated drinking water was for PFOA [19].

Table 3 PFOS and PFOA uptake through consumption of drinking water and fish and fish products

Substance and percentage of uptake from drinking water	Uptake from drinking water	Uptake from average consumption of fish and fish products (ng/kg BW/day)	Uptake from high consumption of fish and fish products (ng/kg BW/day)
PFOS	0.24	45 to 58	140 to 230
Percentage of uptake from drinking water		0.4% to 0.5%	0.1% to 0.2%
PFOA	0.31	1.7 to 2.1	4.5 to 7.5
Percentage of uptake from drinking water		15% to 18%	4% to 7%

Adapted from EFSA [15].

Table 4 PFOS and PFOA dietary exposure model (ng/kg BW/day) according to uptake scenarios and corresponding TDI

Criterion	Average consumption	High consumption[b]
Average PFOS content	2.30 to 3.69	up to 8.92
Percentage of TDI[a]	1.5% to 2.5%	5.9%
High PFOS content	8.53 to 10.22	up to 26.02
Percentage of TDI	5.7% to 6.8%	17.3%
Average PFOA content	0.71 to 0.95	up to 2.07
Percentage of TDI	0.05% to 0.06%	0.14%
High PFOA content	up to 5.7	up to 13.11
Percentage of TDI	0.38%	0.87%

[a]TDI for PFOS = 150 ng/kg BW/day, TDI for PFOA = 1, 500 ng/kg BW/day (adapted from EFSA [15]); [b]the 95th percentile of the assumed amount of consumption was chosen for the calculation. The model calculation was adapted from BfR [17].

In a follow-up study, it was shown that elimination of PFCs from humans occurs slowly. The geometric mean of the PFOA concentrations in plasma decreased on an average of 10% per year for men, 17% per year for women, and 20% per year for children [20].

Another study showed that there was no increased PFC exposure in this region in 2006 before contamination of the drinking water. Samples of blood from 30 residents that had been drawn between 1997 and 2004 contained PFOS and PFOA concentrations comparable with those of the general population in Germany [21].

After concentrations as high as 0.64 μg/L were measured in drinking water in Arnsberg in 2006, the German Drinking Water Commission derived a critical limit of 0.3 μg/L for a health-based, lifelong exposure to PFOS and PFOA in drinking water. PFOS and PFOA concentrations in drinking water can be reduced by active charcoal filtration. Use and manufacture of PFOS are strictly limited by legal regulation, and a voluntary reduction of PFOA is being sought. Therefore, the focus of a study by Wilhelm et al. [22] was placed on short-chain C4-C7 compounds that are presently finding use as substitutes for PFOS and PFOA. In a new approach to evaluate short-chain PFCs, based on their half-life in humans, the following preliminary health-related indication values were considered safe for a lifelong exposure via drinking water: 7 μg/L for perfluorobutanoic acid [PFBA], 3 μg/L for perfluoro-n-pentanoic acid [PFPeA], 1 μg/L for PFHxA, 0.3 μg/L for perfluoroheptanoic acid [PFHpA], 3 μg/L for perfluorobutanesulfonic acid [PFBS], 1 μg/L for perfluoropentane-1-sulfonic acid [PFPeS], 0.3 μg/L for PFHxS, and 0.3 μg/L for perfluoroheptane sulfonic acid [PFHpS]. A long-range minimum quality goal or general precautionary value for all PFCs in drinking water was set at ≤ 0.1 μg/L [22].

Table 5 Arithmetic/geometric mean of PFOS concentration in the blood (μg/L)

Test person	Resident of Arnsberg	Reference population
Children	24.6/22.1	5.2/4.8
Women	26.7/23.4	3.2/2.8
Men	28.5/25.3	6.4/5.8

Residents of Arnsberg were compared with the reference population (adapted from Hölzer et al. [19]).

A study by Mak et al. [23] compared PFC concentrations in tap water from China with that from Japan, India, the USA, and Canada. Samples were collected between 2006 and 2008. Tap water from Shanghai, China contained the highest concentration of PFCs (arithmetic mean sum PFCs 0.13 μg/L; PFOA 0.078 μg/L). The lowest values were obtained from Toyama, Japan (0.00062 μg/L). In addition to PFOS and PFOA, drinking water appears to also contain short-chain PFCs such as PFHxS, PFBS, PFHxA, and PFBA. In relation to the guidelines set down by the United States Environmental Protection Agency [US EPA] and the Minnesota Department of Health (PFOS 0.2 μg/L, PFOA 0.4 μg/L, PFBA 1.0 μg/L, PFHxS 0.6 μg/L, PFBS 0.6 μg/L, PFHxA 1.0 μg/L, PFPeA 1.0 μg/L), tap water from these countries should not present a health risk for consumers, in respect to PFC contamination [23].

In a review article from Rumsby et al. [24] on PFOS and PFOA in drinking water and in diverse environmental bodies of water, the authors also conclude that PFOS and PFOA are detectable worldwide. Aside from situations in which there are unusual sources of contamination, the concentrations measured are, however, below existing health-based guidelines specified by various international bodies (0.3 to 0.5 μg/L). Nonetheless, further studies of short-chain PFCs such as PFBS must be undertaken. This substance has a shorter half-life, is less toxic, and is not bioaccumulative, but it is nonetheless persistent, and its possible degradation products remain unknown [24].

D'Eon et al. [25] point out that perfluorinated phosphonic acids [PFPAs] should also be measured in future environmental monitoring studies. These substances were detected in 80% of all surface water samples and in six out of seven sewage treatment plant outflow samples in Canada. C8-PFPA was detected in concentrations from 0.088 ± 0.033 to 3.4 ± 0.9 ng/L in surface water and from 0.76 ± 0.27 to 2.5 ± 0.32 ng/L in sewage treatment plant outflow samples. Since they are structurally similar, one can assume that just like perfluorocarboxilic acids and perfluorosulfonic acids, PFPAs are also persistent [25].

Human exposure via fish consumption

In addition to drinking water, PFC accumulation in fish is also of particular importance for the internal contamination of humans. According to the exposure assessment of the German BfR consumption of salt water and

fresh water, fish accounts for approximately 90% of the total dietary exposure to PFOS [17].

The fact that fish are often highly contaminated is a result of the pronounced biomagnification of these substances via the aquatic food chain. The role of fish consumption is apparent in a model calculation by Stahl et al. [26]. Based on the recommendation of the BfR of 0.1 μg PFOS/kg BW/day as a preliminary daily tolerable uptake, a 70-kg adult should not exceed 7 μg of PFOS [26]. Eating reasonable amounts of fish with high levels of contamination, i.e., from bodies of water with unusual sources of PFCs, may in itself result in reaching or exceeding this limit for the short term [26]. For example, eating 8 g of eel from Belgium with a concentration of 857 μg PFOS/kg fresh weight or eating 0.6 g of trout from the upper Sauerland region of Germany with a measured maximum level of 1, 118 μg/kg fresh weight, is already adequate. Consumption of a normal portion (300 g) of these trout would result in exceeding the limit by a factor of 57 [26]. PFC contamination of fish was also dealt within the following studies:

As an example, analysis was made from a total of 51 eels, 44 bream, 5 herring, 5 mackerel, 3 carp, and 4 trout from various bodies of water in Germany (North Sea, Baltic Sea, Lake Storko in Brandenburg, rivers in Lower Saxony, rivers and lakes within the city limits of Berlin). None of the fish fillet samples had PFOA levels above the limit of detection (0.27 μg/kg); however, PFOS concentrations of 8.2 to 225 μg/kg fresh weight were measured in fish from densely populated regions. With regard to the TDI of 150 μg/kg BW/day [15] and assuming the consumption of fish on a regular basis, the PFC concentrations in 33 of the 112 fish examined represent a potential health risk to heavy consumers of fish [27].

In a Swedish study, the authors also came to the conclusion that consumption of fish from fishing grounds with high concentrations of PFCs in the water can play an important role in dietary PFOS exposure [28]. Fish from Lake Vättern (mean 2.9 to 12 μg/kg fresh weight) had higher PFOS concentrations in the muscle tissue than fish from the brackish water of the Baltic Sea (mean 1.0 to 2.5 μg/kg fresh weight). A PFOS uptake of 0.15 ng/kg BW/day was estimated for a moderate consumption (two portions of 125 g/month) and 0.62 ng/kg BW/day for a higher consumption (eight portions per month) of fish from the Baltic Sea. A PFOS uptake of 2.7 ng/kg BW/day was calculated for people who eat large amounts of fish from Lake Vättern.

No foods that have been examined to date other than fish were found to have a level of contamination great enough to result in reaching the TDI for PFOS or PFOA, assuming realistic consumed amounts. By way of example, according to the model calculations shown above, an adult in the USA would have to consume 12 kg of beef (0.587 μg PFOS/kg) or 12 L of milk (0.693 μg PFOS/L) per day (at the measured levels of contamination in the USA) in order to reach the TDI [26].

Furthermore, offal from game contained the highest concentrations of PFOS and PFOA of all foods. The PFOS concentrations in offal from game were 100-fold higher than those in muscle tissues [17]. Data from a number of studies reporting PFC concentrations measured in diverse foods and tap water [7,14,17,29] are summarized in Table 6.

A detailed, up-to-date survey on the presence of PFCs in foods was also recently published by the EFSA [30] with the title 'Results of the monitoring of perfluoroalkylated substances in food in the period 2000 to 2009.'

When making an exposure assessment, it is important to take into account the fact that many different foods are generally consumed. Studies with the aim of representing the total dietary intake are both quantitatively and qualitatively inadequate. For example, in the various studies including those of the EFSA and the BfR, only a selection of foods were included. In addition, the number of samples was, in part, too small to provide a representative value. For these reasons, the exposure assessments presently available should be considered exploratory. Specific regional sources of contamination can increase PFC levels in foods and drinking water. Furthermore, individual dietary habits, i.e., a predilection for fish or offal from game, must be considered, and additionally, perfluorinated compounds other than PFOS and PFOA must be monitored. Since most studies have examined fresh and unpackaged foods, the effects of migration of PFCs from packaging and cooking utensils on the food products have not been taken into consideration.

Exposure of food to food contact materials

When coming into contact with foods, paper and cardboard packaging are protected from softening by treatment with, among other things, water- and oil-resistant perfluoro chemicals. Fluorotelomer alcohols [FTOH] may be present as contaminants in the coatings. About 1% of the FTOH can be converted to PFOA in the body [31,32]. Furthermore, PFOA is used in the production of polytetrafluoroethylene [PTFE] nonstick surface coatings for cooking utensils or paper coatings and may therefore be present in residual amounts [33]. A migration of < 6 μg/kg (< 1 μg/dm^2) FTOH into food has been calculated as the sum of 6:2 FTOH, 8:2 FTOH, and 10:2 FTOH in an acetone extract of treated paper under the assumption of complete migration [15,33]. Powley et al. [34], using liquid chromatography coupled with tandem mass spectrometry were unable to detect a migration of PFOA from PFTE-coated cooking utensils (LOD 0.1 ng/cm^2).

Table 6 PFOS and/or PFOA concentrations of various foods (μg/kg)

Food product	Substance	Germany [17]	Europe [7]	Spain [29]	UK [14]
Grain products	PFOS	n.r.	< LOQ	< 0.069	< 10 ± < 2
	PFOA	n.r.	< LOQ to 0.5	< 0.080	< 5 ± < 1
Milk	PFOS	n.r.	< LOQ to 0.5	< 0.014	< 0.5 ± < 0.1
	PFOA	n.r.	< LOQ	0.056	< 0.5 ± < 0.1
Milk products	PFOS	n.r.	0.04 to 0.08	0.121	< 5 ± < 1
	PFOA	n.r.	< LOQ	< 0.040	< 5 ± < 1
Eggs	PFOS	0.51	0.08 to 0.5	0.082	1 ± 0.2
	PFOA	1.6	< LOQ	< 0.055	< 1 ± < 0.2
Fats and oils	PFOS	n.r.	< LOQ	< 0.099	< 0.5 ± < 0.1
	PFOA	n.r.	< LOQ	< 0.247	< 1 ± < 0.2
Fish	PFOS	9 to 67	0.2 to 60	0.407	< 5 ± < 1
	PFOA	1.3 to 2	< LOQ to 2	< 0.065[a]	< 3 ± < 0.6
Meat	PFOS	n.d.	0.03 to 0.5	0.045	< 10 ± < 2
	PFOA	n.d.	< LOQ to 1	< 0.053[b]	< 2 ± < 0.4
Offal from game	PFOS	172	n.r.	n.r.	n.r.
	PFOA	4.3 to 6.9	n.r.	n.r.	n.r.
Fruits	PFOS	n.r.	0	< 0.017	< 2 ± < 0.4
	PFOA	n.r.	< LOQ to 0.3	< 0.036	< 5 ± < 1
Vegetables	PFOS	n.d.	< LOQ to 0.5	0.022	< 3 ± < 0.6
	PFOA	n.d.	< LOQ to 0.3	< 0.027	< 10 ± < 2
Potatoes	PFOS	1.2	4 to 8	n.r.	10 ± 2
	PFOA	n.d.	0.4 to 2	n.r.	1 ± 0.2
Candies/Honey/Sugar	PFOS	n.d.	0.8 to 1.2	n.r.	1 ± 0.2
	PFOA	0.5	< LOQ	n.r.	< 1 ± < 0.2
Tap water	PFOS	0.004 to 0.008	< LOQ to 0.01	n.r.	n.r.
	PFOA	0.02 to 0.13	< LOQ to 0.2	n.r.	n.r.

[a]Fish; [b]pork; n.r., not reported; n.d., not detected; LOQ, limit of quantification.

Begley et al. [35] showed that nonstick cooking utensils contribute less to PFC exposure to food than coated papers or cardboard boxes. Residual amounts of PFOA in the range of a few micrograms per kilogram or nanograms per gram were all that could be detected in PTFE cooking utensils. Of the total amount of PFOA in a PTFE strip, 17% (30 ng/dm^2) migrated into the food simulant heated to 175°C for 2 h. In contrast, some paper and cardboard surface coatings contained large amounts of PFCs. For example, microwave popcorn bags were found to contain 3 to 4 mg/kg (11 μg/dm^2).

After heating, the PFOA concentration in the popcorn itself was about 300 μg/kg. PFOA migrated into the oil that coated the popcorn. Migration was enhanced by a temperature of 200°C [35].

Sinclair et al. [36] examined the emission of residual PFOA and FTOH from nonstick cooking utensils and microwave popcorn bags upon heating to normal cooking temperatures (179°C to 233°C surface temperature). Heating nonstick frying pans released 7 ng to 337 ng (0.11 to 5.03 ng/dm^2) PFOA in the gas phase. Furthermore, concentrations of 6:2 FTOH and 8:2 FTOH of < 0.15 to 2.04 ng/dm^2 and 0.42 to 6.25 ng/dm^2 were detected. Repeated use of some frying pans was observed to result in a reduction in PFOA concentrations emitted in the gas phase. However, this was not the case for all frying pans from all of the manufacturers tested. In addition, 5 to 34 ng PFOA and 223 ± 37 ng (6:2 FTOH) as well as 258 ± 36 ng (8:2 FTOH) per bag were detected in the emitted vapor from microwave popcorn bags [36].

Tittlemier et al. [37], in the Canadian Total Diet Study, examined food samples between 1992 and 2004 for contamination with *N*-ethylperfluorooctyl sulfonamide [*N*-EtFOSA], FOSA, *N*,*N*-diethyl-perfluorooctanesulfonamide, *N*-methylperfluorooctyl sulfonamide, and *N*,*N*-dimethyl-perfluorooctanesulfonamide. FOSA, in ng/kg and a few μg/kg amounts, was detected in all food products tested (pastries, candies, milk products, eggs, fast-food products, fish, meat, and convenience foods). The highest concentrations (maximum 27.3 μg/kg) were found in fast-food products (French fries, sandwiches, pizza), which are foods that are commonly packaged in grease-proof paper. Dietary FOSA uptake in Canada was

estimated to be 73 ng/person/day. The *N*-EtFOSA concentrations in the samples seem to drop throughout the time period of sampling. This is possibly the result of fact that manufacturing of perfluoro octylsulfonyl compounds was discontinued [37,38].

In studies of packaged food products carried out by Ericson Jogsten et al. [39], PFHxS, PFOS, PFHxA, and PFOA were detected at levels above the LOD (PFHxS 0.001 μg/kg, PFOS 0.008 μg/kg, PFHxA 0.001 μg/kg, PFOA 0.063 μg/kg) in at least one mixed-food sample. Among the packaged foods tested were goose liver paté, deep-fried chicken nuggets, frankfurters, marinated salmon, and head lettuce [39].

Similar to the results of Begley et al. [35], the US Food and Drug Administration [FDA] named coated paper as the largest possible source of fluorochemicals. According to the FDA, nonstick frying pans are, by comparison, an insignificant source of PFCs [15]. In the ninth list of substances for food contact materials, the EFSA Panel on food additives, flavourings, processing aids and materials in contact with food [AFC] recommends limiting the use of ammonium perfluorooctanoate [APFO] for articles with repeated use to those on which the coating is baked at a high temperature. According to the analytical data, APFO, as auxiliary material in the production of PTFE, could not be detected at levels above the LOD of 20 μg/kg in the finished product. In the worst case, the AFC determined an APFO migration of 17 μg/kg food [15]. As a result of advances in food technology, contamination of foodstuffs during manufacturing, packaging, or cooking only plays a minor role in the total exposure of humans to PFCs [15].

The German Federal Environment Agency has rated the uptake of PFCs through the use of nonstick pots and pans as low. The available data are, however, not yet adequate for a reliable assessment of PFC exposure through food contact materials [4].

Several studies point out the possibility of underestimation of PFC exposure through food contact materials. Mixtures of perfluorooctanesulfonamide esters are often used in the manufacture of water- and greaseproof papers and cardboards. These perfluorooctylsulfonyl compounds have yet to be studied. They may remain as residues in the coatings and migrate into the food.

D'Eon and Mabury [40] examined the formation of PFCA through the biotransformation of polyfluoroalkyl phosphate surfactants [PAPS]. The authors showed that, in spite of their large molecular size, these substances are bioavailable and that PFOA and other PFCs may be formed by their biotransformation. PAPS can probably be degraded by dephosphorylating enzymes in organisms because of the phosphate-ester bond between the fluorinated part and the acidic head group. However, it should be noted that the rats in this study were fed high oral doses of 200 mg/kg PAPS. Renner raises concerns of the fact that PAPS may migrate much more effectively into emulsions such as butter, margarine, or lecithin additives than into food simulants such as oil or water [40,41].

The fact that studies using conventional food simulants do not accurately reflect the actual migration of fluorochemicals into food was confirmed by Begley et al. [42]. They recommend an emulsion containing oil as simulant for greasy food products. The authors measured the migration of three PAPS from the paper packing material, finding 3.2 mg/kg in popcorn after preparation and 0.1 mg/kg in packaged butter after a 40-day storage by 4°C [42].

Lv et al. [43] determined the contents of PFOA and PFOS in packing materials and textiles by means of liquid extraction under pressure and subsequent gas chromatography coupled with mass spectroscopy analysis. PFOA concentrations of 17.5 to 45.9 μg/kg and PFOS concentrations of 17.5 to 45.9 μg/kg were found in the packing materials and textiles tested [43].

Given the present state of knowledge, it is not possible to say whether the use of nonstick-coated cooking utensils or packaging materials with PFC-based coating lead to a significant increase in dietary internal PFC contamination of humans.

Additional potential pathways of exposure leading to internal polyfluorinated compound contamination of humans

PFCs may also enter the body by ingestion of dust and dirt particles and by contact with products that have been treated with substances that contain PFCs or its precursor compounds [9,44]. These may include carpets, upholstered furniture, or textiles. These routes of entry may be of particular importance in regard to children because contact can occur indirectly by hand-to-mouth transfer or directly if an infant sucks on the product. Another route that must be considered is inhalation of PFCs in indoor or outdoor air [10,45,46] as well as the inhalation of waterproofing sprays. Dermal exposure may also occur by skin contact with PFC-treated products [17].

Exposure via non-food personal items

An estimate of exposure via non-food products is difficult because of the large number of possible applications of PFCs such as for jackets, trousers, shoes, carpets, upholstered furniture, and as cleaning agents. In addition, only data are available concerning possible PFCs exposure via non-food products. In order to make an estimation of exposure, research groups such as Washburn et al. [47] have resorted to the use of models.

In this study, the concentrations of deprotonated PFOA [PFO] (the anion of PFOA) were determined by

Table 7 PFO concentrations in consumer articles (from Washburn et al. [47])

Product group	Concentration according to information on product composition (mg PFO/L)	Calculated total concentration in the end product (mg PFO/kg end product)	Results of the extraction tests from the end product (ng PFO/cm^2 end product)
Industrially cleaned carpeting	30 to 80	0.2 to 0.6	< 0.2 to 23 (n = > 60)
Carpeting treated with carpet care product	1 to 50	0.2 to 2	28 to 50 (n = 14)
Treated clothing	< 1 to 40	< 0.02 to 1.4	< 0.01 to 12 (n = > 100)
Treated upholstered furniture	< 1	< 0.034	0.4 to 4 (n = 3)
Treated home textiles	< 1 to 40	< 0.02 to 1.4	not tested
Latex paint	50 to 150	0.02 to 0.08	not tested
Cleaning product	50 to 150	0.005 to 0.05	not tested

extraction tests and information about the composition of the products. Values from the study by Washburn et al. [47] are shown in Table 7.

Age-specific behavior was taken into account in order to assess the PFO exposure of consumers through contact with these products. A one-compartment model was chosen to determine the contribution of PFC-treated non-food products to the concentration of PFO in serum, and a dermal absorption coefficient of 1.0×10^{-5} per hour was adopted. The values obtained are hypothetical and are categorized as more typical exposure [MTE] or reasonable maximum exposure [RME] scenarios. An assumable daily total PFOA exposure via non-food articles for adults was estimated at 0.09 ng/kg BW (MTE). The maximum uptake of PFOA was estimated at 3.1 ng/kg BW (RME). According to this assessment, the exposure would drop by one or two orders of magnitude upon reaching adulthood because of the low frequency of hand-to-mouth transfer [15,47].

Exposure via indoor and outdoor air

Based on studies in Japan [48] and Canada [49], the EFSA determined the lifetime average daily dose [LADD] via ingestion, inhalation, and skin contact with contaminated house dust in interior rooms. The corresponding data are presented in Table 8. These calculations by the EFSA are based on mean PFC concentrations of 0.440 ng PFOS/kg and 0.380 ng PFOA/kg in house dust. The exposure to PFOS and PFOA through inhalation was estimated at 0.022 ng/m^3 and 0.019 ng/m^3, respectively [15].

In a recent study by Kato et al. [50], 39 samples of house dust that had been collected in diverse countries worldwide in 2004 were tested for concentrations of 17 PFCs. Six of the compounds were detected in 70% of the samples tested. The highest mean values measured were for PFOS, PFBS, PFHxS, perfluorooctanesulfonamide ethanol [FOSE], 2-(*N*-ethyl-perfluorooctanesulfonamido) acetic acid (Et-PFOSA-AcOH), and 2-(*N*-Methyl-perfluorooctanesulfonamide) ethanol [Me-FOSE] [50]. The values are shown in Table 9.

Data have been published on the inhalation exposure to PFOS and PFOA for Norway, the UK, Japan, and North America. As a result of the large variability of the PFC concentrations in outdoor air, the EFSA calculated LADD values for 'high' and for 'low' PFC exposures via inhalation of outdoor air. The PFOS and PFOA concentrations of air and dust that were used as basis for calculation, as well as the LADD values, are shown in Table 10.

Consequently, the uptake of PFOS and/or PFOA from outdoor air, even assuming a high concentration of PFCs, amounts to less than 0.5% or 17%, respectively, of the contamination via indoor air and, in comparison to dietary uptake, would therefore appear to be negligible [15].

Table 8 PFOS and PFOA uptake via inside air (ng/kg BW/day; from EFSA [15])

Exposure source	PFOS uptake	PFOA uptake
Ingestion of house dust	0.57	0.49
Skin contact with house dust	0.36	0.31
Inhalation of house dust	0.006	0.005
→ LADD[a]	0.93	0.81

[a]LADD, lifetime average daily dose.

Table 9 PFC concentrations in 39 samples of house dust (from Kato et al. [50])

Substance	Mean value (µg/kg)
PFOS	480
PFBS	359
Et-FOSA-AcOH	244
Me-FOSE	219
FOSE	208
PFHxS	186

Table 10 PFOS and PFOA uptake via ingestion and inhalation of outdoor air (from EFSA [15])

Outdoor air contamination	Low uptake		High uptake	
	PFOS	PFOA	PFOS	PFOA
In dust (μg/kg)	30	400	100	4000
In air (ng/m^3)	0.001	0.003	0.01	0.3
→ LADD (ng/kg BW/day)	0.00069	0.0063	0.0041	0.14

Fromme et al. [38] summarized human exposure to PFCs via outdoor and indoor air in western countries. A comparison of the various PFCs in outdoor air shows that the levels of FOSE or FOSA, PFOS, and PFOA concentrations decrease according to the sequence city, country, and outlying regions. Furthermore, there appears to be a north-south gradient since the maximum 8:2 FTOH concentrations were 0.19 ng/m^3 in the northern hemisphere and 0.014 ng/m^3 in the southern hemisphere. In addition, it must be assumed that there are seasonal variations in PFOS and PFOA concentrations in outdoor air. Samples taken in the spring contained higher concentrations of PFCs than samples from the winter. [38].

Total exposure

The individual pathways of exposure according to EFSA [15] and Fromme et al. [38] are summarized, and the resulting total exposure to PFCs is calculated in Table 11. The calculated total exposure according to the data of the EFSA [15] and Fromme et al. [38] are of the same order of magnitude for PFOA. For PFOS, the total exposure derived from the data of the EFSA [15] is significantly higher than the result obtained using the data from Fromme et al. [38]. This resulted from the higher values for dietary exposure according to the EFSA [15]. According to this assessment, exposure via drinking water and outdoor air appear to be insignificant, barring special sources of contamination.

Fromme et al. [51] initiated a study, the Integrated Exposure Assessment Survey [INES] in which PFC concentrations in foods, indoor air, and house dust were correlated with concentrations in blood. The blood concentrations of the 48 INES participants varied between 4.9 to 55.0 μg/L for PFOS and 2.7 to 19.1 μg/L for PFOA. Further details have not yet been published since the study is ongoing.

Zhang et al. [52] took a different approach. The daily uptake, calculated from blood concentrations using a one-compartment model, was found to agree closely with the daily PFOS uptake via food and house dust (0.74 vs. 1.19 ng/kg BW for men and 1.2 vs. 1.15 ng/kg BW for women) [52].

Pre- and postnatal exposures

PFC exposure of the fetus (prenatal) and nursing infants (postnatal) has also been shown in studies of mother-child pairs.

Prenatal exposure

PFOS was detected in cord blood samples in studies from Northern Canada, Germany, Japan, the USA, Canada, and Denmark [37,53-57]. This also applies to PFOA, with the exception of the Japanese study [54]. Thus, PFCs are considered to cross the placental barrier. This was also shown in animal studies [58].

In the northern Canadian study, the mean PFOS- and PFOA-cord blood concentrations in humans were 17 μg/L and 3.4 μg/L, respectively. In the other studies, the values were from 3 to 7 μg/L for PFOS and 1.6 to 3.4 μg/L for PFOA. In the German study, PFOS concentrations in cord blood were reported to be lower than the mother's blood by a factor of 0.6 (7.3 μg/L vs. 13 μg/L). By contrast, however, the PFOA concentrations were a factor of 1.26 higher in cord blood than in the mother's blood (3.4 μg/L vs. 2.6 μg/L) [53].

Inoue et al. [54] also compared PFOS concentrations in the mother's blood with the cord blood of the fetus. The concentration in the maternal blood varied from 4.9 to 17.6 μg/L, whereas the cord blood concentration had a PFOS level of 1.6 to 5.3 μg/L. A strong correlation

Table 11 Estimate of total PFC uptake for adults (ng/kg BW/day)

Source of contamination	EFSA [15]	Fromme et al. [38]	EFSA [15]	Fromme et al. [38]	Fromme et al. [38]	Fromme et al. [38]
	PFOS	PFOS	PFOA	PFOA	FTOH	FOSE/FOSA
Diet	60 to 200	1.5 to 4.48	2 to 6	2.82 to 11.5	n.r.	0.217-6.87
Fish	45 to 58	n.r.	1.7 to 2.1	n.r.	n.r.	n.r.
Drinking water	0.24	0.023 to 0.130	0.31	0.022 to 0.087	n.r.	n.r.
Indoor air + house dust	0.93	0.0047 + 0.032 to 4.22	0.81	0.0009 + 0.016 to 1.03	0.038 to 0.105 + 0.103 to 1.02	0.460 to 2.05 + 0.983 to 2.03
Outdoor air	0.001 to 0.004	0.0001 to 0.001	0.006 to 0.14	0.001 to 0.012	0.003	0.001 to 0.012
Total uptake	60.9 to 200	1.56 to 8.84	2.82 to 6.95	2.86 to 12.6	0.144 to 1.13	1.66 to 10.9

n.r, Not reported.

was found between the PFOS concentration in the mother's blood and in cord blood (r^2 = 0.876). In this study, PFOA was only found in the mother's blood [54].

Monroy et al. [56] also made comparative measurements of PFC concentrations in mother's blood (n = 101) in the 24th to 28th week of gestation and at the time of birth as well as in cord blood (n = 105). These authors established higher PFOS concentrations in the mother's blood during pregnancy than at the time of birth. PFOS concentrations in cord blood were lower than those in the mother's blood samples.

Fei et al. [57] also examined PFOS and PFOA concentrations in the blood of women during the first trimester (n = 1, 400) and during the second trimester (n = 200) of pregnancy. They also analyzed cord blood (n = 50) after birth. The values from these last two studies are shown in Figure 1.

Postnatal exposure

The presence of PFOS and PFOA in human breast milk was demonstrated in studies from Sweden [59] and China [60], among others. The PFC concentrations measured in these studies were similar. In another study by Völkel et al. [61], PFOS and PFOA concentrations were also determined in 57 human milk samples from Germany and 13 samples from Hungary. The PFOA concentrations measured in this study (0.201 to 0.46 μg/L) were similar to those reported by So et al. [60] and Kärrman et al. [59]. Only 11 PFOA values were greater than the LOD of 0.2 μg/L. In the Swedish study, the same problem emerged, whereby only one sample contained concentrations greater than the blank level of 0.209 μg/L.

In 24 pooled samples of human milk (1, 237 individual samples) obtained in the year 2007 from 12 provinces of China, Liu et al. [62] measured PFOS concentrations of 0.049 μg/L (mean) and for PFOA, 0.035 μg/L. The concentrations of PFCs varied greatly between different geographic regions. High concentrations of PFOA were measured in Shanghai (0.814 μg/L in rural areas and 0.616 μg/L in urban areas) [62].

PFOS and/or PFOA concentrations measured in human milk samples by Kärrman et al. [59], So et al. [60], Völkel et al. [61] and Liu et al. [62] are shown in Table 12.

Using the data from the Swedish study, for example, an infant who weighs 5 kg and drinks 800 mL human milk per day would have a daily uptake of 0.048 to 0.38 μg PFOS and 0.17 to 0.39 μg PFOA [15]. If the data from Shanghai are used, the infant would ingest more PFOA (consumed volume = 742 mL/day, BW = 6 kg) amounting to 0.088 μg/kg BW [62], thereby nearly reaching the TDI of 0.1 μg/kg BW/day recommended by the German Drinking Water Commission.

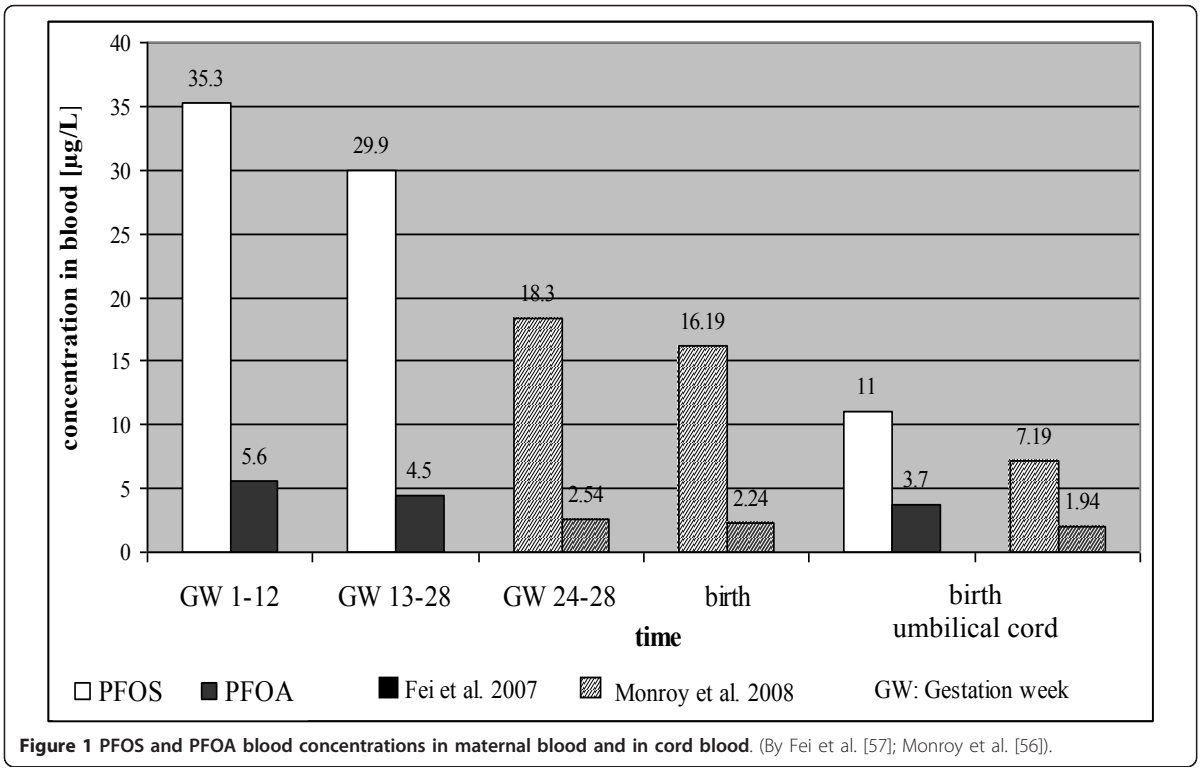

Figure 1 PFOS and PFOA blood concentrations in maternal blood and in cord blood. (By Fei et al. [57]; Monroy et al. [56]).

Table 12 PFOS and PFOA concentrations (μg/L) of human breast milk

Substance	Sweden	China		Germany
	Kärrman et al. [59]	So et al. [60]	Liu et al. [62]	Völkel et al. [61]
PFOS	0.06 to 0.47 0.201 (arithmetic mean)	0.045 to 0.36 0.121 (arithmetic mean)	0.049 (median)	0.028 to 0.309 German samples 0.096 to 0.639 Hungarian samples
PFOA	< 0.209 to 0.492	0.047 to 0.21 0.106 (arithmetic mean)	0.035 (median)	0.201 to 0.46

It can be seen in the study by Kärrman et al. [59] that the mean PFOS concentration of 0.201 μg/L in human milk is correlated with the serum PFOS concentration of 20.7 μg/L (r^2 = 0.7), reaching a level of about 1% of the serum concentration. A similar and even stronger correlation (r^2 = 0.8) was also determined for PFHxS (milk 0.085 μg/L, serum 4.7 μg/L). The total concentration of PFCs was 32 μg/L in serum and 0.34 μg/L in milk. The authors calculated a PFC uptake of about 0.2 μg/day for infants. The PFOS and/or PFHxS concentrations in human milk samples that had been obtained between 1996 and 2004 showed little variation throughout that time period, providing no evidence of a possible temporal trend [59].

Tao et al. [63] analyzed PFC concentrations in human milk samples from various Asian countries. The PFOS concentration varied between 0.039 μg/L in India and 0.196 μg/L in Japan. The mean PFHxS concentrations ranged from 0.006 μg/L (Malaysia) to 0.016 μg/L (Philippines). The mean PFOA concentration in Japan was 0.078 μg/L. In addition, the average PFC uptake of nursing infants from seven Asian countries was compared to the dietary uptake values from adults in Germany, Canada, and Spain. The PFOS uptake of nursing infants (11.8 ± 10.6 ng/kg BW/day) was 7 to 12 times higher, and the PFOA uptake (9.6 ± 4.9 ng/kg BW/day) was 3 to 10 time higher than the dietary exposure of adults to these substances [63].

Llorca et al. [64] also analyzed human milk samples for PFC contamination. The milk samples, from donors living in Barcelona, Spain, were all from at least 40 days after birth. PFOS and perfluoro-7-methyloctanoic acid were detected in 95% of all samples. Concentrations of 0.021 to 0.907 μg/L PFOA were measured in 8 out of 20 human milk samples. According to this study, infants ingest 0.3 μg PFCs/day while nursing [64].

According to the results of these studies, nursing contributes to PFC exposure of infants. The mechanism by which these compounds pass from the mother's blood to the milk is not fully understood. Bonding to proteins would appear likely [38,65].

PFC contaminations of infant formulas were examined in two studies. Tao et al. [63] detected PFC concentrations above the LOD in only a few cases[a]. Llorca et al. [64] found six PFCs in all baby formulas of various brands as well as in baby cereals. Elevated concentrations (as high as 1.29 μg/kg) of perfluorodecanoic acid [PFDA], PFOS, PFOA, and perfluor-7-methyloctanoic acid were detected. Contamination of baby food is likely the result of migration of the compounds from the packaging or containers used during production [64].

Human internal contamination

Taves [66] and Shen and Taves [67] were the first to show the presence of organic fluorides in human blood. Until the 1990s, however, the presence of these compounds was not considered of importance. Only since 1993 have PFC concentrations in the serum of exposed workers been the subject of study. The PFOS concentrations in the serum were found to be between 1, 000 and 2, 000 μg/L. Data on serum concentrations in the general population have only been available since 1998. These values were approximately 100 times lower than in occupationally exposed workers [15,68,69].

The plasma to serum ratio for PFHxS, PFOS, and PFOA is 1:1, independent of the concentration, whereas the ratio of serum or plasma to whole blood was stated to be 2:1. This indicates that the PFC concentration in whole blood is only 50% of the concentration in plasma and/or serum. The difference is the result of the distribution volume of red blood cells in the samples since fluorochemicals are neither found intracellularly nor bound to the red blood cells [70].

Kannan et al. [71] examined 473 blood/serum/plasma samples from people of various countries. Of the four PFCs measured (PFOS, PFHxS, PFOA, FOSA), PFOS was quantitatively the dominant component in blood. The highest PFOS concentrations were detected in samples from the USA and Poland (> 30 μg/L). In Korea, Belgium, Malaysia, Brazil, Italy, and Colombia, blood PFOS concentrations were in the range of 3 to 29 μg/L. The lowest PFOS concentrations were measured in samples from India (< 3 μg/L). In this study, the PFOA concentrations were lower than the values for PFOS, except in India and Korea. The joint occurrence of the four PFCs varied according to the country of origin of the samples. This suggests differences in the exposure pattern in the individual countries [71].

Kärrman et al. [72] measured plasma PFOS concentrations from residents of Australia, Sweden, and the UK

with levels of 23.4 μg/L, 33.4 μg/L, and 14.2 μg/L, respectively. Ericson et al. [73] determined average values of 7.64 μg PFOS/L and 1.8 μg PFOA/L in blood samples from the Spanish population [15].

Calafat et al. [74], within the framework of the National Health and Nutrition Examination Surveys [NHANES] from 1999 to 2000, also examined serum samples from the US population for concentrations of 11 different PFCs. The group of 1, 562 participants in the study was made up of male and female subjects, three ethnic groups, and four age categories (12 to 19 years, 20 to 39 years, 40 to 59 years, 60 years and older). Consequently, these data are representative of the exposure of the US population to PFCs. PFOS, PFOA, PFHxS, and FOSA were detected in all serum samples [74]. The values are presented in Table 13.

Wilhelm et al. [75] took three biomonitoring studies as a basis to arrive at a reference value for PFOA and PFOS in the blood plasma of the general population in Germany. Two studies were carried out in southern Germany [76,77] and one in North Rhine Westphalia [19]. Although these studies are not representative of the general population of Germany, they present the best basis for deriving a reference value for internal contamination with PFOS and PFOA. Based on the 95th percentile, the following reference values were suggested: for PFOA, 10 μg/L for all groups and for PFOS, 10 μg/L for children of school age, 15 μg/L for adult women, and 25 μg/L for men [75].

The mean PFOA concentration in the blood for the European population is within the region of 4 to 20 μg/L; their mean PFOS serum concentration is within the range of 4 μg/L (Italy) and 55 μg/L (Poland). PFOS is the quantitatively dominant component of PFCs in all of the blood samples measured worldwide. In general, PFOA concentrations in serum are lower than concentrations of PFOS [15].

Olsen et al. [69] determined the PFOS concentrations in serum to be 6.1 to 58.3 μg/L and in human liver, 4.5-57 μg/kg (n = 31). The mean liver to serum ratio for PFOS concentration was 1.3:1. Liver to serum ratios could not be established for PFOA, PFHxS, and FOSA because 90% of the concentrations of these substances were below the LOD[a] [69].

Table 13 PFOS and PFOA serum concentrations (μg/L) of the US population (from Calafat et al. [74])

Substance	10th Percentile	50th Percentile	95th Percentile
PFOS	15.1	30.2	75.6
PFOA	2.8	5.1	11.9
PFHxS	0.8	2.1	8.7
FOSA	< 0.1	0.3	1.4

Kärmann et al. [78] analyzed blood samples from 66 Swedish study participants. Concentrations of 12 PFCs were determined (PFBS, PFHxS, PFOS, perfluorooctanesulfonamido acid, FOSA, PFHxA, PFOA, perfluorononanoic acid [PFNA], PFDA, perfluoroundecanoic acid [PFUnA], perfluorododecanoic acid [PFDoA], perfluorotetradecanoic acid [PFTDA]) along with the concentrations of other 'traditional' persistent organic pollutants [POPs]. The mean concentrations of PFCs in whole blood were 20 to 50 times higher than the total concentrations of polychlorinated biphenyls [PCB] and p, p'-dichlorodiphenyldichloroethylene. Similarly, the PFC concentrations were 300 to 450 times greater than for hexachlorbenzene and the sum of the six chlordanes and the three polybrominated diphenyl ethers. However, the PFCs and the POP that were measured behaved differently in regard to their distribution in the body, making an additional comparison of total body contamination necessary. PFCs are mainly found in the blood and the liver, whereas polychlorinated and polybrominated POPs are chiefly present in the fat tissue and blood lipids. The reason for these differences appears to be related to the different basic structures and the binding behavior in blood of these substances [40,79,80]. Whole blood contains about 0.5% blood lipids, and thus represents only a small part of the total body contamination of PCB for example. The total body contamination was calculated using the proportionate weights of the main distribution tissues. This analysis showed a similar total body contamination for PFCs and for the POP that had been analyzed to be about 1.6 mg PFOS and 1.7 mg for PCB153, one of the most abundant individual PCB congeners [72].

Gender and age-dependent differences

No correlation between the PFOS concentration and age or gender were found in studies by Olsen et al. [69] on US citizens or in the studies by Kannan et al. [71]. Data of Calafat et al. [74,81] show significantly higher PFOS and PFOA concentrations in men than in women; however, an age-related difference was not found. Harada et al. [82] reported higher PFC serum concentrations in Japanese men than in women, and in addition, they also reported a rise in PFC serum concentrations in women with increasing age so that by age 60, the concentrations in women were comparable to those in men. The situation was similar for PFOA [82].

Kärrman et al. [83] determined a rise in PFOS serum concentrations with increasing age. PFOS, PFOA, and PFHxS concentrations in blood were also higher in men than in women. Ericson et al. [73] confirmed higher PFHxS and PFOA concentrations in blood of male subjects. Concentrations were significantly different between age groups 25 ± 5 years (18 participants) and 55 ± 5 years (30 participants) only for PFHxS and FOSA