

REVIEW

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PFAS: forever chemicals—persistent, bioaccumulative and mobile. Reviewing the status and the need for their phase out and remediation of contaminated sites

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Abstract

Background Per- and polyfluorinated alkyl substances (PFAS) have received increasing scientific and political attention in recent years. Several thousand commercially produced compounds are used in numerous products and technical processes. Due to their extreme persistence in the environment, humans and all other life forms are, therefore, increasingly exposed to these substances. In the following review, PFAS will be examined comprehensively.

Results The best studied PFAS are carboxylic and sulfonic acids with chain lengths of C4 to C14, particularly perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). These substances are harmful to aquatic fauna, insects, and amphibians at concentrations of a few µg/L or less, accumulate in organisms, and biomagnify in food webs. Humans, as the final link in numerous food chains, are subjected to PFAS uptake primarily through food and drinking water. Several PFAS have multiple toxic effects, particularly affecting liver, kidney, thyroid, and the immune system. The latter effect is the basis for the establishment of a tolerable weekly dose of only 4.4 ng/kg body weight for the sum of the four representatives PFOA, PFOS, perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS) by the European Food Safety Authority (EFSA) in 2020. Exposure estimates and human biomonitoring show that this value is frequently reached, and in many cases exceeded. PFAS are a major challenge for analysis, especially of products and waste: single-substance analyses capture only a fragment of the large, diverse family of PFAS. As a consequence, sum parameters have gained increasing importance. The high mobility of per and polyfluorinated carboxylic and sulfonic acids makes soil and groundwater pollution at contaminated sites a problem. In general, short-chain PFAS are more mobile than long-chain ones. Processes for soil and groundwater purification and drinking water treatment are often ineffective and expensive. Recycling of PFAS-containing products such as paper and food packaging leads to carryover of the contaminants. Incineration requires high temperatures to completely destroy PFAS. After PFOA, PFOS and a few other perfluorinated carboxylic and sulfonic acids were regulated internationally, many manufacturers and users switched to other PFAS: short-chain representatives, per- and polyfluorinated oxo carboxylic acids, telomeric alcohols and acids. Analytical studies show an increase in environmental concentrations of these chemicals. Ultra-short PFAS (chain length C1–C3) have not been well studied. Among others, trifluoroacetic acid (TFA) is present globally in rapidly increasing concentrations.

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Conclusions The substitution of individual PFAS recognized as hazardous by other possibly equally hazardous PFAS with virtually unknown chronic toxicity can, therefore, not be a solution. The only answer is a switch to fluorine-free alternatives for all applications in which PFAS are not essential.

Keywords PFAS, Persistence, Mobility, Toxicity, Ecotoxicity, Bioaccumulation, Exposure, Trifluoroacetic acid, Sum parameters, Non-target analysis, Monitoring, Contaminated sites, Remediation, Essential uses, Regulation

Background

Per- and polyfluorinated alkyl substances (PFAS) are non-aromatic organic chemical compounds in which the hydrogen atoms have been either completely (perfluorinated) or largely (polyfluorinated) replaced by fluorine atoms. These substances have been synthetically manufactured since the end of the 1940s, do not occur naturally and are exclusively of anthropogenic origin. The most well-known members of this group of substances are perfluorinated alkyl carboxylic and alkyl sulfonic acids such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). The production and use of PFOA and PFOS are now restricted or banned globally [1]. As a consequence, they are increasingly being replaced by other per- and polyfluoroalkyl substances having similar properties. Shorter (C4–C6) or longer chain (C9–C14) PFAS are being detected more frequently in products, foodstuffs, in human blood and in the environment. Perfluorinated alkyl carboxylic and alkyl sulfonic acids are increasingly being replaced by per- and polyfluorinated oxo carboxylic acids [2] such as ADONA (perfluoro-4,8-dioxo-3H-nonanoic acid, ammonium salt), C6O4 (perfluoro-{acetic acid, 2-[(5-methoxy-1,3-dioxolan-4-yl)oxy]}}, ammonium salt) and HFPO-DA (2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoic acid).

Due to the exceptionally high stability of the C–F bond there are neither biological nor abiotic degradation mechanisms that lead to mineralization of these substances. In some cases, so-called precursors, non-fluorinated moieties are transformed [3], but a perfluorinated residue always remains.

PFAS are employed in countless applications, both in consumer products as well as in industrial processes [4]. Since they are extremely stable, it is not surprising that they are being detected increasingly in humans and in the environment. Of particular concern are soil and groundwater contamination where remediation is extremely difficult. Since some PFAS show adverse biological effects even in very low concentrations the field of chemical analysis is challenged to develop methods for very sensitive detection of as many PFAS as possible.

In general, all chemicals with a -CF₂- or -CF₃ group belong to the PFAS [5, 6]. Thus, short-chain fluorinated and chloro-fluorinated hydrocarbons (HFCs and CFCs),

which damage the ozone layer and/or have a high global warming potential, also belong to the substance group PFAS, as do fluorinated polymers such as polytetrafluoroethylene (PTFE) or polyacrylates, whose side chains are per- or polyfluorinated. In total, more than 4700 chemicals are counted as PFAS [5]; other sources refer to as many as 12,000 substances [7]. The total quantity of fluoropolymers produced alone is estimated at 320,000 tons annually worldwide [8, 9].

The focus of discussion is increasingly turning to possibilities for strict PFAS regulation. In a recent review, authors from the US EPA provide an overview on the diversity of PFAS in the environment, their distribution, their environmental fate, and options for remediation of resulting damage [10]. The division of several thousand PFAS into categories according to their structural characteristics has been proposed [6, 11, 12]. For example, the Organization for Economic Cooperation and Development (OECD) divides the PFAS into 15 subgroups [13]. The European Union (EU), which is currently preparing a plan to restrict PFAS as a whole group of substances, is following the subgrouping approach of the OECD [14].

Pressure to comprehensively regulate the entire substance group of PFAS is growing worldwide. In the so-called Zurich Statement of 2018, more than 50 scientists called for new approaches to the assessment and management of PFAS as a group of substances [15]. This publication reviews various aspects of properties, applications, occurrence and regulative approaches regarding PFAS. It specifies arguments and facts substantiating the urgency to phase out PFAS as completely as possible and to remediate contamination to protect environment and humans.

Technical characteristics and applications

PFAS are characterized by their high thermal and chemical stability. They do not decompose at high temperatures of several hundred degrees and/or under the influence of aggressive chemicals, making them of interest for numerous technical applications. This property is the result of the extraordinary stability of the carbon–fluorine bond (485 kJ/mol), which, for example, is significantly higher than the bond energy of the carbon–oxygen single bond (358 kJ/mol). The strongly electronegative property of the fluorine atom

is not only responsible for the fact that the trifluoromethyl groups (-CF₃) are desirable building blocks, but also that many PFAS are water repellent as well as oil and dirt repellent. This opens up a wide range of applications, particularly for the surface-active PFAS (perfluorinated tensides, PFT) with polar functional groups. The compilation by Glüge et al. [4] makes it evident that virtually no area of life or industrial sector is free of fluorochemicals. Two hundred applications in 64 use categories have been identified. Thus, very diverse sources of environmental and human exposure must be considered. The most important areas of application are:

- Some fluorinated hydrocarbons are still widely used as propellant gases, refrigerants and extinguishing agents, as well as in plastic foams (polystyrene and polyurethane).
- Textiles and leather are impregnated with PFAS to render them water and dirt repellent [16]. This is particularly the case for outdoor and work clothing as well as for home textiles and carpets. Polymers with fluorinated side chains are often used to coat materials. Waterproofing sprays often contain PFAS, for example polyfluorinated silanes, such as trichloro (1*H*,1*H*,2*H*,2*H*-tridecafluoro-*n*-octyl)silane.
- The water- and oil-repellant properties of PFAS are welcome for the surface treatment of paper and printed products. Studies by a number of environmental organizations show that food packaging (including that which is actually compostable) such as coffee cups, disposable dishes and pizza boxes can be significantly contaminated with PFAS [17]. Oil beading containers from compostable plant fibers, e.g., contained up to 680 mg/kg dry matter (dm) fluorine (median). First investigations in Hesse, a federal state of Germany, on water and ethanol extracts of coated food contact material confirm these results: in every third sample, von Abercron [18] discovered more than 100 µg organic fluorine per gram paper, the same as found in the USA [19]. Recycling of impregnated paper can thus result in PFAS contamination of recycled paper.
- The use of PFAS in fire-extinguishing foams is based on the surface-active properties of PFAS, e.g. PFOS. Extinguishing exercises and operations using these foams have occurred particularly often at airfields, refineries, oil platforms and other sites with highly inflammable liquids.
- PFAS in ski wax increases the gliding properties.
- PFOS and its substitutes such as 6:2 fluorotelomer sulfonic acid (6:2-FTS) are used in electroplating with chromium VI as wetting agents to prevent emergence of toxic chromate aerosols and to improve the draining properties of pickling solutions.
- PTFE and other fluoropolymers are used to coat pots and pans and other surfaces. This prevents foodstuffs and residues from sticking to the surfaces and the products can withstand high thermal and chemical stresses. Fluoropolymers have a great variety of applications. In their production PFOA and its substitutes such as ADONA and HFPO-DA often serve as emulsifiers. Fluorine-free processing aids have rarely been used [20].
- Perfluoropolyethers (PFPE) exist as liquids or greases and are used in electronic industry as lubricants [21].
- Cosmetics such as sun protection and skin and hair care products often contain PFAS to make them water-repellent. Besides PTFE fluoroalcohol (C₉–C₁₅)-phosphates play a significant role [22, 23].
- PFAS may be found in numerous building products such as floor coverings, cables, coated woods, solar panels and glasses [24].
- The oil and gas industry as well as the mining industry are broad fields of application. Numerous, diverse PFAS are used to reduce the viscosity of crude oil, in drilling fluids, among other applications [4]. For instance, a side-chain fluorinated aromatic compound was found in the vicinity of an oil-producing area in northern China [25].
- Short-chain and ultra-short-chain perfluorinated compounds such as tris(pentafluoroethyl)-trifluorophosphate (FAP) and bis(trifluoromethylsulfonyl)-imide (NTf₂) are increasingly used in ionic liquids, such as those found in lithium batteries [26, 27].
- Certain pesticides contain PFAS as co-formulants, e.g. as wetting agents, although PFOA is now being replaced by other substances. In addition, PFAS have been shown to be released from fluorinated HDPE containers into pesticides transported in these containers [28].
- Fluorochemicals are of growing importance as pesticides [29]. Approximately 45 pesticide active ingredients approved in the EU contain trifluoromethyl (-CF₃) groups (e.g. flufenacet or diflufenican), which after transformation in the environment contribute to the spread of trifluoroacetic acid (TFA) [30, 31].
- This also applies to certain biocidal products and pharmaceuticals, for example λ-cyhalothrin, fipronil and flocoumafen or flecainide and sitagliptin, respectively. Meanwhile, about 30% of all newly approved active pharmaceutical ingredients are organofluorine compounds [32]. Inoue et al. identified 342 fluorinated active pharmaceutical substances [33].

Two manufacturing processes for organofluorines dominate: electrochemical fluorination and oligomerization. Electrochemical fluorination, in particular, produces many unintentional by-products, the identity, occurrence and distribution of which are virtually unknown [10]. A complete acquisition of data regarding the amounts manufactured and used is not possible due to the lack of transparency. However, there are indications that in spite of the critical discussions concerning PFAS their production continues to increase. For example, the number of patent applications in the USA with “perfluor” in the patent text has increased from ca. 200 per month in 2000 to ca. 400 in 2012 [34].

The EU intends to regulate PFAS as a substance group [35]. To mitigate human and environmental exposure, PFAS are to be restricted in their applications. Treatment as a substance group is meant to prevent the substitution of an individual representative of the group with another, equally critical, but less well studied PFAS (“regrettable substitution”). Rather, the aim is to switch to fluorine-free alternatives and to completely end unnecessary applications, for example, in cosmetics. Another argument for the grouping approach is that it is practically impossible to study the individual toxicity of hundreds of relevant PFAS compounds aiming to develop safety thresholds in a timely manner.

For this purpose, the concept of “essential uses” is to be applied. The Montreal Protocol already recognized this approach and defined applications as essential that were necessary for health and the security and functioning of society. No technically and economically suitable alternatives should be available. Cousins et al. [36] tested a number of PFAS applications and divided them into three groups: (i) non-essential uses, e.g. ski waxes, (ii) substitutable uses, e.g. most uses of firefighting foams where fluorine-free substitutes with adequate performance exist, (iii) essential uses, e.g. medical devices, for which currently there are no adequate alternatives. The authors specified their proposal in a further publication and pointed out that this approach is suitable to significantly accelerate risk management of the applications of hazardous substances [37]. The concept of ‘functional substitutions’ as developed in the USA [38], which assesses function and necessary performance, can be usefully linked with the concept of essential uses [39]. At the same time, it should be noted that trade-offs in performance can be justified. For example, water and oil repellency need not be as effective for leisure wear as it is for functional clothing for fire departments or in the medical sector. Glüge et al. tested this concept on a number of examples. They determined that for consumer-related applications such as the impregnation of carpets, knowledge of alternatives is generally adequate to establish

the substitutability of the PFAS application. In contrast, industrial applications, e.g. in the semiconductor industry, often proved to be very complex and it was difficult to assess the substitutability of PFAS applications [40]. The concept of essential uses is currently also discussed in North America to be eventually implemented in chemicals management [41]. The EU Commission plans to include this concept in the upcoming revision of the REACH regulation [35]. However, Commission postponed the presentation of its proposal. Apparently, it is difficult to define the criteria for essential uses precisely.

Indeed, for many widespread applications fluorine-free alternatives are available, e.g., fluorine-free firefighting foams [42] and impregnating agents for water-repellent textiles [43]. Straková et al. could show that due to legal restrictions on PFAS in Denmark fluorine-free food contact materials became available [17]. The OECD published a report on PFAS alternatives in coatings, paints and varnishes [44], as well as alternatives to PFAS-containing food contact materials [45, 46]. The use of PFAS in chromium electroplating and synthetic pickling solutions are also not without alternatives (use of chromium III instead of chromium VI) [47]. In many areas, however, uncertainty prevails as to which alternatives are suitable. Websites such as [PFAS-Free Products—PFAS Central](#) can be helpful in finding appropriate PFAS-free alternatives. Controversial discussions on the dispensability of certain applications are to be expected. Regulation should therefore be an impetus for government and industry to initiate research programs to develop suitable, non-hazardous alternatives for the remaining PFAS applications and to fill existing data gaps.

Pathways of entry into the environment

The many diverse applications of PFAS lead to numerous and varied inputs into the environment. Wang et al. published a global inventory for emission of PFCA (C4–C14) and quantified a number of entry routes. The authors also included precursor substances that are transformed into PFCA in the environment. According to their calculations 2610 to 21,400 tons of PFCA have been released into the environment from 1951 to 2015 mostly with a continuously increasing tendency, especially in the Asian region [48, 49]. In part, PFAS are emitted directly into the environment, e.g. as fire-extinguishing foam or as ski wax; in others they reach the environment via sewage from electroplating operations, laundries, dry cleaners and cosmetics from private households. Von Abercron measured significantly higher AOF concentrations in discharges from industrial wastewater treatment plants than from municipal treatment plants [50]. In wastewater treatment plants polyfluorinated precursors are partially oxidized to PFCA, whereby concentrations in the effluent

may be higher than in the influent [51]. PFAS are to some extent bound by sewage sludge [52]. Not incinerating this material and using it for agricultural purposes leads to soil and groundwater contamination. Abrasion particles from polymeric PFAS as well as nano-sized fluorinated polymers are also found in sewage sludge, combined with microplastics from other polymers.

Many PFAS reach the environment as constituents of waste. For example, near Rastatt in Baden-Württemberg, Germany, large-scale soil and groundwater contamination is the result of application of PFAS-contaminated sludge from production of impregnated paper [53] (see “PFAS contaminated sites” section). In general, product streams are problematic when waste products are collected separately and subsequently recycled, e.g., of paper, food packaging materials and textiles. During recycling PFAS are transferred into and contaminate the secondary products. Consequently, products containing PFAS as a rule are not recyclable and thus contradict the goals of a ‘circular economy’ [54].

In Europe, in the past decades production wastes and municipal wastes were mostly disposed of in landfills. In other parts of the world disposal of (organic) waste in landfills is still common. It is calculated that landfills are nowadays the largest share of PFAS [55]. In particular, older landfills that are not state-of-the-art may lead to significant groundwater contamination. Propp et al. analyzed PFAS in leachate impacted groundwater near 20 historic landfills in Ontario (Canada) [56]. In several cases, the sum of 17 PFAS exceeded 1 µg/L.

But even modern landfills which largely prevent emissions to the environment do not provide safety for several decades or centuries. The lifetime of the liners at the basis of a landfill is generally shorter than the half-life of most PFAS, in particular the side-chain fluorinated polymers which can hydrolyze and are a continuous source of non-polymeric PFAS. An investigation of 22 leachate samples from municipal landfills in Germany showed that contamination with PFAS is significant dominated by short-chain PFBA and PFBS [57]. Leachate is usually collected and may be pretreated, e.g. by reverse osmosis, before it is discharged into the sewage system.

To date, there are few and conflicting data on the conditions under which PFAS are fully mineralized during incineration [58]. The high degree of stability of the C-F bond results in a problem for waste disposal. Presumably treatment of at least 1100 °C for more than 2 s is adequate to completely cleave the majority of PFAS [59–62, Appendix C]. There is evidence that organofluorines may largely be transformed into inorganic fluoride by best available techniques (BAT) incineration of domestic waste (minimum temperature 850 °C) [63]. On the other hand, mineralization of carbon tetrafluoride

(CF₄), thermal cleavage of which is especially difficult, requires an incineration temperature of more than 1400 °C [64]. Incineration of PFAS results in the formation of short-chain fragments and hydrofluoric acid (HF), which, together with other acidic components of the raw exhaust gas, are removed by means of basic substances. Any unburned PFAS and their derivatives are to be bound by adsorption (e.g. to activated charcoal, coke or lime) or wet scrubber and thus eliminated from the raw exhaust gas. However, there is still a lack of sufficient and valid experimental data on the effectiveness of the elimination of PFAS and their fragments from the raw exhaust gas [58, 65]. An estimate of the efficacy of possible methods to remove a range of more than 160 relevant PFAS is given in [65]. For anionic PFAS like PFOA and PFOS, an effective retention is assumed by incineration plants having a wet scrubbing cleanup step of the flue gases [65, 66]. PFAS have been detected in condensate, fly ash and slag of waste incinerators in the Netherlands; the highest levels in condensate were quantified for perfluorobutanoic acid (PFBA), perfluorohexanoic acid (PFHxA), perfluorononanoic acid (PFNA) and perfluorodecanoic acid (PFDA), especially [65–67]. For the numerous neutral PFAS of technical importance, in contrast, an effective retention from exhaust gas is probably unlikely [65]. Presumably, sufficiently high temperatures (as high as 1400 °C) are reached in cement kilns if fed with the main burner where alkaline conditions prevail for neutralization of hydrofluoric acid (HF), to destroy PFAS almost completely; however, validated studies on this are also lacking.

Also of importance regarding the distribution of PFAS in the environment is the atmospheric pathway. Fluorotelomer alcohols such as 6:2 FTOH (1*H*,1*H*,2*H*,2*H*-Perfluorooctanol) and 8:2 FTOH (1*H*,1*H*,2*H*,2*H*-Perfluoro-1-decanol) are so volatile that they can be detected in relevant concentrations in indoor air [68]. In 2013 Schlummer et al. measured the concentrations of fluorotelomer alcohols in the indoor air in German stores that sell outdoor and sports textiles or carpets. The concentrations were three orders of magnitude higher than in the outdoor air of urban areas [69]. These concentrations, e.g., from impregnated carpets lead to such high human exposure that the atmospheric pathway, together with exposure from contaminated foodstuffs must be viewed as an important source for uptake of PFAS by humans. In the vicinity surrounding of production facilities for fluoropolymers and other PFAS in Gendorf (Bavaria) as well as in Dordrecht and Helmond (Netherlands), substantial and extensive pollution of the air, and, as a result of atmospheric deposition, of the soil were determined [70–74] (see “PFAS contaminated sites” section). Another input into the atmosphere

of possible importance is shown by Vierke et al. [75]: the aerosol above aeration tanks of a sewage treatment plant showed particle- and gas-phase concentrations of anionic and especially neutral FTOH up to 11 ng/m³ (average sum of FTOH). When calculating a mass balance for perfluorocarboxylic acids in Lake Vättern (Sweden), Björnsdotter et al. [76] determined that the entries for PFOA through atmospheric deposition were of a similar order of magnitude as those from rivers and sewage discharge. This explains the extensive transport of PFAS to remote areas where air and seawater measurements reveal the problematic characteristics of this group of substances globally [77–80]. In accordance with these observations, Cousins et al. showed that the rainwater concentrations of PFOA, PFOS and the sum of the four PFAS evaluated by the European Food Safety Authority (EFSA) (see “[Toxicological evaluation](#)” section) often exceed limit and guidance values for drinking water [81]. Even in Antarctica and in the Tibetan highlands the concentrations were just below those levels. In depth profiles, Joerss et al. [82] were able to demonstrate that PFAS accumulate in Arctic Sea water. Propagation over the water is linked to the atmospheric pathway because a transition occurs from the aerosol droplets above the water surface in which PFAS are highly enriched into the atmosphere, resulting from spray drift [83, 84].

Occurrence in the environment

The numerous and diverse emissions and the extensive distribution of entry pathways for PFAS (see “[Pathways of entry into the environment](#)” section) lead to a ubiquitous contamination of the environment. For example, Lesmeister et al. [85] described the pollution situation of the Rhine River between 2009 and 2020 with predominantly perfluoroalkyl carboxylic and sulfonic acids, with the highest values measured for C4- and C8-acids. Li et al. emphasize the global distribution of short-chain PFAS (C4–C7), of which PFBA and PFBS amount to more than 50% [86]. In a recent review, Kurwadkar et al. presented a comprehensive picture of the global distribution of PFAS in water and sewage [87]. In Chinese and German rivers that are polluted with industrial PFAS, Joerss et al. detected 86 different compounds, among them 35 carboxyl- and 21 sulfonyl derivatives, as well as 22 fluorinated mono-, di- and polyether carboxylic acids [88].

The current knowledge on background contamination of soils is incomplete, partly due to the different analytical methods used. Investigation campaigns in North Rhine Westphalia, Germany, and in Baden-Württemberg, Germany [89, 90], as well as a recent study from Vorarlberg in Austria [91] show a diffuse contamination, presumably resulting from precipitation: Humer and Scheffknecht were still able to measure 0.05 to 0.1 µg/L

PFAS (sum of perfluorinated carboxylic acids) in soil eluates, even in “uncontaminated” samples. Entry via the atmospheric pathway has likely been underestimated. Washington et al. [92] studied the hydrolysis of PFAS side-chain polymers (polyacrylate with fluorotelomer alcohols as side chains) in soil and water; half-lives were in the order of 10 to 100 years. This persistence contributes to background levels of PFAS in marine and terrestrial ecosystems due to high production volumes. The authors consider 10–60 ng/kg as diffuse background contamination of soil [93].

Soil contamination often leads to groundwater contamination, in particular in contamination sites (see “[PFAS contaminated sites](#)” section). Long-chain PFAS are more tightly bound in soils than short-chain compounds [94]. For this reason, the latter pass into the groundwater more rapidly. When contaminated surface or groundwater is used as drinking water, it will also contain PFAS if, as a result of the properties of this special group of substances, the barriers in drinking water treatment are overcome. These barriers are not even present if contaminated ground- or surface water is used for irrigation in home gardens or for fishponds without treatment so that PFAS can accumulate in soil, crops or fish and thus find their way into human food [95–100].

Meanwhile, PFAS levels in soils and waters, in organisms, in food, and in humans are being determined in monitoring programs [101]. In this context, the concentrations of PFOA and PFOS (so-called legacy PFAS) have decreased over the past 10 to 20 years in environmental media like North and Baltic Sea, rivers [85, 102, 103], groundwater [104] and soil [73, 101], or in biota (fish, crustaceans, poplar and beech leaves, earth worms, roe deer, herring gulls) [101, 103, 105, 106] and especially in human blood [103, 107] (as well as in human breast milk [108], see “[Human exposure from food](#)” section), since these two substances are already strictly regulated under chemical regulations. In contrast, concentrations of other PFAS, which have been less studied and are used as substitutes, are increasing [70, 72–74, 102, 104, 105, 109, 110]. For example, data from the German Environmental Specimen Bank (UPB) [111] show an increase in contamination of fish with long-chain PFAS in the past 25 years (Fig. 1) [112].

Some of the PFAS that have become widespread in the meantime such as per- and polyfluorinated oxocarboxylic acids are not yet recorded in the monitoring programs. By means of the TOP assay (Total Oxidizable Precursor—see “[Sum parameters for PFAS](#)” section), which also recognizes numerous unknown precursors, it can be shown that the concentrations of the PFAS sum in sediments and in bream are often many times higher than the values of individual determinations [113, 114]. The transfer of

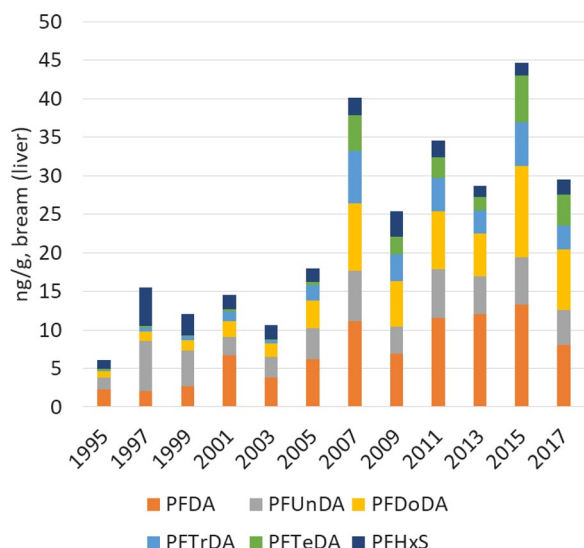


Fig. 1 Increase in concentration of longer-chain perfluorocarboxylic acids in the liver of bream at Bimmen (Lower Rhine) © Environmental Specimen Bank [112]

contaminants to humans via food can be seen, for example, in the analysis of eggs from chickens that were fed with feed from a contaminated site [115, 116].

Contamination of fish is of relevance in respect to human uptake, too. Values between 1.8 and 30 ng/g fresh matter (fm) of the sum of PFOS, PFOA, PFHxS (perfluorohexane sulfonic acid) and PFNA were found in fillets of fish (perch, whitefish and tench) from Lake Constance in Central Europe [117]. In seven fish species from the Belgian North Sea, Byns et al. [106] found mean PFOS concentrations in muscle tissue up to 3.0 ng/g fm. Teunen et al. [118] measured median PFAS concentrations of 21 to 22 ng/g fm in perch and eel as well as in mussels from 44 locations all over Flanders, Belgium. The PFAS profile was dominated by PFOS in fish and PFOA in mussels. Rüdél et al. [119] investigated mean PFOS concentrations of 3.2 and 8.0 ng/g fm in roach and perch, respectively, from German inland and coastal waters. In Bremen and Lower Saxony, Germany, PFOS concentrations up to 1000 or 2000 ng/g fm, respectively, were found in fillets of individual river fish caught at two locations near a contaminated site [100]. Bioaccumulation and biomagnification of e.g. PFOS can be clearly seen: if bream have a load of 1 ng/g fm in muscle tissue the concentration in the liver will be on average 100 ng/g fm. As with warm-blooded animals [120], the liver is apparently the target organ for accumulation of PFAS in fish [121]. Other animals that feed on fish such as white-tailed eagle, harbor seal, and otter show loads up to 6200 ng/g fm in the liver according to individual studies conducted by the University of Athens (see Table 1) [122]. Robuck

Table 1 PFOS-concentration in biota samples from the German Environmental Specimen Bank [122]

Sample type	PFOS-concentration (ng/g fm)
Bream (Filet)	1
Bream (Liver)	100
Herring gull (eggs)	35
White-tailed eagle (Liver)	625
Harbor Seal (Liver)	693
Otter (Liver)	6182

et al. analyzed PFAS in the livers of seabirds feeding on fish at the U.S. Atlantic coast, where PFOS dominated, but PFOA and PFOS substitutes (ether carboxylic- and -sulfonic acids) were also found at concentrations up to about 100 ng/g [123].

PFAS can also be detected in animals living in forests [124, 125]. Studies by the Hessian State Laboratory showed that wild boars are more strongly contaminated than roe deer. Values as high as 18.6 ng/g fm for the four PFAS in muscle tissue, with a peak value of 1470 ng/g fm in liver were found in wild boars [124].

Forever chemicals

The outstanding property of all PFAS is their extraordinary persistence: they are hardly degradable under natural conditions. In the case of partially fluorinated hydrocarbons slow, microbial transformation processes are known to occur with degradation of the non-fluorinated part of the molecule, however, the remaining perfluorinated residue will persist for a very long time. Consequently, partially fluorinated precursors that are slowly converted into perfluorinated molecules in the environment [3] cannot be considered suitable alternatives. There is virtually no way to cleave multiple carbon-fluorine bonds on a carbon atom by a biological or abiotic process under environmental conditions. For this reason, PFAS are referred to as “forever chemicals”. Regardless of their ecological or toxicological properties, extremely persistent substances pose a threat to the environment simply because they are irrecoverable and lead to environmental pollution lasting decades to centuries and eventually longer [126–130].

In addition, a number of PFAS such as the long-chain carboxylic and sulfonic acids PFOA and PFOS are highly bioaccumulative (see “Bioconcentration and biomagnification in the food chains” section) and according to the EU’s REACH regulation (REACH: Registration, Evaluation and Authorization of Chemicals) are classified as PBT substances (PBT: persistent, bioaccumulative, toxic).

Furthermore, many PFAS are mobile when dissolved in water. They penetrate the unsaturated soil zone and can then be carried for great distances via groundwater. The shorter the carbon chain the higher the mobility. When 364 groundwater measuring points in Hesse, Germany, were sampled for 21 different PFAS, contamination was found at 90% of the monitoring wells [113]. Zhao et al. evaluated studies on groundwater investigations dating from 1999 to 2021 and found that short-chain PFAS and other alternatives to PFOA and PFOS are increasingly being detected [131]. A review from Johnson et al. [132] lists C3-, C4- and C5 perfluoroalkyl carboxylic acids (PFCA) with average groundwater concentrations of 2.2, 1.4 and 3.7 µg/L and C3–C5 perfluoroalkyl sulfonic acids with 22, 4.9 and 25 µg/L, respectively, for the same period; the review comprises about 21,000 data points for sites distributed in 20 countries worldwide. Thus, PFAS also pose a threat to many drinking water supplies. The German Federal Environment Agency (UBA), therefore, classifies a number of PFAS as PMT substances (PMT: persistent, mobile and toxic) [133]. Due to their mobility (besides persistence and toxicity), perfluorobutane sulfonic acid (PFBS) and hexafluoropropylene oxide dimer acid (HFPO-DA) have been classified by the European Chemical Agency (ECHA) as SVHC (SVHC: substances of very high concern) [134].

Bioconcentration and biomagnification in the food chains

PFAS can accumulate in aquatic organisms and along food chains, especially long-chain molecules such as PFOS, PFNA and EtFOSA (*N*-ethyl perfluorooctane sulfonamide) [135]. They bioaccumulate by binding to proteins in the blood, liver and kidney [136]. Binding on phospholipids is also discussed [137]. Excretion only occurs very slowly. In muscle tissues of nine fish species from rivers of south China, Pan et al. [138] only detected long-chain perfluorinated alkylcarboxylic- and -sulfonic acids from C8 upwards: the bioconcentration factors (BCF) fish(muscle)/water of the carboxylic acids were found between about 60 (PFNA) und 3200 (PFUnDA), that of PFOS between 500 and 2500; in the liver the measured BCF were about ten times higher. These values are lower than those of fish from other waters (PFOS: 5500–25,000). Tal and Vogs determined the BCF fish(total)/water for several species as 3–100 (PFOA), 8–250 (PFHxS) and 82–5400 (PFOS), the highest accumulation being measured in the blood plasma of zebrafish (PFOA 930, PFHxS 870 und PFOS 13,200) [139]. Studies from Belgium showed that both mechanisms play a significant role in bioaccumulation of long-chain PFAS: bioconcentration via exchange with the surrounding medium and biomagnification via consumption of food [106, 118].

Biomagnification of long-chain PFAS in food chains is also extremely significant, so that concentrations in predators such as seals, sea birds and otters are often orders of magnitude higher than in their diet (see Table 1) [122]. Androulakis et al. demonstrated enrichment in Northern European top predators in studies on 56 PFAS [140].

In contrast to bioconcentration in aquatic animals and the biomagnification in the related food chain, enrichment in plants favors short-chain over long-chain PFAS. Uptake apparently occurs through contaminated soil or irrigation water into the vegetative parts of the plants [94–99, 141–145]. A study of the vicinity of a PFAS production site in China reported that bioaccumulation factors (BAF) soil → plant (Σ PFAS) were seen to be as high as 48 for the green plant parts above-ground [141, 146]. Lesmeister et al. evaluated the bioaccumulation factors for numerous perfluoroalkyl carboxylic and sulfonic acids. The authors confirmed the chain-length dependency in vegetative plant parts and urge investigation of polyfluorinated precursors, oxo carboxylic acids and ultra-short-chain PFAS [147].

If crop plants are involved, this enrichment can contribute substantially to contamination of human nutrition. The use of PFAS-contaminated groundwater to supply fishponds can also contribute to human exposure (see “[Human exposure from food](#)” section). PFAS have also been detected in honey samples, most commonly PFHpA (perfluoroheptanoic acid, <17–440 ng/kg, *n* = 16 of 26 samples), occasionally PFOA, PFNA, PFDA and PFHxS PFOS in trace amounts [148] (cf. extreme enrichment in honeybees, see the following section).

Ecotoxicological effects

Aquatic toxicity has only been well investigated for individual PFAS such as PFOS. There is considerable variation with respect to trophic levels, individual species, and the various PFAS. According to current knowledge the manifold toxic effects of perfluorinated acids such as PFOA are triggered by activation of nuclear receptors, oxidative stress or direct interaction with membranes [149]. Changes in the tissue level follow; thyroid disorders, fatty liver or cell death result in negative effects on fertility rate, hatching rate, embryonic development or motor functions. At PFOS concentrations of 0.5 µg/L over a period of 28 days rainbow trout show changes in hormone levels and in clinical-chemical parameters [150]. After 120 days of exposure to PFDA or PFTrDA (perfluorotridecanoic acid) (10 µg/L) both male and female zebrafish showed significant changes in steroid levels [151]. Chronic no observed effect concentrations (NOEC) for mortality of larvae and juveniles are specified as 10 µg/L PFDA or 100 µg/L PFTrDA and for adult fish as 1000 µg/L

PFDA or 10 µg/L PFTrDA [151]. After exposure to only 10 µg/L fluorotelomer alcohol 8:2 FTOH for a period of 4 weeks serious disruptions in sex hormones were observed, that at 30 µg/L resulted in significant reduction in egg diameter and sperm density, leading to a 30% decrease in hatching rate [152]. After 6 days exposure to 15 µg/L PFOS turbot embryos and larvae showed skeletal deformation of the larvae, at 30 µg/L alterations to the yolk sac and pericardial edema [153]. Water fleas and other invertebrates are also affected by chronic exposure to PFOS and PFBS as well as the telomer acid 10:2-FTCA (2*H*,2*H*-perfluorododecanoic acid) at concentrations of just a few µg/L and below [154–157]. Development of larval Mediterranean mussels is also impaired by PFOA and PFOS when acutely (48 h) exposed at levels as low as 0.1 µg/L [158].

Li et al. [98] reported on the effects of 13 different PFAS (primarily perfluoroalkanoic acids and telomer carboxylic acids) on green algae (mostly *Chlorella* sp. and *Pseudokirchneriella subcapitata*). The EC₅₀ values range from about 0.3 mg/L PFUnDA (perfluoroundecanoic acid) to ca. 260 mg/L PFBA and 1100 mg/L 5*H* 4:1 FTOH (1*H*,1*H*,5*H*-perfluoro-1-pentanol) [98, 159].

At concentrations of 2–10 µg/L PFBS, PFOA and PFOS also have toxic effects on insect larvae such as chironomids or dragonflies [154, 160–163]. The reproductive capacity and the behavior of pollinator insects such as honey bees and bumble bees are also affected by PFOS: Honey bee broods are almost completely inhibited after 4 weeks exposure to 20 µg/L in sugar syrup [164]. Development of ground bumble bee drones is completely inhibited after 11 weeks exposure to 1000 µg/L in sugar water; an extreme accumulation to more than 2 µg/g bw was observed in bumble bees at 100 µg/L (BAF=28) [165].

Embryonal and larval development of leopard frogs is slightly up to significantly impaired after 40 days exposure to PFHxS, PFOS, PFOA or H4PFOS (tetrahydroperfluorooctane sulfonic acid) at 10 µg/L, most severely by PFHxS [166]. A significant reduction in development of American bullfrog tadpoles was observed at 144 µg/L [167]. After 2 months exposure to 100 µg/L PFOS after metamorphosis African clawed frogs showed liver cell degeneration [168]; at only 0.1 µg/L PFOS an increase in the expression of TRBa mRNA in the brain and tail tissue occurred, a sensitive indicator of thyroid function disorder [169].

Similar to Giesy et al. [170] and Ulhaq et al. [171], Duchêne verified, on the basis of numerous publications on 18 PFAS, a tendency of increasing toxicity to aquatic organisms with the chain length [172].

Growth of terrestrial vertebrates such as reptiles (Bahama-Anolis) is also reduced in the presence of low

PFOS concentrations (3 mg/kg bw per day); PFHxS caused reduced viability [154].

Earthworms, unlike organisms of other trophic levels, have effective detoxification mechanisms; therefore, in the chronic test (35 d) effects are observed only at PFAS concentrations (PFOS, PFOA, N-EtFOSE (N-ethyl perfluorooctane sulfonamidoethanol) above 50–500 mg per kg soil [173].

Crop plants may gain in biomass or undergo a loss of yield depending upon species, PFAS compound and length of exposure: growth of wheat and oilseed rape is promoted by the presence of 0.3 mg/kg PFOA and PFOS in the soil for 70 days [174], whereas photosynthesis in cucumbers was reduced by 0.2 mg/kg PFOA [175]. Concentrations of 6 mg/kg PFOA or greater disrupted root growth in sorghum, whereas 50 mg/kg are required for the same effect in Chinese cabbage. Further effects of PFAS on terrestrial plants occur at substantially higher concentration ranges of 40–400 mg/kg [98].

In summary, numerous publications report on diverse aquatotoxic effects of PFAS in the lower µg/L range, in some cases even lower. PFAS of different structure and organisms of varying trophic levels and habitats have been studied. For the majority of the several thousand per- and polyfluorinated alkyl substances that are used technically and are found in the environment, however, data is either completely missing or is insufficient.

Biological effects of PFAS on experimental animals and on humans

Perfluorinated alkyl carboxylic acids and sulfonic acids with chain lengths C6–C14 have been most thoroughly studied. For other PFAS, e.g. short-chain members, telomer alcohols and acids or fluorinated oxo carboxylic acids only a few research results are presently available. A number of reviews report the numerous and varying biological effects of PFAS on experimental animals as well as on human beings [176–184]. The mechanisms that may be responsible for the pro-carcinogenic effects of PFAS are described by Boyd et al. in a review [185].

PFAS are now not only ubiquitous in the environment, they are found in the blood of almost all humans living in developed countries as well as in the organs of human fetuses (liver, lung, heart, CNS, fatty tissue) (see “[Human exposure from food](#)” section) [178, 179, 186]. Long-chain PFAS are slowly excreted in urine and feces, in females via breast milk and menstrual fluid, additionally [187].

Results from experimental animal studies

Animal toxicological studies on the livers of rodents have shown that PFOS and PFOA are apparently not genotoxic, but instead act as liver tumor promoters. Exposure to PFOS and PFOA is reported to be accompanied

by an increase in liver mass (hyperplasia and hypertrophy of hepatocytes) [181, 182, 184]. Evidently, activation of the peroxisome proliferator-activated receptor alpha (PPARα) may take part in the biological effects of PFAS; however, this will require final clarification [178].

Exposure of adult rats to PFDoDA (perfluorododecanoic acid) leads to cognitive deficits [188], and findings in mice show that early exposure (neonatal, postnatal) to PFOS, PFOA and PFHxS affects the cholinergic system and brain development [189].

Exposure especially of mice to various PFAS leads to a reduction in the T-cell dependent antibody response [183].

Results from studies on humans

Toxicological results on humans are summarized in Table 2. Particularly relevant data are:

In particular, effects of PFAS on the immune system must be emphasized [190]. Epidemiological studies on children have shown that the formation of vaccine antibodies is significantly decreased dependent upon the levels of PFAS in serum [191, 192]. The results of these studies have led, among others, to EFSA’s toxicological evaluation of PFAS (PFOA, PFOS, PFHxS and PFNA) [183] (see “Toxicological evaluation” section).

A dose-dependent reduction in birth weight of children was attributed to exposure to PFOA [193, 194] and PFOS [194–196] in the USA, Japan and the Faroe Islands. Furthermore, findings from Kashino et al. [197] showed that intrauterine exposure to long-chain PFAS is apparently negatively correlated with birth size of newborns.

An important target organ for PFAS is the liver. The complexity and importance of metabolic changes in the liver has been described in detail by Jin et al. [198].

Table 2 Toxicological results on humans

Affected organ/function	Consequences
Toxicokinetics	Uptake via water, soil, plants, foodstuffs [99, 183]
Uptake	Excretion via cord blood, breast milk and menstrual fluid [187]
Excretion	Higher PFAS concentrations in children than in adults [380–384]
1. Liver: hepatotoxic	NAFLD, liver fibrosis, markers change [198, 200, 385–388]
2. Kidney: nephrotoxic	Reduced excretion of toxins [204, 389, 390]; increased incidence of CKD [203, 391]; ferroptosis [392]
3. Lungs/bronchi	Promotion of asthma in youth [393]
4. Endocrinic system	Thyroid [217, 394–396]; steroid(cortisone) [397–399] and sex hormones [398, 400, 401]
5. Metabolism	(a) Glucose [402]; type 2-diabetes [403–406]; gestational diabetes [213] (b) Fat [387, 407–409] (c) Bile acid [387] (d) Total and non-HDL cholesterol [410–412]
6. Fertility: toxicity to reproduction, embryotoxic, fetotoxic	(a) Delayed occurrence of desired pregnancy/childlessness [413, 414] (b) Miscarriage [415] (c) Lifelong effects on organ health and development of disease [416–422] (c) Pregnancy/mother: hypertension [423], preeclampsia [423–425] (d) Pregnancy/child: miscarriage [139, 426, 427], reduced birth weight [195, 196, 428], reduced fetal growth [139, 193, 194, 197, 427, 429–433], reduced fetal head growth [434–436], tendency to premature birth [437], increased mortality [438], intrauterine disorder of the thyroid hormones [194, 213, 439]
7. Brain, Neurotoxicity	ADHD [419, 440–452]; Alzheimer dementia [453–456], ASD [446, 457–459], dopamin-metabolism [440, 447, 460], brain structure/-volume [461], hearing loss [462], reduced IQ [407, 453, 459, 463, 464], short-term memory [465], Parkinson [454, 466], Developmental delay [448, 467], linguistic development [217], eye-hand coordination [399, 467], behavior [468, 469], cerebral palsy [470], stroke [471], neurobehavioral function and cognition [472–475], neuronal network function [476]
8. Bones	Osteoporosis [410, 448, 477–484]
9. Immune system	(a) Reduced formation of vaccine antibodies [182, 183, 191, 192, 485, 486] (b) Autoimmune diseases: Colitis ulcerosa [487]
10. Heart, Circulatory system	Cardiovascular issues [488–492] Hypertension [410, 488, 493, 494]
11. Genetics: epigenetic	PFAS-effects can be transferred to following generations [455, 495–499]
12. Cancer	(a) Kidney cancer [209, 500–506], testicular cancer [209, 500–502, 505] (b) Secondary effects (fatty liver → liver cirrhosis→): liver cancer [201, 507] (c) Breast cancer (postmenopause) [508]

Studies of 7- to 19-year-old children and adolescents indicate that exposure to PFAS is associated with the occurrence of non-alcoholic fatty liver disease (NAFLD) [198]. In the USA, 30 million inhabitants are affected by NAFLD, 10% of them already in childhood, especially severely overweight children (38%) [199]. Even prenatal exposure to PFAS leads to increased liver disease in children in a dose-dependent manner [200]. In general, an association with the occurrence of liver cancer is seen [201]. Moreover, the liver plays a role in the enterohepatic circulation of PFAS. Reabsorption from bile into blood and liver reduce their elimination and enhance their accumulation [202].

The incidence of initially asymptomatic “chronic kidney disease” (CKD) is on the rise worldwide and affects approximately 10% of adults in the USA and between 1 and 17% of the population of Europe, depending on region [203]. Since PFAS are not effectively removed from the body by the kidney as excretory organ concentrations in this organ are comparatively high. This is exacerbated by the peculiarities of kidney function (reabsorption) because the substances are repeatedly transported through the renal tubules. In this respect, damage to the kidneys by the surface-active PFAS is evident and of great importance because of the number of individuals affected—practically all people. Even more astonishing is the fact that to date there exists no prospective and/or longitudinal study on the effect of PFAS on the kidney’s cleansing function. However, many case–control studies indicate an impairment of the kidney’s cleansing function, since with increasing PFAS levels in the blood, the estimated glomerular filtration rate (eGFR)—a measure of kidney function—decreases. For example, Kataria 2015 found a decrease in eGFR of approximately 7 and 9 mL/min per 1.73 m² by PFOA and PFOS, respectively, in children when comparing the lowest to the highest quartiles [204]. Wen et al. report that some PFAS promote autophagy and apoptosis of kidney cells [205]. The authors call for a more accurate assessment of the long-term accumulation risk in humans.

Furthermore, Fenton sees PFAS, with high probability, as the trigger for kidney cancer (as well as testicular cancer) [178]. In 2019, IARC (International Agency for Research on Cancer) rated PFOA as having limited evidence of causing kidney and testicular cancer [206]. Shearer et al. [207] and Steenland et al. [208] confirm the evidence for kidney cancer caused by PFOA from epidemiological studies.

In the opinion of the Agency for Toxic Substances and Disease Registry at Center for Disease Control (ATSDR) additional indications of other types of cancer exist [209], for example for PFOA, PFOS, PFHxS, PFDA, and PFUnDA for the initiation of prostate cancer in cases in

which a first-degree family member has prostate cancer, and for an increased risk of breast cancer with PFOSA (perfluorooctanesulfonamide) [210–212].

Effects on the hormone system of pregnant women have been observed at comparatively low PFAS concentrations; in particular, long-chain PFAS affect levels of thyroid, but also of sex hormones, with long-term consequences for organ development (genitals, liver, kidney, brain) in the child and for metabolic disorders in the mother such as gestational diabetes [213, 214]. Based on current knowledge PFAS affects the comprehensive effective homeostasis of the thyroid hormones [178, 179, 194]. PFAS like PFOS and PFOA are, therefore, considered to be endocrine disruptors [215, 216]. The authors of a recent paper suggest that prenatal exposure to PFAS in combination with other endocrine disruptors such as bisphenol A and phthalates can impair linguistic development of children in the first year of life [217].

For human studies, the EFSA has selected four endpoints as potentially critical effects of PFOS and/or PFOA [182]:

- Increase in low density lipoprotein (LDL) level and total cholesterol in serum (risk factor for cardiovascular disease),
- Increase in the level of alanine aminotransferase (ALT) as a marker for the effects on liver cells,
- Reduced birth weight and
- Influences on the immune system in terms of reduced formation of vaccine antibodies.

The most relevant effects of PFAS on humans are illustrated in Fig. 2.

Toxicological evaluation

Until 2020 the EFSA only toxicologically evaluated PFOA, PFOS and their salts; a first opinion was published in 2008 [184]. Decisive for PFOS was a study on the subchronic toxicity to *Cynomolgus* monkeys in which a NOAEL (no observed adverse effect level) of 30 µg/kg bw per day was derived. At the next-higher dose level of 150 µg/kg bw per day the animals showed changes in lipids and thyroid hormones. Assuming an overall uncertainty factor of 200 as a basis resulted in a TDI (tolerable daily intake) of 0.15 µg/kg bw per day [184]. This is equivalent to a TWI (tolerable weekly intake) of 1.05 µg/kg bw per week. The EFSA estimates the exposure of PFOS through alimentary uptake in humans to be about 0.06 µg/kg bw per day, but for the group of most highly exposed individuals “may slightly exceed the TDI”. On the basis of increase in liver weight in male rats a BMDL₁₀ (benchmark dose lower limit for a 10% response) of 300 µg/kg bw per day was established for PFOA.

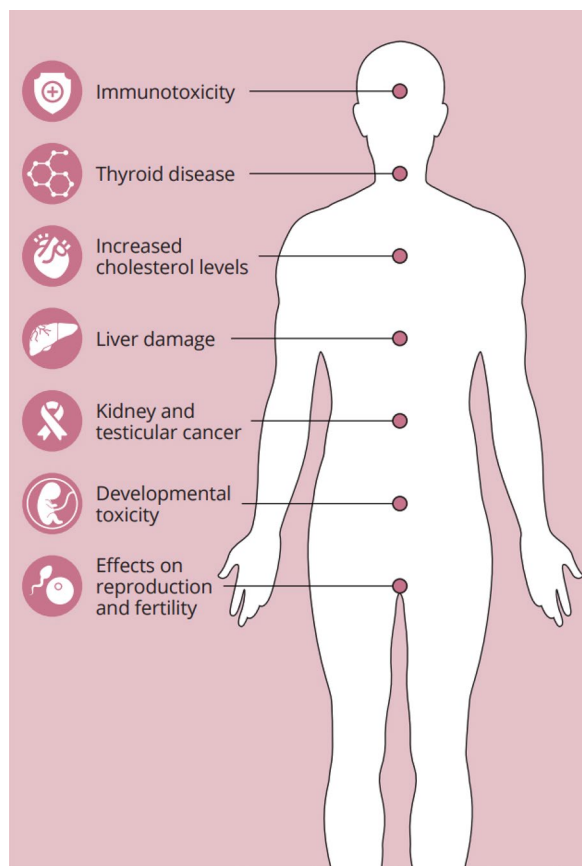


Fig. 2 Illustration of reported effects of PFAS on humans © HBM4EU <https://www.hbm4eu.eu/> [218]

Applying an overall uncertainty factor of 200 results in a TDI of 1.5 $\mu\text{g}/\text{kg}$ bw per day [184], corresponding to a TWI of 10.5 $\mu\text{g}/\text{kg}$ bw per week. The EFSA estimated the dietary exposure to PFOA to be 0.002 $\mu\text{g}/\text{kg}$ bw per day for average consumption and 0.006 $\mu\text{g}/\text{kg}$ bw per day for high consumers. Further information on the exhaustion of TDI values at that time can be found in [184].

In 2018 the EFSA published new insights into the risk assessment of PFOS and PFOA based on epidemiological studies (human data). Regarding alimentary exposure of PFOS and PFOA, increase in cholesterol levels in adults was identified, along with others, as a “critical effect.” Using benchmark dose (BMD) modeling [219], EFSA derived a TWI for PFOS of 13 ng/kg bw per week and for PFOA of 6 ng/kg bw per week. The EFSA closes its “Scientific Opinion” with the sentence “For both compounds, exposure of a considerable proportion of the population exceeds the proposed TWIs” [182].

Meanwhile, several thousand PFAS are known (see “Background”). This raises the question of the toxicological evaluation of PFAS mixtures in regard to human PFAS exposure. Until now mainly individual chemical

substances have been evaluated toxicologically, but a collective evaluation of a substance group only exists for the polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/PCDF) and dioxin-like polychlorinated biphenyls (dl-PCB), which, as a result of their structural similarity, share binding of the cellular Ah receptor. Because of this commonality, toxicity equivalent factors (TEF) can be derived and used to calculate toxicity equivalents [220]. This approach is rarely followed since common biological features like these usually do not exist. Thus, for the toxicological evaluation of four PFAS, EFSA has used a comparatively new approach [221]: first, human exposure is estimated, followed by the estimation of the toxicity of the respective mixture or its individual components. Subsequently, the combined exposure is compared to the combined toxicity.

This is the manner in which EFSA evaluated the compounds PFOA, PFOS, PFHxS and PFNA [183]. These PFAS contribute most to human exposure via the dietary intake of fish, meat and meat products, fruits and products thereof, as well as eggs and egg products. They are accordingly found at the highest levels in serum. These four PFAS show roughly similar toxicokinetic properties, accumulation behavior and comparatively long half-lives. According to EFSA they in general exhibit the same effects in the organism [183], allowing a common toxicological evaluation [221]. Based on the available data from animal studies and from humans EFSA’s CONTAM PANEL “Contaminants in the Food Chain” identified the immune system [191, 192] as the most important target of these PFAS. In this respect the panel assumes that the four PFAS mentioned have comparable potentials in regard to their effects on the immune system. They subsequently compared the combined exposure to PFOA, PFOS, PFHxS and PFNA with their combined toxicity: this was based on a German study [192] of breastfed infants showing that the sum of the levels of the four PFAS in the serum of these 1-year-old children (internal exposure) were inversely related to the titers of antibodies to *Haemophilus influenzae* type b (Hib), diphtheria, and tetanus. The lowest BMDL₁₀ of 17.5 ng/mL for was derived for PFOA, PFOS, PFHxS and PFNA with respect to titers against diphtheria. Using “PBPK modeling” (physiologically based pharmacokinetic modeling) [222] and assuming a lactation period of 12 months, this BMDL₁₀ corresponds to a daily intake by the mother of 0.63 ng/kg bw or a weekly intake of 4.4 ng/kg bw, respectively, for the sum of the four PFAS. The EFSA correspondingly set the TWI at 4.4 ng/kg bw per week [183]. This TWI covers the other critical endpoints set by the EFSA, such as the increase in serum cholesterol, reduced birth weight and the comparatively high serum level of ALT. The EFSA-derived TWI of 4.4 ng/kg bw for the sum

of PFOA, PFOS, PFNA and PFHxS should be considered as the current benchmark for limit and guideline values with regard to the assessment of PFAS contamination with potential human exposure. However, the present evaluation leaves open the consideration of other PFAS present in serum, for which no feasible approach is currently known. If future toxicological evaluations show different decisions, e.g., of the US EPA or the World Health Organization (WHO) [223] these should be considered.

Toxicological evaluations of xenobiotics and the ADI (acceptable daily intake) or TWI values derived from them are subject to constant change, as seen in Fig. 3 or in the literature [220]. This is primarily due to new findings on the substances to be assessed. The dramatic reduction of TWI values for PFAS [183], however, shows that at least in this case the usual system of minimizing the uncertainty caused by incomplete or inadequate data through the use of uncertainty factors apparently was not adequate.

The work of Caporale et al. [217] raised the attention to endocrine effects of PFAS. Consideration should be given to including this category of effects of PFAS in future evaluations.

The approach of Bil et al. should also be further examined and developed; these authors determined the relative potencies of 16 PFAS for liver toxicity and suggested using “relative potency factors” (RPF) to determine the effect of PFAS mixtures [224]. The EU SCHEER Scientific Committee agreed to the use of the RPF for the derivation of Environmental Quality Standards (EQS) and recommended to relate it to the more sensitive endpoint immunotoxicity [225]. A corresponding approach was published by Amstutz et al. [226]. Behnisch et al. [227] presented another RPF approach is, which is based on a bioassay targeted on thyroid hormone disruption (see “Biological effect test for PFAS” section).

Evaluation of the other PFAS that occur in serum is also urgently needed; particular attention should be given to the short-chain PFAS, which accumulate particularly in plants and are detected in increasing concentrations in the environment and in food (see “Bioconcentration and biomagnification in the food chains” section). More attention also needs to be paid to substances that are being increasingly used, such as fluorinated-chlorinated PFAS and oxo acids like HFPO-DA, C6O4 and ADONA. For HFPO-DA (GenX), US EPA determined a chronic reference dose of 3 ng per kg bw and day (PFBS reference dose and draft PFOA and PFOS values are 300, 0.0015 and 0.0079 ng per kg bw and day, for comparison [228, 229]).

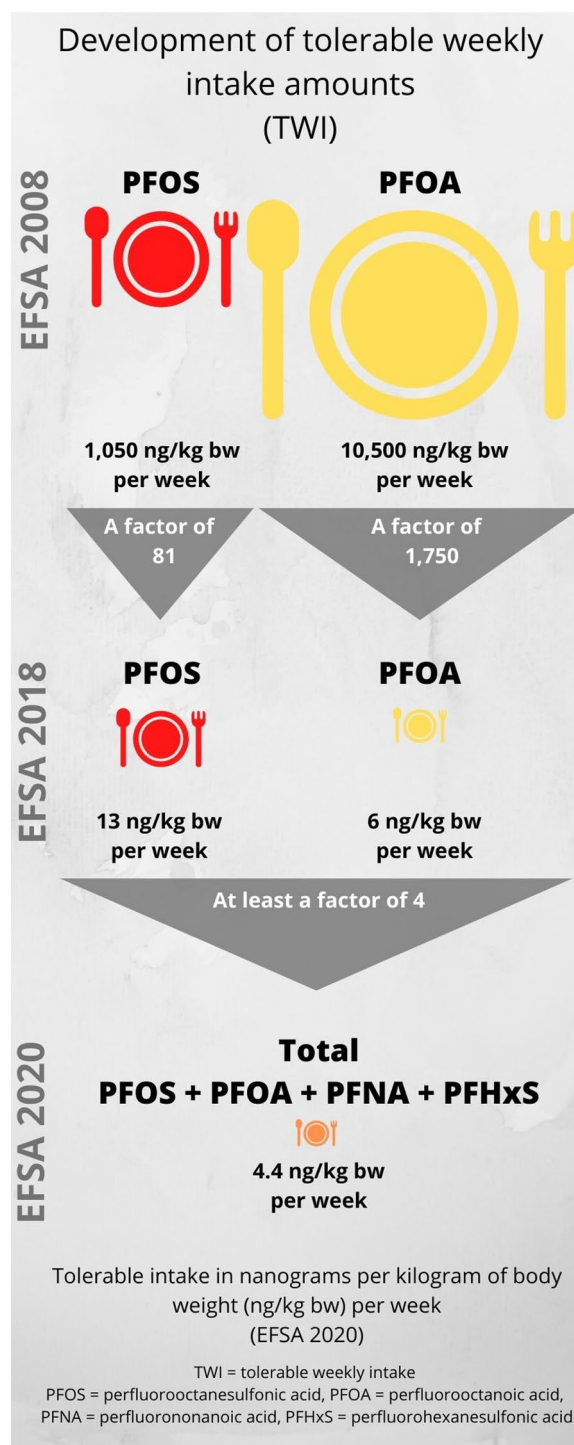


Fig. 3 Development of tolerable weekly intake amounts (TWI) from 2008 to 2020 © Own representation based on Kowalczyk (BfR); with increasing knowledge of the biological properties and the toxicity of PFAS the values for the tolerable weekly intake (TWI) were reduced [182–184]

Human exposure from food

Human exposure to PFAS can be detected by human biomonitoring (HBM) studies determining levels in blood serum. Adolescents 12 to 18 years of age were examined for 12 different PFAS in a large-scale study in nine European countries (HBM4EU). The results show decreasing serum concentrations of PFOA and PFOS, but an increase in concentrations of other PFAS [218]. A German human biomonitoring study of children aged 3–17 years whose blood plasma was analyzed for 12 PFAS showed that plasma concentrations exceeded the HBM-I value of 2 ng/mL for PFOS in 21% of children and adolescents and 7.3% exceeded the HBM-I value of 5 ng/mL for PFOA [230]. Below the HBM-I value, no adverse health effects are expected. Concentrations greater than the HBM-II values, at which health consequences are possible, were only reached in rare cases: in only 0.2% of the participants concentrations of PFOS greater than the HBM-II value were determined. The authors [218, 230] note that aside from household dust, consumer products, cosmetics and various other sources, food and drinking water appear to be major uptake pathways for PFAS. PFOA added to sunscreen is absorbed transdermally by the body; in a self-assay, a small amount of the substance crossed the skin barrier and was detected in the blood of the test person [231]. A Belgian study shows that 77% of the adults exceeded HBM-I values for PFOS and PFOA in 2014. The authors showed that the consumption of lean fish, shellfish, potatoes and locally grown food e.g. chicken eggs is associated with higher PFAS blood levels. The use of cosmetics can be a possible route of exposure to PFAS [232], which was also demonstrated in another study [233]. These studies indicate that increased attention should be given to ongoing blood serum testing to estimate population exposure to PFAS.

Also critical is the transfer of PFAS from mother to child during the nursing period. Fromme et al. determined a median value of 40 pg/mL breast milk for PFOS [234]. Breast milk from 50 women was tested for the presence of 39 PFAS in a US study [108]. The authors ascertained an anticipated daily uptake for 18 PFAS in >50% of the samples studied. Based on these data, if the EFSA TWI of 4.4 ng/kg bw and week for PFHxS, PFOS, PFOA, and PFNA were used for a 1-month-old infant, this TWI would be exceeded by 12-fold. The EFSA TWI is, however, derived from a life-long weekly uptake [235]; therefore, exceeding the TWI as described here can only be considered an indication of that comparatively high uptake of PFAS via breast milk. Thus, a reduced immune competence of affected infants cannot be ruled out. From the comparison with other breast milk studies Zheng et al. conclude that the concentrations of regulated PFOA and PFOS are in decline, whereby concentrations

of short-chain and other long-chain representatives are increasing significantly [108], in accordance with measured concentrations in blood serum (see above [218]).

The German Federal Institute for Risk Assessment (BfR) has published the results on food products tested in Germany 2007–2020. The results show that in addition to foodstuffs of animal origin, for children the dietary intake of PFHxS, PFOA, PFOS and PFNA from milk and milk products apparently plays a greater role than for adults [235]. Thus, entry of PFAS into the environment and food chains must be urgently reduced. Here, soils and the concentration enrichment in crops are of particular importance, also in view of the climate-induced increases in the use of ground- and surface water for irrigation of arable lands [53, 236] (see “[Bioconcentration and biomagnification in the food chains](#)” section). Therefore, more attention must be paid to short-chain PFAS such as PFBA, PFBS as well as to TFA. Maximum levels of PFOS, PFOA, PFNA and of PFHxS in foodstuffs were intensively discussed in relevant committees and interested groups, whereby the focus is on possibilities for further marketing of foods that contain PFAS [237]. In August 2022, the EU Commission published a recommendation that member states in collaboration with food business operators during the years 2022 to 2025 should monitor the presence of PFAS in food. A wide variety of foodstuffs should be covered reflecting consumption habits. Here, not only PFOS, PFOA, PFNA and PFHxS are to be analyzed, but also, where possible, other compounds which have a different alkyl chain length and may occur in food, drinking water and/or human serum in relevant concentrations. For PFOS, PFOA, PFNA and PFHxS, the Commission specifies limits of quantification (LOQ) to be applied. If indicative levels are exceeded, further investigations are recommended [238]. In the case of foodstuffs, particular attention should be paid to PFAS levels in the liver as well as in the edible tissues of fish; the liver apparently represents a target organ for PFAS accumulation in warm-blooded animals and especially in omnivores such as wild boar [120, 124]; fish fillets may also be particularly contaminated: In fillets of fish from the central European Lake Constance (perch, whitefish, tench), levels between 1.8 and 30 ng/kg fm were found for the sum of PFOS, PFOA, PFNA, and PFHxS [117] (see “[Occurrence in the environment](#)” section). On the basis of the EFSA TWI of 4.4 ng/kg bw per week [183] for these four PFAS, a 70 kg adult would only need to have one meal of 200 g of fillets contaminated with 1.8 ng/g fm to reach the TWI and at maximum value would exceed it by 20-fold. Short-chain PFAS have not yet been included in these calculations. Recently, the EU Commission has adopted a regulation with maximum levels of perfluoroalkyl substances in

certain foodstuffs (PFOS, PFOA, PFNA, PFHxS and for the sum of PFOS, PFOA, PFNA, and PFHxS) [239].

At about 10%, drinking water makes a significant contribution to exposure of humans to PFAS, whereby drinking water supplies downstream of contaminated areas are of special importance [182, 183] (see “Regulations of PFAS” section). The drinking water contamination is widespread, e.g. in the US 200 million people are affected by levels above 1 ng PFOS and PFOA [240]. In China approximately 100 million people are exposed to drinking water with PFAS levels above stringent and science-based international limits [241].

Ultra-short-chain PFAS—trifluoroacetic acid

PFAS with chain lengths of C1 to C3 (ultra-short-chain PFAS) are often not included in analytical measurements. Toxicological and ecotoxicological properties of these substances have also been only sparsely investigated. Recent publications show that the relevance of these molecules has obviously until now been underestimated. This is evident in surveys of Canadian rivers and rain water in which 40% of PFAS contamination was attributed to ultra-short-chain molecules [242]. Neuwald et al. examined 46 samples from 13 drinking water supplies in Germany [243]. The authors identified numerous ultra-short-chain PFAS in a concentration range of 1–10 ng/L, whereby the anions of trifluoroacetic acid (TFA), trifluoromethanesulfonic acid (TFMS) and pentafluoropropionic acid (PFPrA) were detected in almost all samples. It is known that between 100 and 1000 tons of TFMS are produced each year in the EU, used in the manufacture of chemicals and optic, electric and electronic equipment [244].

TFA as the smallest of the perfluorocarboxylic acids takes on a special status among the PFAS. It is a strong acid and is used in biotechnology and chemical syntheses. Pollution of the Neckar River resulting from the discharge of a chemical company in the town of Bad Wimpfen (Baden-Württemberg, Germany) attracted attention a few years ago [245]. However, TFA is not only a regional problem, but is ubiquitous. Neuwald et al. measured TFA in drinking water samples with an average of 1 µg/L, by far the highest concentration found for ultra-short-chain PFAS [243]. It is found in precipitation, bodies of surface water, groundwater, soil and in the air, whereby concentrations are increasing significantly. The concentration in surface water in the area around Beijing in 2012 was 17-fold higher than in 2002 [246]. Even in remote bodies of water, in mountainous areas and in the oceans, concentrations of 100 to 600 ng/L have been measured [31, 247, 248, 261]. It is contested that TFA (to a small extent) is being formed naturally in deep

sea vents [249]. However, most TFA occurs as a result of thermal disintegration of fluoropolymers like PTFE [250, 251] and is formed through degradation of chemicals that contain a -CF₃ group. Certain pharmaceutical substances and especially pesticides and biocides thus play an important role in local and regional water pollution [30, 31, 252]. Annual emission from pesticides in Germany is estimated at 400–500 tons [30]. Apparently, TFA is principally formed from partly fluorinated fluorohydrocarbons such as 1,1,1,2-tetrafluoroethane (R134a) and polyfluorinated propenes such as 2,3,3,3-tetrafluoropropene (R1234yf). 2360 t/a of the TFA emissions are attributed to these refrigerants and propellants in 2020 [30]. R1234yf, in particular, contributes to the increasing environmental concentrations of TFA. R1234yf and other fluorinated propenes such as R1234ze and R1234zd are widespread substitutes for fully halogenated FCKW that are damaging to the ozone layer and/or contribute to the greenhouse effect. The fluorinated substitutes have a relatively low greenhouse potential and disintegrate quickly into the derivative TFA. For 2030 in the EU, Behringer et al. estimate a theoretical TFA formation potential from refrigerants and propellants of 37,000 tons/year, even increasing, if R1234yf continues to be used in automotive air-conditioning systems [248].

Freeling et al. investigated nearly 1200 precipitation samples from seven sites in Germany from February 2018 to January 2019 for TFA and found a medium concentration of 0.21 µg/L, resulting in a wet deposition of 68 tons TFA for the 12-month investigation period [253].

Like other ultra-short-chain PFAS, TFA is a classic ‘forever chemical’. It is spread over the globe and is non-recoverable from water by standard treatment processes. Even if the harmful effects of TFA known at present are limited, urgent measures must be taken to prevent further entry into the environment, such as the disuse of R1234yf as a refrigerant in automotive air-conditioning units, which can also use CO₂ [30]. Diffuse emissions of TFA in the environment are apparently increasing. Most notably, this leads to a long-term contamination of bodies of groundwater, used for or intended to be used for drinking water [30]. A yearly overall input of 170 kg is estimated for Lake Vättern (Sweden), whereby 98 kg are derived from atmospheric deposition. The balance of all inputs and outputs shows a total amount of 2600 kg, a yearly TFA increase of 150 kg (more than 5%) [76]. Since 1995 TFA concentrations measured in German rivers have increased from 0.04–0.3 to 1.0 µg/L and greater [31]. Modeling by UBA shows that in a “business as usual” scenario the TFA contamination via precipitation by 2050 will increase ten times to 4 kg per km² per year in Germany [248, 254].

In time series from the Environmental Specimen Bank TFA concentrations in poplar and beech leaves as well as spruce and pine needles from various locations in Germany were found to have increased by a factor of 5 between 1990 and 2020 [255, 256]. The concentration enrichment in plants seems particularly critical regarding human exposure, since crops such as rice, soy, wheat or sunflowers concentrate TFA with a BAF of 10 to 1000 [257–259]. Relatively high concentrations of TFA are also found in human blood serum. Duan et al. [260] measured a median of 8.5 ng/mL TFA in the serum of Chinese adults.

The data on the toxicology of TFA appears to be incomplete. Some animal studies on the TFA toxicity have been published recently: according to the ECHA registration dossier [261], the sodium salt of TFA showed effects on the rat liver in a subchronic oral feeding study, the corresponding NOAEL being 8.4 mg/kg bw per day (male). From this point of departure, ECHA derived a chronic no-effect level for the general population of 42 µg/kg bw with an overall uncertainty factor of 200 [261].

In a current chronic toxicity study sodium trifluoroacetate was administered to rats by drinking water for 52 weeks with a recovery period of 6 weeks. In the absence of any treatment-related adverse effects, the NOAEL for this study was reported to be 600 mg/L, corresponding to a daily dose of about 38 mg/kg bw (male) and 64 mg/kg bw (female), respectively [261]. According to the German UBA the same study revealed a dose-dependent increase of the enzyme ALT, an indicator of possible liver damage, already at drinking water concentrations of 120 mg/L [262, 263]. From the NOAEL of 30 mg/L corresponding to 1.8 mg/kg bw per day, a TDI of 18 µg/kg bw was derived applying an overall uncertainty factor of 100 [262, 263].

In mice, TFA as a metabolite of 2-bromo-2-chloro-1,1,1-trifluoro-ethane (halothane) passes the placental barrier and accumulates in the fetus and amniotic fluid [264]. TFA was also found in breast milk of monkeys as metabolite of the refrigerant 1,1,1-Trifluoro-2,2-dichloroethane (HCFC-123) [265], whereas in two recent studies on rats, TFA did not show any developmental effects with NOAEL of 150 and 382 mg/kg bw per day, respectively [261], in rabbits, on the other hand, major abnormalities have been observed at 375 and 750 mg/kg bw per day as well as, to a lesser extent, at the lowest dose level of 180 mg/kg bw per day predominantly affecting the eyes [261]. The malformations of rabbit eyes caused by the water soluble and persistent TFA anion, which can accumulate in fetus and amniotic fluid, require further attention [261]. Potential reprotoxic effects on humans need to be elucidated.

Analysis of per- and polyfluorinated alkyl substances (PFAS)

The vast number of PFAS compounds with numerous substance groups having disparate physical–chemical characteristics poses an almost impossible challenge for the analytical laboratory. Only a limited number of PFAS can presently be identified as individual substances and/or quantified with the analytical methods available. Determination of sum parameters for organic fluorine compounds can potentially reduce this gap in methodology with relatively minor effort.

Complete, concurrent extraction of different PFAS substance groups from solid and aqueous matrices requires extensions or modifications to conventional extraction methods for perfluorinated carboxylic and sulfonic acids. For the determination of PFAS in exhaust gases and waste air from combustion and industrial plants suitable and validated sampling procedures are currently unavailable, even for individual, defined PFAS substance groups, except one method in development [266] (see below).

Analysis of individual PFAS substances

Methods for sensitive and specific determination of perfluorinated carboxylic and sulfonic acids with four and more carbon atoms in aqueous and solid environmental, food and human samples have been well established since the first decade of the twenty-first century. The analytes are first enriched by means of extraction and are then measured by coupling high-performance liquid chromatography with tandem mass spectrometry (LC–MS/MS). Since isotope-labeled reference compounds are available for the majority of perfluorinated carboxylic and sulfonic acids with 4 to 14 carbon atoms, addition of these standard substances before extraction makes quantitative determination at trace levels reliable and accurate.

Aqueous matrices

Enrichment of perfluorinated carboxylic and sulfonic acids with four or more carbon atoms in aqueous matrices is performed by solid-phase extraction (SPE) with a weak anion exchanger and elution with methanol. The German Standard DIN 38407-42 [267] from 2011 describes the analysis of seven perfluoroalkyl carboxylic acids and three perfluoroalkyl sulfonic acids in water with a lower limit of quantification (LOQ) of 10 ng/L each. Currently, good laboratories routinely achieve an LOQ of about 1 ng/L. A number of laboratories have also successfully expanded the methods to include long-chain perfluorinated carboxylic acids with 11 to 14 carbon atoms, fluorinated oxo carboxylic acids (PFOA substitutes ADONA and HFPO-DA), perfluorinated

fluorotelomer sulfonic acids (e.g. H4PFOS) and in some cases other PFAS.

The ISO 21675 standard [268], published in 2019, included the analysis of 30 individual substances with low LOQs, 0.2 ng/L for most substances), however, it does not cover all 20 perfluorinated carboxylic and sulfonic acids with 4 to 13 carbon atoms, the sum limit value for which is fixed in the new EU Drinking Water Directive [269].

In August 2022, the Technical Committee Water Analysis of the European Committee for Standardization (CEN) has published the draft of the European standard EN 17892 for determination of perfluorinated substances in drinking water [270]. In addition to the 20 perfluorinated carboxylic and sulfonic acids in the Drinking Water Directive [269], the method has been validated for nine other PFAS that play a role in environmental samples, including fluorotelomer sulfonic acids and the PFOA substitutes ADONA and HFPO-DA. For most substances an LOQ of 1 ng/L can be achieved. The applicability of the method to other aqueous matrices like ground- and surface water has to be validated in each case.

The new EU Drinking Water Directive limit of 100 ng/L for the sum of 20 perfluorinated carboxylic and sulfonic acids is mathematically equivalent to a limit of 5 ng/L per individual substance [269]. As a general rule of thumb, the LOQ of an analytical method for limit monitoring must be at least a factor of 5–10 lower than the limit value. For the analysis of the 20 PFAS, an LOQ of 0.5–1 ng/L per individual substance must therefore be reliably achieved in the routine.

Solid matrices

Perfluorinated carboxylic and sulfonic acids are enriched from solid samples by extraction with methanol. The German standard DIN 38414-14 [271], published in 2011, describes the analysis of seven perfluoroalkyl carboxylic and three perfluoroalkyl sulfonic acids in soil, compost, and sludge, each with an LOQ of 10 µg/kg dm. However, a limit of quantification of 10 µg/kg dm is clearly too high to detect background PFAS contamination of soils. Even with a concentration of 2–4 µg/kg dm for the sum of PFOA and PFOS, one must assume a (pre-)contamination of the soils [91]. However, some laboratories are already at this time achieving an LOQ in the range of 1 µg/kg dm per individual substance [91]. In addition, several analytical laboratories have succeeded in extending the method to include the determination of other PFAS in a similar manner to that used for water analysis. For the analysis of 40 PFAS single substances in soil, sludge and sediment, a new standardization project is currently under development by a CEN committee in the Netherlands. The LOQs are to be in the lower µg/kg

dm range. However, this European standard will not be ready until 2023 at the earliest.

The routine analysis of perfluoroalkyl carboxylic and perfluoroalkyl sulfonic acids in food is presently possible with an LOQ of approximately 1 µg/kg fm per individual substance; under ideal conditions an LOQ of 0.1 µg/kg fm can also be achieved. Currently, there is a method in development and validation in state research laboratories in Germany for the simultaneous determination of 22 PFAS in food with LOQs in the lower ng/kg range [272].

After EFSA in 2020 significantly lowered the TWI value for the sum of the four common PFAS PFHxS, PFOS, PFOA, and PFNA to 4.4 ng/kg bw [183], the EU Commission has amended Regulation (EC) No. 1881/2006 to include maximum levels of these four PFAS in certain foodstuffs in December 2022 [239]. For the individual substances, the maximum levels for some food groups are in the range of 0.2–0.3 µg/kg FM. This means that significantly lower analytical LOQs are necessary for food monitoring now, i.e. well below 0.1 µg/kg per PFAS individual substance.

For the analysis of PFAS single substances in products and waste, fundamental development and standardization work on sample processing, especially on extraction methods, is necessary. The extraction method standardized for soil and sludge should be suitable for different types of waste and products, however this will require testing. Although the Regulation (EU) 2019/1021 (EU POP regulation) has set limit values for PFOA and related compounds in waste there is, however, no analytical method available for most of these substances nor does a standard exist. This means that for many PFOA-related substances a surveillance of valid limit values in waste is not possible. For determination of PFOS in products CEN only developed a technical specification without validating it [273]. In this context it is important to keep in mind that a large share of PFOS and other PFAS in products are part of side-chain fluorinated polymers. Currently, there is no method which can quantify these covalently bond PFAS.

Air and exhaust gas

Determination of perfluorinated carboxylic and sulfonic acids and other ionizable PFAS, as well as volatile neutral PFAS such as fluorotelomer alcohols, in ambient air has been conducted in various urban and rural areas [79, 274–277]. Active air sampling was predominant; a review of methods can be found in Wu et al. [278]. However, in virtually all studies, the semi- to low-volatile ionizable PFAS were determined only in the particulate matter deposited on glass or quartz fiber filters. On the other hand, the sorbents used in the sampling cartridges to capture gaseous PFAS such as polyurethane (PU) foams

and/or XAD-2 granules (a styrene–divinylbenzene copolymer) were analyzed only for volatile neutral PFAS.

A study in Bavaria, however, showed that perfluorinated carboxylic and sulfonic acids with four or more carbon atoms deposited on the glass fiber filter are volatilized by the air flow when the sampling period exceeds 2 days. This volatilization sets in earlier and more intensely the shorter the chain length and thus the more volatile the substance is [279]. Therefore, if air sampling lasts more than 2 days the gaseous fraction of ionizable PFAS must be analyzed, in addition to the particle-bound fraction. For this purpose, the same sampling technique (combination of glass fiber filter and two subsequent PU foams) as standardized for the determination of PCDD/PCDF, polychlorinated biphenyls, and some polybrominated flame retardants is basically suitable [71] (VDI guidelines [280–282]). Wu et al. showed that by extending such a sampling cartridge with activated charcoal, it is possible to detect additional groups of volatile neutral PFAS such as diiodofluoroalkanes (FDIAs) in ambient air [278].

In contrast to water and solids, however, there is no standardized method for the determination of one or more groups of PFAS in air, so that there are no continuous and state-organized monitoring programs for the detection of PFAS in ambient air in the EU. This results in corresponding knowledge gaps on the volatilization of PFAS and their atmospheric dispersion. The crucial steps for validation and standardization are sampling and enrichment for instrumental-analytical determination.

Some studies on the occurrence of PFAS in outdoor air have been conducted with passive samplers, including the Global Atmospheric Passive Sampling Network, in which air samples from 21 monitoring sites in the western part of the Northern Hemisphere were analyzed for volatile neutral and semi-volatile ionizable PFAS in 2009, 2013, and 2015 [78]. The highest concentrations were found for the volatile fluorotelomer alcohols 6:2 FTOH and 8:2 FTOH, consistent with studies using active air sampling [276, 277].

Up to now, only few studies have been published on the occurrence of PFOS and PFOA in exhaust gas and waste air from combustion and industrial plants and thus on their release into the atmosphere [65]. Suitable and validated sampling methods—even for the classic perfluorinated carboxylic and sulfonic acids with four to ten carbon atoms—have not yet been established. For PFAS emission measurements, the US EPA's OTM-45 method is currently the only method claiming standardization [266]. The method has the status “in progress” and is therefore not yet validated. The OTM-45 describes a complex and small-scale sampling and processing procedure with up to eight subsamples and four individual

analyses, which, according to emission experts, is too complicated and costly for European practice. From individual emission measurements carried out in Germany, there are still unpublished indications that, when it comes to sampling, the complete capture of PFAS from exhaust gas and waste air is probably the greatest challenge. Achieving sufficiently LOQs is also essential—as it is for ambient air measurements. In thermal plants, moreover, fragments of the PFAS such as TFA can occur. For example, when nine aqueous daily samples were analyzed from the acidic first flue gas scrubber of a sewage sludge mono-incineration plant in southwestern Germany, TFA concentrations in the range of 1 µg/L were found in all samples [283]. Therefore, the selection of a limited number of suitable PFAS lead substances seems necessary and practicable for emission measurements.

There is thus a comprehensive and urgent need for the development and standardization of sampling for exhaust gas and waste air measurements of PFAS [65], especially since plants from numerous industries are potential PFAS emitters.

Non-target analysis of PFAS

Mass spectrometers with a very high mass resolution and mass accuracy (HRMS, high-resolution mass spectrometry) have been available for about 10 years. This basically allows the determination of the exact masses of the molecular and fragment ions of a substance contained in the sample and ultimately the molecular formula of the compound. On this basis, by applying user-specific or external mass spectrometric databases it is in principle possible to identify unknown substances contained in the sample. Due to the exact atomic mass characteristic of the element fluorine, per- and polyfluorinated compounds can be identified in this manner.

By coupling high-performance liquid chromatography with a high-resolution mass spectrometer (LC-HRMS), this non-target analysis can be applied particularly well to aqueous samples, since the samples can be injected directly without a prior extraction step. This allows the determination of a large number of compounds from different substance groups, provided that the substances are analytically detectable under the chromatographic and mass spectrometric conditions applied. Even unknown fluorine-containing compounds can in principle be detected by non-target analysis.

However, since a prior enrichment step would not or would only incompletely detect numerous substance groups of PFAS, the direct measurement of water samples results in higher LOQs than with specific PFAS analysis of single substances analysis or a subset detectable with the respective extraction. Therefore, non-target analysis of original water samples is still too insensitive

for PFAS monitoring of surface or groundwater. Nonetheless, an important potential application can be the analysis of wastewater, since the LOQs would be sufficient for this purpose.

Joerss et al. [88] analyzed river water affected by industrial point sources in Germany and China with LC-HRMS after solid-phase extraction on a cartridge consisting of four sorbents with different properties thereby achieving a compromise between good sensitivity and capture of numerous various groups of PFAS. Comparing raw data with a substance list of 3655 PFAS in total 86 PFAS from 18 structural groups were tentatively identified, among them eight compounds which have not been reported in the environment yet. 17 of the 86 PFAS were confirmed by analytical standards.

In a guideline, the Wasserchemische Gesellschaft (Society of Water Chemistry) of the Gesellschaft Deutscher Chemiker (German Chemical Society) has defined basic quality criteria for the application of non-target analysis by LC-HRMS in water analysis [284], which should also be considered for the identification of unknown PFAS. A clear identification of an unknown substance with non-target analysis is ultimately only possible if the suspected compound is available as a reference substance for a confirmatory measurement [285]. Even for the now widely used oxo carboxylic acid C6O4, this is not the case [286]. Thus, the limited availability of reference standards from the large substance group of PFAS currently places strict limits on the application of non-target analysis for the identification and quantification of PFAS.

Recently, the application of Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR MS) has been described as another solution for the non-target screening of PFAS in a firefighting foam product [287]. FT-ICR MS offers the highest mass resolution and accuracy and a wide dynamic range.

Sum parameters for PFAS

Adsorbable organically bound fluorine (AOF)

In this sum parameter, the fluorinated organic compounds contained in a water sample are first adsorbed on activated charcoal. Inorganic fluorine species like fluoride can also adsorb on activated charcoal. To avoid resulting false high values of AOF, fluoride is removed from the activated charcoal by washing with a nitrate solution. The loaded charcoal is then burned in a stream of oxygen and the combustion gases are absorbed in an aqueous solution. The fluoride ions formed from the generated hydrogen fluoride are quantitatively determined by means of combustion ion chromatography (CIC), thus indirectly determining the sum of fluorinated organic compounds contained in the sample [288]. In routine use, an analytical limit of detection (LOD) of 1.3 µg F/L and an LOQ of

2.0 µg F/L are achieved [50], which is sufficiently low for monitoring (industrial) wastewater. However, the AOF method is not sensitive enough for monitoring the limit of 0.5 µg/L for the sum of all PFAS in the new EU Drinking Water Directive [269]. In a recent study, Han et al. [289] optimized the AOF method and achieved an LOD of 0.3 µg/L and an LOQ of 0.4 µg/L.

Since ultrashort PFAS in particular do not adsorb well on activated charcoal, the AOF may more or less underestimate the true total PFAS content in a sample, depending on the nature and composition of the fluorinated substances. For example, in the studies by Han et al. [289] and von Abercron et al. [50], the recoveries for several short-chain PFAS were actually low. Examining various water samples from 13 drinking water sources in Germany, Neuwald et al. [243] demonstrated the non-detection by the AOF of the ultrashort PFAS TFA, PFPrA, and TFMS, which are practically ubiquitous and even dominant in many samples.

On the other hand, the AOF also detects fluorine-containing compounds that do not belong to PFAS, such as monofluorinated compounds and some pharmaceuticals and pesticides with fluorinated aromatics as well as their metabolites, so that in individual cases the PFAS content can also be overestimated, especially in the low concentration range up to approx. 10 µg/L. According to a first pilot study, this seems to occur partly in surface water [50].

A German standard for AOF determination in aqueous samples is available since October 2022 [290]. The extraction is performed with synthetic activated charcoal, and the lower LOQ is 2.0 µg/L, expressed as fluorine. In the standard method, a drop of pH value of the sample before adsorption is avoided and the washing step to eliminate fluoride is performed with a neutral nitrate solution [288]. In June 2022, the application for writing it as an ISO standard was submitted [291].

Von Abercron [18] has shown in a pilot study that the AOF method can also be successfully used to detect PFAS in aqueous and ethanolic extracts of paper and paperboard food packaging. The LOQ is about 20 µg F/g paper, which corresponds to the indicator value set in Denmark for PFAS in food packaging.

Extractable organically bound fluorine (EOF)

In the EOF method for water, sediment, and soil samples as well as biological tissues (Han et al. [289] lists eight references for this), the PFAS contained in the sample are first enriched by SPE and simultaneously separated from fluoride. Subsequently, the SPE eluate is combusted and the fluoride formed is quantified by CIC similar to the AOF procedure. Since the common EOF procedures use weak anion exchange resins for the SPE step [292],

they are most likely ineffective in detecting cationic and some other PFAS (see below). At the German Federal Institute for Materials Research and Testing (BAM), the determination of fluorine in the SPE eluate is performed by high-resolution-continuum source-graphite furnace molecular absorption spectrometry (HR-CS-GFMS), adding gallium salt solutions. The resulting in-situ formation of gallium fluoride in the graphite furnace allows fluorine to be quantified selectively and with high detection capability, resulting in an instrumental LOQ that is about a factor of four lower than that achieved by ion chromatographic determination after combustion (CIC) [293]. For the overall procedure of EOF determination in water samples after SPE enrichment, Metzger et al. [292] report an LOQ of 18 ng F/L, which seems sufficiently low for monitoring surface waters. For EOF determination in soils and sediments with HR-CS GF MAS, the extraction method was optimized and simplified (four times with acidified methanol in an ultrasonic bath), such that an additional SPE step is unnecessary [294]. This achieves an LOQ for the overall method of 10.3 µg F/kg. The German standard DIN 38414-17 for EOX determination (sum of organohalogen compounds containing chlorine, bromine or iodine) [295] does not include organofluorine compounds. There is no standardization activity yet for the EOF determination.

TOP assay (total oxidizable precursor)

The TOP assay is suitable for aqueous samples including soil eluates and solid samples. In this process, the addition of a strong oxidizing agent (e.g., peroxydisulfate) to the extract oxidizes the polyfluorinated precursor compounds contained therein to corresponding perfluoroalkyl carboxylic acids [296], which are then analyzed using established single-substance analysis with low LOQs of 1–10 ng/L for water samples. Thus, the TOP assay is significantly more sensitive than other sum parameters such as AOF and EOF.

The TOP assay is limited by the spectrum of perfluorinated oxidation products covered by the analytical method used. In addition, some precursors are only incompletely oxidized or not oxidized at all. For example, perfluorinated oxo carboxylic acids such as HFPO-DA and fluoropolymers are not detected. A detailed description of this problem can be found in Zhang et al. [297] and Held [3]. Various polyfluorinated substances can give rise to the oxidation products trifluoroacetic acid and/or perfluoropropanoic acid, but these are not detected by the standard analysis of perfluorocarboxylic acids [243]. This requires modification of the TOP assay and additional analysis of these two short-chain perfluorocarboxylic acids with ion chromatography [3, 298] or

hydrophilic interaction chromatography (HILIC) after enrichment adapted to these ultrashort PFAS with a modified SPE method [243].

The standardization process of the TOP assay for aqueous soil eluates and groundwater is currently ongoing. For this purpose, a first draft standard for the determination of perfluoroalkyl carboxylic acids with four to ten carbon atoms has been prepared in Germany; an inter-laboratory test has recently been carried out.

The TOP assay has recently been increasingly applied to solids such as soils, sediments and suspended solids. For this purpose, the assay has been adapted by adding the oxidant directly to the original sample prior to extraction. This allows extraction losses of unknown polyfluorinated precursor compounds to be avoided. This direct TOP assay (dTOP) gains LOQs in the range of 0.1 to 10 µg/kg for soil samples being more sensitive than the EOF assay [299]. The dTOP assay was also successfully applied to biological samples by Göckener et al. [115]. Standardization activities for the TOP assay for solid samples are not yet known; an international or at least European standard protocol for soil is, however, urgently needed [299].

Completeness of PFAS extraction

In the PFAS analysis of soil and other solid (environmental) samples with the methods established until now, the extraction is always carried out with methanol, regardless of whether this is followed by a single-substance analysis or a determination of the sum parameter EOF or TOP. Methanol extraction yields good recoveries for anionic PFAS (carboxylic and sulfonic acids) and—as far as known—also for neutral PFAS (e.g. fluorotelomer alcohols). However, cationic and zwitterionic PFAS are not completely extracted from the solid sample by this method [3] and are not adequately quantified. Thus, the determination of a PFAS sum parameter performed in this manner may yield systematically low levels. Therefore, for a complete coverage of all PFAS compounds from soils, Nickerson et al. [300] proposed an optimized sequential extraction with basic methanol followed by an acidic extraction, which allows a better coverage of cationic and zwitterionic PFAS.

Held [3] concludes that only the application of several sum parameters in combination and an optimized extraction of soil samples can provide a sufficiently reliable estimate of the level of PFAS contamination. The optimized extraction of PFAS from solid samples must, therefore, find its way into the—not yet begun—standardization efforts of the TOP assay (for solids) and the EOF determination.

TOF assay (total organically bound fluorine)

In the TOF assay, a sum parameter for solid samples, the entire sample is combusted according to DIN 51723 [301]. Hydrogen fluoride is formed from the fluorinated organic compounds contained in the sample, including fluoropolymers and polymers with fluorinated side chains (and inorganic fluorine compounds). The hydrogen fluoride is collected in an aqueous buffer solution and quantitatively determined as inorganic fluoride by means of ion chromatography according to DIN EN ISO 10304-1 [302]. The sum of PFAS contained in the sample includes fluorinated polymers in addition to small molecules and fluorinated aromatics (in contrast to the AOF for water samples). However, the proportion of fluoropolymers in the TOF value cannot be determined.

The TOF assay is well suited for the analysis of materials and products such as food packaging since these materials do usually not contain inorganic fluoride. Since fluoride is not separated from fluorinated organic substances, the TOF assay is not suitable for samples which may contain inorganic fluoride in the mg/kg range. The rather high LOQ of 1 mg F/kg strongly limits its suitability for environmental samples [17]. Standardization is still necessary. The TOF assay is in principle also applicable for the examination of solid waste.

Biological effect test for PFAS

Since 2009, many PFAS, like PFOA, are known to bind strongly to transthyretin (TTR), the transport protein for the thyroid hormone L-thyroxine (T4) [303]. This can cause a reduction in thyroid hormone levels in humans and animals. The binding of chemicals to transthyretin and the resulting displacement of T4 can be measured by the TTR-TR-CALUX bioassay, which combines two bioassays and can also be applied to extracts of (environmental) samples [227]. Here, TTR and T4 are first added to the pre-purified extract and incubated. Then, the TTR-bound T4 is separated and added to a culture of the human U2OS cancer cell line. In these genetically engineered cells, the firefly luciferase gene is linked to the so-called thyroid responsive elements (TREs). In this way, a reporter gene is obtained for the presence of T4 and other substances that activate the TREs. Now, when the cells are incubated with T4, they produce not only proteins whose gene expression is associated with TREs under normal circumstances, but also the enzyme luciferase. After addition of luminol, the substrate for luciferase, and incubation of the cells, the light emission of the luminescent product is measured. The higher the T4 concentration in the cell culture medium, the stronger the light intensity is. When incubated with TTR, the amount of TTR-bound T4 is decreased, if the sample extract contains substances that also bind to TTR and compete for

binding T4. This corresponds to the concentrations and potencies of action of the TTR-binding substances. The light intensity is then correspondingly weaker. The TTR-TR-CALUX bioassay would allow the derivation of RPF for PFAS (similar to the DR CALUX for PCDD/PCDF) [227].

Such bioassays have the advantage over chemical single-substance analysis in that a defined biological effect is measured that is triggered by the totality of all substances present in a sample that are capable of binding to the specific protein—regardless of their structure and ability to be chemically determined. Coupling the bioassay with instrumental analysis of the sample for compounds known to elicit this effect, a concentration with the equivalent effect can be calculated, taking into account the respective potency of each substance. An effect equivalent in the bioassay that is significantly higher than the value determined from the result of the chemical analysis indicates the presence of unknown substances that have not been detected by the single-substance analysis method used.

Since the effect of PFAS on the thyroid hormone system is a sensitive endpoint for humans (see “[Biological effects of PFAS on laboratory animals and on humans](#)” section), this bioassay (and possibly others) can be a useful supplement to the instrumental analysis of PFAS single substances as relevant sum parameter.

PFAS-contaminated sites

Contamination of soils and waters takes place along the entire life cycle of PFAS: from the production of PFAS to the use of PFAS in manufacturing (e.g. production of fluoropolymers and textiles), the use of products containing PFAS (e.g. firefighting foams and pesticides) and the disposal of PFAS (e.g. landfills, disposal of sewage sludge). With the Stockholm Convention’s Guidance for the inventory of PFOS [304], a draft guidance with an approach for the systematic survey of the PFOS inventory has been available since 2017. This guidance, which can also be transferred to other PFAS, provides contracting states with a tool to identify emission sources, waste management measures and contaminated sites.

In addition to diffuse discharges via the atmospheric pathway and the agricultural application of contaminated materials such as sewage sludge and residual materials from paper production, in recent decades there have been numerous, sometimes massive PFAS discharges into soil and groundwater through so-called point sources [61, 62]. Aqueous Film Forming Foam (AFFF) with PFOS as film-forming agent is of particular importance in this context. The use of PFAS-containing extinguishing foams in firefighting has led to massive soil and groundwater contamination in many places worldwide.

Large quantities of such extinguishing foam concentrates are kept on hand, especially at civil and military airports, and at industrial plants such as refineries and tank farms. In addition, large quantities of firefighting foams containing PFAS have also been released in the past during firefighting exercises. In principle, every fire station also represents a potential point of entry, since this is where the foam concentrates are decanted, the extinguishing equipment maintained and tested, and cleaned after operations.

In 2009, PFOS was included in Annex B of the Stockholm Convention. With Regulation (EU) No. 757/2010 amending POP Regulation (EC) No. 850/2004 (POP: persistent organic pollutant), the limit for PFOS in fire-extinguishing agents was reduced to 0.001 percent by weight. Even before this final ban on the use of PFOS-containing extinguishing foams, numerous alternative fluorosurfactant-containing foam extinguishing agents came onto the market, in particular polyfluorinated substances such as H4PFOS, which, however, pose comparable risks to soil and water. To avoid such “regrettable substitutions”, the EU plans to restrict all PFAS in fire-extinguishing agents [305] (see “[Regulation of PFAS](#)” section).

Another major use of PFOS was as a wetting agent in the chromium plating of metal and plastic surfaces in electroplating shops. Here, too, polyfluorinated chemicals are now frequently used instead of PFOS [47]. In an inventory of PFAS contamination of soil and groundwater in the German state of North Rhine-Westphalia, 73% of the cases reported by May 2021 could be attributed demonstrably or presumably to the use of fire-extinguishing agents. 12% of the cases could be traced back to electroplating [306]. Thus, 85% of the detected soil and groundwater contamination with PFAS originated from one of these two activities.

Further PFAS contamination may originate in particular from the use of these substances in textile finishing, semiconductor and paper industries as well as in the chemical industry. Landfills where waste containing PFAS has been deposited can also be responsible for point source contamination due to escaping leachate.

So far, there is no obligation for municipalities in Germany to systematically record suspicious areas and to verify or exclude a suspected contaminated site by appropriate investigations. Especially for the damage caused by firefighting foams, contemporary witnesses have to be interviewed and documents of the fire departments as well as reports in the local press about large fires have to be evaluated. A guideline from the German Working Group on Soil Protection of the Federal States and the Federal Government (LABO) on the systematic recording of PFAS suspected sites has

been available since 2015 [307] and could serve as a basis for corresponding recommendations in other EU member states.

If PFAS enter the groundwater via the soil, they can lead to contamination plumes several kilometers long due to their mobility, depending on the characteristics of the aquifer. For example, a PFAS input from extinguishing agents in Düsseldorf has been documented to spread at a rate of about 200 m per year [308]. If such contamination remains undetected, the PFAS can, for example, reach soils and crops outside the narrower contamination area when groundwater is used for garden wells and for irrigation of agricultural land. Due to their persistence, concentrations of PFAS in topsoil then increase and may enter the food chain via accumulation in crops (see “[Bioconcentration and biomagnification in the food chains](#)” section). Similarly, the production of drinking water may be affected by these contaminants.

Examples of PFAS contamination from point sources are numerous. Bremen Airport is a case in point: Decades of use of PFAS-containing firefighting foams during functional tests of extinguishing equipment and firefighting exercises on the site have resulted in evidence of massive soil and groundwater contamination with PFAS. The pollutants have spread beyond the airport site via the drainage system of the site and adjacent water systems. Studies of fish show very high levels of contamination in some cases, resulting from accumulation in muscle tissue and internal organs (see “[Occurrence in the environment](#)” section) [309].

Beyond such point sources, some large-scale PFAS pollutions of soil and groundwater are among the most massive known contaminated sites (“mega sites”).

The application of compost made with contaminated paper sludge has resulted in pollution of agricultural soils in the Rastatt and Baden-Baden area of Baden-Württemberg, Germany. More than 1,000 hectares (2471 acres) of soil and 180 million m³ of groundwater are affected, in part directly by the sludge, and in part indirectly by contaminated irrigation water [53, 310, 311]. As a result, crops on these lands are contaminated. With regular pre-harvest monitoring, high levels of contamination of field crops are recorded, which may then no longer be marketed as food. The Ministry of Food, Rural Areas and Consumer Protection of Baden-Württemberg (MLR) since 2015 set assessment values for the pre-harvest monitoring which include values for short-chain PFAS [312]. In its newest communication it took into account EFSA’s TWI value of 4.4 ng/kg bw as a benchmark for long-chain PFAS (see “[Toxicological evaluation](#)” section) [313]. The affected drinking water suppliers purify their water by reverse osmosis or activated charcoal

filters (see “Purification of PFAS-contaminated water” section). In 2019 the state parliament of Baden Württemberg concluded that—according to current knowledge—remediation of these widespread groundwater and soil contaminations is impossible with reasonable measures [311].

Originating at an industrial plant producing fluorochemicals, including PFOA as an emulsifier for manufacturing PTFE and other fluoropolymers, PFOA contamination of soils and groundwater took place over an area of 230 km² in the vicinity of Gendorf (Bavaria, Germany) [104]. The production of PFOA at this site has since been replaced by ADONA. Here, in addition to wastewater and penetration into groundwater, the atmospheric pathway played a significant role in the widespread contamination.

Very extensive PFAS contamination in the vicinity of PFAS production plants was found in Dordrecht and Helmond (Netherlands) [72–74]. The PFOA used previously as emulsifier was replaced by HFPO-DA, which now can also be detected in soil, groundwater, surface water, plant and blood samples.

Probably the most extensive contamination of soil and groundwater in Europe has been found in central Veneto (Italy) [314]. Originating from a production plant belonging to the Miteni company, a groundwater plume of PFOA and other PFAS (including the oxo acids HFPO-DA and C6O4) extends over an area of 595 km² with a population of about 140,000 inhabitants, particularly affected by contaminated drinking water (Fig. 4). Measurements of blood serum showed widespread elevated levels [315].

Contamination of the surroundings of PFAS production sites is also common in the United States. Examples are inter alia industrial plants of Solvay in New Jersey [316] as well as of 3M in Minnesota [317] and in North Carolina [109, 110]. In many cases the landfills and deposits around the production facilities contribute strongly to the contamination of soil and waters. Thus, it is necessary to explore the locations of all PFAS production facilities and related landfills systematically to prevent risks for population and environment.

In the cases mentioned above, remediation is no longer possible, but only a limitation of the damage and the spread and thus the exposure to the population.

The remediation of contaminated PFAS sites is extraordinarily expensive and long-lasting. In the case of groundwater damage, “pump and treat” is often used, i.e., pumping the contaminated groundwater and treating it, for example, by adsorbing the PFAS on activated charcoal (see “Purification of PFAS-contaminated water” section). Remediation of contaminated soils also quickly reaches its limits. The simplest solution, excavation and landfilling, is not possible in Germany due to the lack of availability of suitable landfill space. In individual cases, separating the soil by grain size can help to reduce the volume of waste to be landfilled or incinerated at high temperatures to the more heavily contaminated fine-grain fraction. In the case of large-scale contamination, however, these methods are unsuitable in any case, not only because of the volumes involved.

Moreover, the provisions of the Stockholm and Basel Conventions should be taken into account. These stipulate that waste is to be disposed of in a manner that destroys the POPs [1] if a value of 50 mg/kg for PFOS is exceeded. On 23 November 2022, the European Parliament and Council have passed Regulation (EU) 2022/2400 amending Annexes IV and V to Regulation (EU) 2019/1021 (EU POP Regulation) with new concentration limits for PFOA and PFHxS and their related compounds in waste [318]. From 10 June 2023 a limit value of 1 mg/kg for PFOA and its salts and 40 mg/kg for the sum of PFOA-related compounds will be in force. The same concentration limits are set for PFHxS and its salts and the sum of PFHxS-related compounds, respectively. Such waste shall be destroyed or irreversibly transformed in an environmentally sound manner. The Commission shall review these concentration limits no later than 30 December 2027.

Alternative treatment processes, however, are not yet technically mature [61, 62]. Large-scale soil washing (on-site) is in its infancy for PFAS, as are in-situ remediation processes. Among others, methods of immobilizing PFAS in soils by clay minerals or other adsorbents are being tested. Alternatively, PFAS could be flushed into groundwater by irrigating the soil and extracted from it by pumping. The suitability of these methods depends very much on the local situation, including hydrogeological conditions. There is still a considerable need for research and development.

(See figure on next page.)

Fig. 4 Map of the PFAS-contaminated area of the Veneto Region. Red Area: municipalities supplied by PFAS-contaminated waterworks. Red Area A (dark red): municipalities of the Red Area located on the groundwater contamination plume. Red Area B (light red): municipalities of the Red Area located outside the groundwater contamination plume. Dashed white area: groundwater contamination plume. Pink dot: location of the chemical plant that gave origin to groundwater contamination. Yellow lines: borders of municipalities. Red lines: borders of provinces. Blue lines: rivers. Black thick line: borders of the new areas included in the Red Area in 2018 (nine additional municipalities, some of them only partially included). The box on the lower right corner indicates the position of the represented area in the Veneto Region, northeastern Italy. © Map from Gisella Pitter [315]

For the assessment of soil and groundwater contamination, the German Federal Ministry for the Environment and Consumer Protection (BMUV) published a “Guideline for PFAS Assessment” [319]. Decisive for the assessment of groundwater contamination are the insignificance thresholds (GFS values), which were derived in 2016 by the German Working Group on Water Issues of the Federal States and the Federal Government (LAWA) on the basis of toxicological data for seven individual compounds [320]. The most important exposure pathway is considered to be the soil → groundwater route. If the concentrations in an eluate (water/solid ratio 2:1) exceed these GFS values, the soil can no longer be used without restrictions. Soils with concentrations up to 5 to 10 times of the insignificance thresholds (GFS values) can still be used for technical structures, but only subject to compliance with safety measures (e.g. groundwater monitoring). If the contents are higher, they are considered waste and must be disposed of. However, these limits (e.g. 1 µg/L for PFOS) are so low that in many cases they will be exceeded and no true relief is likely to occur with respect to landfilling.

The pathways soil → plant and soil → human (direct contact) are not mapped for PFAS in the new version of the Federal Soil Protection and Contaminated Sites Ordinance (BBodSchV) [321]; the BMUV guideline [319] considers exposure via plants to be relevant, but does not yet specify any assessment standards. In a recent study by the German UBA, the transfer of PFAS into plants was investigated in more detail [322]: it confirmed the chain-length dependence of the transfer into the plant (see “[Bioconcentration and biomagnification in the food chains](#)” section). However, the uptake of PFAS by plants is also strongly influenced by plant species and soil properties. Therefore, test values for this impact pathway have not yet been proposed. The BMUV describes the impact pathway soil → human (direct contact) as not relevant. However, this assessment should be reviewed for the use scenario “children’s play areas” with regard to the EFSA TWI value.

For PCDD/PCDF and dl-PCB, besides contaminated feed the input pathway soil → chicken → egg → human contributes significantly to human exposure to these chlorinated hydrocarbons [323, 324]. This can apparently also be the case for PFAS. A recent Danish study identified contaminated fishmeal as the main source of PFAS burdens in chicken eggs [325, 326]. Since in this case the fishmeal only contributed to the feed by about 5%, the study emphasizes the importance of feed for the human intake via animal products. In contaminated areas, free-range chickens and their eggs should be monitored in addition to crops grown, grazing and wild animals. Good advisory can help to reduce the input via this pathway

and thus the exposure of people living in these areas [327].

In the USA the EPA recently published the proposal to include cases of damage caused by PFOA and PFOS in the so-called superfund. This would implicate that—if the polluters are not able to carry the costs of remediation—financial means of the federal state will be available [328]. In Europe, as a rule, polluters of PFAS contamination are not yet required to finance the remediation. Even where polluters could be held responsible, the very high remediation costs quickly reach the limits of their capacity, so that the costs have to be borne by the general public.

Extensive financing and funding concepts as well as research programs for the development of efficient remediation methods are required. Legal conditions should also be created so that PFAS producers contribute to the costs of necessary remediation measures. It should be considered that the polluter-pays principle is a central element in EU legislation laid down in the EU treaties. Thus, producers of PFAS and PFAS-containing products should be responsible for related damages of health and environment.

In the USA the legal situation is different from Europe. More than 6400 lawsuits are submitted to court since 2005 when citizens sued the producers or companies manufacturing products treated with PFAS, e.g. firefighting foams or impregnated shoes or carpets. The firms are charged to be liable for health problems of citizens. It is not clear how the majority of courts will decide but this challenge may jeopardize the existence of some firms [329]. 3M, an important former PFOS producer, already paid more than 1 billion US \$ in the USA. In 2022, 3M has committed € 571 million for various measures related to PFAS damage emanating from the Zwijndrecht plant in Belgium [330, 331].

Purification of PFAS-contaminated water

The purification of PFAS-contaminated water is complex, only effective to a limited extent and expensive. Both, drinking water treatment and the remediation of contaminated groundwater, therefore, face major challenges. In a publication of the German UBA, Held and Reinhard give an overview of the different processes and their strengths and weaknesses [61, 62]. As Li et al. point out, treatment of short-chain PFAS is usually even less effective than for long-chain homologues [86].

Activated charcoal is primarily used as an adsorbent. However, what has proven successful in groundwater remediation of other organic pollutants such as chlorinated hydrocarbons as well as polycyclic aromatic hydrocarbons (PAHs), has limitations when it comes to PFAS. The loading of the activated charcoal to the point of a breakthrough is low, especially for

short-chain PFAS. Long residence times in the filters are required to reach the required low PFAS concentrations, which necessitates very large plants. In addition, the loaded activated charcoal must either be sent as waste to a high-temperature incinerator or regenerated in rotary kilns and the resulting off-gas stream fed to an afterburner at correspondingly high temperatures. In contrast, ion exchange resins are more effective for short-chain anionic compounds, which is why Riegel recommends a combination of both processes [332]. However, the loading density of the exchange resins is also often low and regeneration is limited.

Membrane processes such as nanofiltration and reverse osmosis are being tested as alternatives, e.g. in comparative studies for the purification of groundwater at Nuremberg Airport [333]. The effectiveness is often insufficient and questions arise about the service life of the membranes and the treatment of the concentrates [334].

Highly contaminated waters such as industrial wastewater or landfill leachate often require pretreatment before they are further purified, e.g. by sorption processes. For example, precipitation of the anionic PFAS with cationic liquid polymers such as perfluorAd^R is suitable for this purpose [334–336]. The process of ozofractionation, in which fine ozone bubbles cause enrichment at interfaces and oxidation of precursors, is apparently effective [61, 62, 337]. The process is commercially available. Furthermore, sonolysis, in which PFAS accumulate in cavitation bubbles that are formed under the influence of ultrasound, is an interesting approach [61, 62].

For the treatment of concentrates from the membrane processes, from regeneration of ion exchange media, and from ozofractionation, electrochemical oxidation can be considered, which is still under development [338]. Various anode materials such as boron-doped diamond [333] or titanium suboxide [339] are used. The process proves to be very effective, but perchlorate and bromate are formed as by-products [338] and an increase of the AOX value is measured [333]. Deposits on the anode can reduce the service life. Thus, the practicality of the process has not yet been proven. Krause et al. tested the treatment of PFAS-contaminated waters by oxidation with supercritical water at 590 °C and 24 MPa resulting in high effectivity [340]. Singh et al. achieved similar positive results using a non-thermal plasma reactor [341]. Both methods are new approaches, the suitability under real-world conditions remain to be proven.

A comprehensive comparison of the energy required for the aforementioned processes is still pending. CONCAWE has evaluated several processes in terms of their energy requirements and costs [337].

Finally, several processes achieved good results on a laboratory scale, but still have a long way to go for

real-world applications. These include extraction of PFAS with ionic liquids [342], reductive defluorination with UV, sulfite, and iodide [343] or UV and hydrogen [344], and the use of zeolites as sorbent media in combination with activated peroxodisulfate [345]. Electrocoagulation of PFAS agglomerates with zinc hydroxide [61, 62] and electrosorption on activated charcoal fleeces (with subsequent desorption) [346] are also still at an experimental stage.

Regulation of PFAS

The recognition that chlorofluorocarbons (CFCs) damage the ozone layer in the stratosphere led as early as 1987 to the adoption of the Montreal Protocol, the most successful global agreement on the restriction of substances. With the Kigali Amendment in October 2016, climate-damaging hydrofluorocarbons were also covered by this agreement [347]. The listed substances are banned or severely restricted worldwide.

The longer-chain PFAS only later came into the focus of international attention. The Stockholm Convention, which restricts or bans persistent organic pollutants (POPs), now includes PFOA and PFOS, along with precursors compiled by the POP Review Committee [348], among the substances whose production and use is to be eliminated worldwide. Only a few applications are still permitted for a limited period. In June 2022, the Conference of the Parties decided to add PFHxS with related compounds to the list of substances to be eliminated (Annex A). Long-chain perfluorocarboxylic acids (C9–C14) are also proposed for inclusion as POPs [348]. The Basel Convention, which regulates transboundary shipments of hazardous wastes, sets maximum levels for wastes containing POPs [1]. PFAS are also among the prominent issues in other international forums such as in Strategic Approach to an International Chemicals Management (SAICM) as issue of concern [349] and in OECD.

The EU has transposed these international agreements into European law. In addition, the perfluorinated carboxylic acids C9–C14 as well as HFPO-DA and several other PFAS like PFBS, PFHxS or PFHpS together with their salts are included in the Candidate List of Substances of Very High Concern (SVHC) under the REACH Regulation [350], which means that their uses will require authorization in the future. Regulation of PFHxA and spray application of a polyfluorinated silane is currently being prepared. In the future, the EU intends to regulate PFAS in a way that is no longer single-substance related, but encompasses as many representatives as possible. The ECHA submitted a proposal in March 2022 to gradually ban the production and use of all PFAS in fire-extinguishing foams at a concentration > 1 ppm within

10 years [305]. Germany, the Netherlands, Denmark, Norway and Sweden are working together on a restriction for the entire substance group of PFAS, including fluorinated polymers. This would implement an EU project on the “Chemicals Strategy for Sustainability” [35]. The proposal has been published by ECHA in February 2023. It is expected that time-consuming negotiations will follow and slow down the process for several years.

The inclusion of fluoropolymers in the restriction of PFAS is controversial. The manufacturers consider fluoropolymers as ‘polymers of low concern’ (PLC) because they were inert, non-bioavailable, and non-toxic [20, 351] and met all the criteria to be considered harmless polymers not requiring regulation. In addition, they argue that these polymers were not substitutable in many applications due to their special properties [20]. In contrast, Lohmann et al. include manufacturing and waste disposal in their assessment [8]. They refer in particular to the use of PFOA or fluorinated substitutes as emulsifiers during manufacture, emissions during the use phase, e.g., when heated strongly, and problems with the disposal of polymer-coated products such as frying and baking pans. These are often not recycled at sufficiently high temperatures (e.g., molten metals) leading to extensive decomposition but not mineralization of the fluoropolymers. From their point of view, fluoropolymers are ‘polymers requiring registration’ (PRR) [352] and should be included in the evaluation of PFAS as a group of substances. A discussion on the potential benefits and risks of fluorinated polymers as well as knowledge gaps are given by Wahlström et al. [9].

In a recent analysis OECD published current knowledge on side-chain fluorinated polymers with acrylates, urethanes, oxetanes, ethoxylates and siloxanes as backbones [353]. These polymers have a wide application range from surface protection (e.g. acrylates and urethanes), surfactants (ethoxylates), wetting agents (oxetanes) to lubricants and medical applications (siloxanes). Although information is limited due to confidentiality and no reporting requirements, they may contain non-polymer unreacted raw material or reaction by-products. In addition, some of them may hydrolyze and release the side chains. This underpins the necessity to include them in the assessment of the PFAS as a group.

It is not only the EU that is trying to get a regulatory grip on the risks and burdens of PFAS. For example, various states in the USA have enacted regulations to restrict or ban the manufacture and use of PFAS-containing consumer products [354, 355].

Because European law governs the restriction and prohibition of chemicals, national regulation by EU member states is rare. Denmark has largely banned the use of PFAS in food contact materials and set an indicator level

of 20 mg F/kg in packaging materials [356]. However, member states play an important role in implementing and monitoring European requirements. For example, the French government’s new PFAS action plan calls for increased control and reduction of emissions from PFAS-processing plants and more monitoring of environmental and population exposure [357].

From the EFSA publication of a TWI of 4.4 ng/kg bw for the sum of the four PFAS most prominent in human serum (see “[Toxicological evaluation](#)” section) a drinking water limit of 2.2 ng/L would be derived. This means that about 29% of German drinking water supplies would be affected [358]. When compared to existing limit and guideline values, obviously there is a need to review their compatibility with this toxicologically justified assessment. The new limit of the EU Drinking Water Directive for the sum of 20 individual substances (perfluoroalkyl carboxylic and -sulfonic acids, C4–C13) is set to 100 ng/L [269]. A preliminary finding suggests that the levels of about 3.7% of drinking water in Germany may exceed this limit [358]. In a draft ordinance of the German Federal Government, a drinking water limit value of 20 ng/L for the sum of the four individual substances evaluated by EFSA is additionally envisaged [359]. The value of 100 ng/L for PFOA and PFOS proposed by the WHO in its draft report is significantly higher. This is explained by the difficulties in purifying contaminated raw water [223]. Denmark already set a limit of 2 ng/L for the sum of the four EFSA substances in 2021 [360]. Furthermore, the new interim health advisories of the US EPA of only 0.004 ng/L PFOA and 0.02 ng/L PFOS in drinking water [361] exceed the limits of currently available routine analysis by far (see “[Analysis of per- and polyfluorinated alkyl substances](#)” section). Effects on the immune system, the cardiovascular system, birth weight and cancer are mentioned as relevant endpoints from human studies [229, 361]. These extremely low values—though toxicologically founded—will concern nearly all raw waters and cannot be achieved by purifying techniques in practice.

Steenland et al. arrive at similarly low values, calculating an extremely high slope factor of 12.8 per $\mu\text{g}/\text{kg}$ bw and day (assumed PFOA half-life in serum 2.3 a) for renal cancer incidence on the basis of a pooled analysis of human serum levels from two studies. This corresponds to a value of only 0.0015 ng/L (1.5 ppq) in drinking water [208], a value in the background exposure range.

The US EPA additionally set final health advisories for PFBS of 2000 ng/L (2000 ppt) and for HFPO-DA of 10 ng/L (10 ppt) in drinking water [361].

Also in need of updating are, for example, the German limit value for sewage sludge of 100 $\mu\text{g}/\text{kg}$ dm for the sum of PFOS and PFOA with regard to application on arable land [362] and the German Insignificance Thresholds

for Groundwater, given for seven individual PFAS [320]. Thus, also the Federal Soil Protection and Contaminated Sites Ordinance (BBodSchV) of 2021, which comes into force in August 2023, refers to the same PFAS thresholds as standards for the impact pathway soil → groundwater [363]. With respect to surface waters, current EU environmental quality standards (EQS) for PFOS are 9.1 µg/kg fm of fish and shellfish and 0.65 ng/L in freshwater [364]. An EQS of 4.4 ng/L for freshwater and groundwater is being considered for the sum of 24 PFAS by the EU Commission in a draft directive based upon the RPF of the individual PFAS (see “[Toxicological evaluation](#)” section [224]). The 24 listed PFAS include in excess of the perfluorinated carbonic and sulfonic acids some telomeric alcohols and fluorinated carboxylic acids [365]. The RPF values will be used, similar to the practice with the “toxicity equivalence factors” (TEFs) for PCDD/PCDF. This would be a helpful approach given the multitude of PFAS found in diverse bodies of water.

In contrast to the aforementioned regulations, the German UBA drinking water guideline value of 60 µg/L for TFA [262, 263] is many times higher as a “precautionary-based maximum value when toxicological data are not complete”. However, the long-term effects of persistent and mobile TFA in the environment are so uncertain that the UBA itself in a background paper considers it necessary to regulate TFA inputs to the environment (see “[Ultra-short-chain PFAS—trifluoroacetic acid](#)” section). In this context, particular reference is made to the difficulty of TFA retention in drinking water treatment [30].

Overall, the limit and guideline values are inconsistent. Sometimes they refer to specific individual substances (especially PFOA and PFOS), sometimes it is a sum value of up to 20 individual substances that must be monitored. A uniform basis for assessment is not apparent. There is an urgent need to move towards sum values for the PFAS that are widely used, also including the perfluoroether acids ADONA, C6O4 and HFPO-DA, which are being increasingly used as PFOA substitutes. Even if sufficient toxicological and/or monitoring data are not yet available for some individual substances, they should be included to prevent inappropriate substitution within the diversity of PFAS.

Fluorinated alternatives of PFOA and PFOS—regulatory gaps

The need to effectively restrict PFAS as an entire group of substances is evident, among others, when considering the properties of alternatives to PFOA and PFOS, including their precursors. Three trends can be identified: (i) replacement by short-chain PFAS, especially C4 compounds such as PFBA and PFBS;

(ii) replacement by polyfluorinated telomeric carboxylic or sulfonic acids such as 6:2 or 8:2 FTS and FTA; and (iii) replacement by perfluorinated oxocarboxylic acids such as ADONA, HFPO-DA, or C₆O₄. A Chinese study presented the sources, distribution, and toxicological and ecotoxicological characteristics of several fluorinated substitutes [366]. For example, many Chinese electroplating companies apparently substitute PFOS with 6:2-chloroperfluoroether sulfonate (F-53B), which is now detected in the environment and in organisms at concentrations similar to PFOS. Wang et al. published a review of alternatives in various applications already in 2013 [2]. They found that publicly available knowledge on the properties of these compounds is extremely sparse. In particular, production and volumes used are also unknown. More accurate figures are generally not publicly available because they are declared as confidential business information (CBI). Monitoring and regulation of PFAS is complicated by the fact that very much information is not freely available and often forensic activities are needed to obtain a clear picture [10]. For example, the manufacturer of C6O4 refused to allow other companies to synthesize this substance as an analytical reference standard [286]. US EPA scientists did not have analytical standards or further information from the manufacturers on chloroperfluoropolyether carboxylates (ClPFPECAs) measured at high concentrations in soil around two chemical plants in New Jersey [316]. Meanwhile, New Jersey has established groundwater quality standards for these substitutes in fluoropolymer production [367]. ClPFPECAs are not only a problem in the USA but also in Europe. In a tributary of the River Po (Italy), this substance was detected downstream of a fluoropolymer production plant [368].

Conclusions

PFAS are a group of substances consisting of several thousand chemicals that are of wide use in the technosphere. They have one characteristic in common: they are counted among the “forever chemicals” because they are characterized by an exceptionally high persistence over decades to centuries. Some are transformed in the environment, but a perfluorinated residue always remains. There is no complete mineralization. However, many PFAS are not inert. On the contrary, toxicological and ecotoxicological data, especially of the most intensively studied perfluorinated carboxylic and sulfonic acids, show that adverse health effects occur even at very low doses or concentrations.

PFAS are toxic to fish and amphibians in the first life stages as well as to invertebrates and to insects in the low $\mu\text{g/L}$ range. Ecotoxic effects of various PFAS on trophic levels and the individual species are triggered by activation of nuclear receptors, oxidative stress or direct interaction with membranes. This is followed by changes at the tissue level with disturbances of thyroid function, fatty liver or cell death, with toxic reproductive effects on fertility, hatching rates, embryonic development or motor functions. Algae and terrestrial organisms are usually less sensitive to these substances.

Long-chain PFAS accumulation in aquatic organisms and biomagnification in terrestrial food chains lead to increasing internal PFAS exposure levels in living organisms, including humans. This is enhanced by irrigation of agricultural land or topping up fishponds with polluted water.

Many PFAS bioaccumulate in the food chains and are excreted only slowly. Some PFAS are highly mobile in the hydrologic cycle and are now found even in polar regions far from sources of emission. These properties have led to ubiquitous occurrence: in biota, in water and soil, in outdoor and indoor air, and in the human body. Legacy contaminated sites are particularly serious, often resulting from the use of PFAS in fire-extinguishing foam and from chromium plating in electroplating facilities, endangering drinking water supplies and crop production. The costs for the remediation of PFAS contamination are usually very high. In most cases in Europe, these are paid for by government authorities. However, the polluter-pays principle laid down in the European treaties places the primary responsibility on the manufacturers of the harmful substances. They should therefore contribute more to the financing of the remediation.

In rodent studies, PFOS and PFOA apparently act as liver tumor promoters. The findings on human exposure to PFAS show effects on the immune system, a dose-dependent reduction in birth weight of children (PFOA, PFOS) as well as a negative association of birth size of newborns towards longer-chain PFAS, a correlation between population exposure to PFAS and chronic kidney disease, as well as endocrine activity and here in particular the influence of PFAS on the extensively effective homeostasis of thyroid hormones. Long-lasting exposure may lead to development of kidney or testes cancer, as shown in animal and epidemiological studies. The occurrence of PFAS in breast milk and the uptake of PFAS by the breastfed infant must also be viewed critically.

The EFSA-derived TWI value of 4.4 ng/kg bw for the sum of the four PFAS PFOS, PFOA, PFNA and PFHxS should be regarded as the current benchmark for limit and guideline values with regard to the assessment of PFAS contamination with potential human exposure.

However, the present evaluation leaves open the consideration of other PFAS present in serum, for which no feasible approach is currently known. If future toxicological evaluations show different decisions, e.g., by the US EPA or the WHO, these should be considered. The proliferation of different guideline and limit values on different, often outdated scientific bases has to be purged. Overall, however, it must be remembered that limits or maximum levels only correspond to peak exposures. Although food and drinking water may contain PFAS, at levels below these limits they continue to be marketable and therefore continue to result in consumer exposure to PFAS. The minimization requirement embedded in drinking water protection therefore calls for the avoidance of contamination even below limit values, especially in the case of persistent and bioaccumulative substances. It should also be borne in mind that both humans and the environment are exposed to a large number of potentially harmful substances—over and above PFAS—which often interact in an additive manner. Appropriate risk assessment procedures for mixtures of substances have been under discussion since some years [369]. In its Chemicals Strategy for Sustainability, the EU Commission proposes the introduction of a ‘mixture assessment factor’ (MAF) [35]. Concentrations of 12 PFAS in blood plasma of 3- to 17-year-old children exceeded the HBM-I levels of PFOS and PFOA (2 and 5 ng/ml, respectively) in 21% or 7.3%, respectively, below which no adverse health effects are expected. In this respect, the management of existing contamination is a problem and the inputs of PFAS into the environment and food chains need to be urgently minimized.

The monitoring of direct releases (e.g. emissions from exhaust gas and exhaust air from industry), resulting in the contamination of environmental media, biota, food and humans, and of the distribution and effects of PFAS must be significantly intensified and expanded. This concerns both the variety of PFAS investigated and the media studied. This is especially true since the long-lived PFAS will remain detectable in the environment for at least several decades after a phase out and will also result in damage to future generations via epigenetic effects. Drinking water sources should be tested annually for PFAS, both in raw water and tap water, at least for the 20 PFAS individual substances listed in the EU Drinking Water Directive, and additionally relevant polyfluorinated compounds, each with a limit of quantification of 0.5–1 ng/L. A corresponding requirement should also apply to all spa and mineral water sources.

Figure 5 summarizes the pathways of PFAS emissions into the environment and their distribution in environmental media, humans, biota and food.

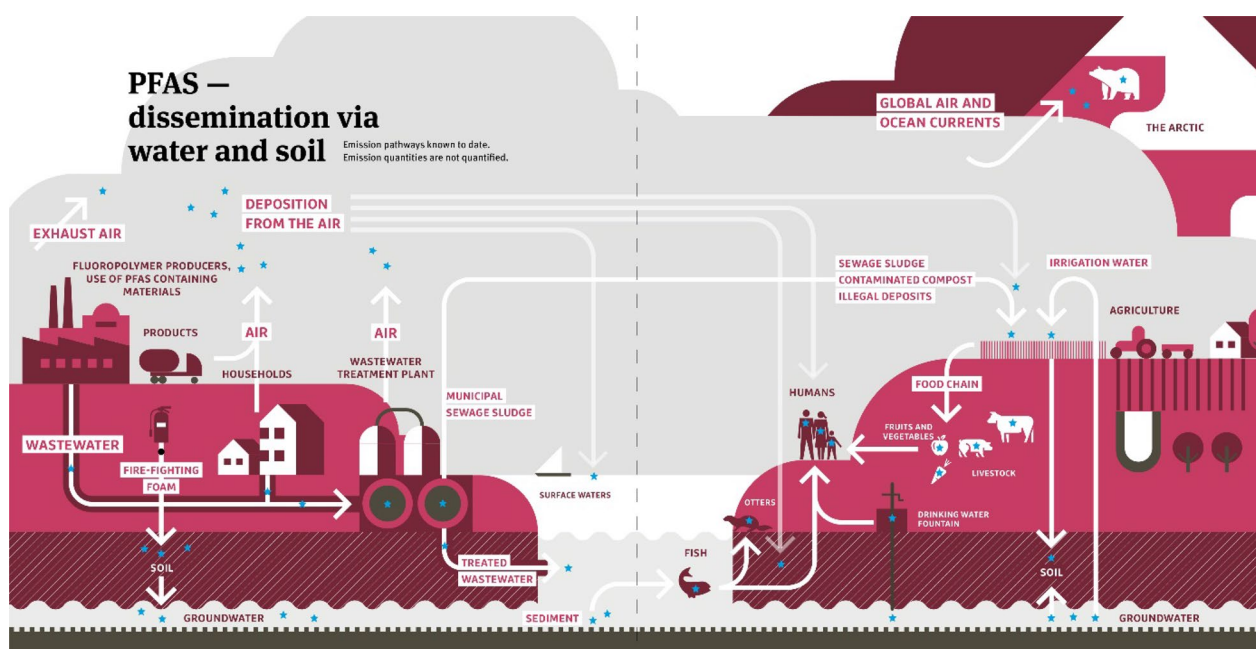


Fig. 5 Dissemination of PFAS via water and soil © UBA [122]

As the main intake of PFAS for newborns and infants is via breast milk, breastfeeding mothers should be advised and given the opportunity to have their breast milk tested for at least the four EFSA PFAS considered particularly relevant (PFOS, PFOA, PFHxS, PFNA).

Further development and validation of analytical methods are necessary for monitoring. The diversity of PFAS and the need to detect them at very low concentrations in the environment, in food and in body fluids are a challenge to the development of powerful chemical analytical methods. In particular, efforts should be made to expand and optimize extraction methodology for soil and other solid environmental media as well as for products and wastes. It will also be essential to optimize and standardize the determination of the sum parameters TOP, AOF and EOF for liquid and solid media, to significantly expand single-substance analysis, and to improve sensitivity. The development and validation of suitable sampling methods for waste gas and exhaust air are priorities for further development. They should allow complete coverage of at least per- and polyfluorinated alkyl carboxylic and -sulfonic acids as well as oxo carboxylic acids and their transformation products. A limited number of representative PFAS lead substances should be defined, which allow the release of PFAS and their fragments to be determined in the off-gas of thermal plants, e.g. waste incineration, even at low concentrations, with validated sampling and analysis. According to current knowledge,

at least PFOA, PFNA, PFHxS, PFOS as well as TFA and PFPrA should be measured.

PFAS and their replacement by fluorine-free alternatives are a challenge for scientific research. This concerns the development of fluorine-free alternatives for applications that are still essential today as well as the scientific derivation of limits and guideline values for further exposure-relevant PFAS. This is particularly important in regard to tolerable intakes for short-chain PFAS and fluorinated oxo carboxylic and -sulfonic acids in connection with their accumulation in crops.

Finally, there is an urgent need for research with regard to the remediation of legacy contaminated sites and the purification of contaminated soils and waters. The methods available to date are often not effective or are still being developed and tested. In the case of major incidents such as those at Rastatt or Dordrecht, the only possible action will be to prevent the further spread of contamination. In these cases, targeted remediation does not appear to be possible in view of the dimensions involved. This also applies to the possibilities for treating drinking water. To ensure that the high remediation costs do not have to be borne by the general public, the polluters of PFAS contamination must be consistently called to account and the legal conditions for the involvement of PFAS producers must be created.

There are many unanswered questions about the safe disposal of PFAS-contaminated waste. The recovery of PFAS-contaminated products during recycling leads to

the carryover of PFAS into secondary raw materials and thus endangers the circular economy. To prevent carryover into secondary products or improper disposal, it will be helpful if manufacturers of PFAS containing articles take back their products after use as an aspect of extended producer responsibility. These products for essential uses may include e.g. medical protective clothing and coated equipment or workpieces.

The destruction of PFAS in waste incinerators and the elimination of PFAS and their downstream products from the waste gas stream of incinerators need to be studied in more detail. Facilities are needed in which the temperatures used result in complete destruction of the fluorochemicals or where the downstream products are effectively removed from the waste gas stream.

The industry countered the growing knowledge about the risks of the now regulated perfluoroalkyl carboxylic and sulfonic acids by substituting them with other PFAS: Short-chain PFAS replaced long-chain, per- and poly-fluorinated telomeric acids and oxo carboxylic and sulfonic acids replaced PFOA and PFOS. These substitutes are also highly persistent or transformed into highly persistent substances. More detailed studies mostly showed that their risk profile differs little from PFOA and PFOS.

Short-chain PFAS accumulate less in aquatic food chains but are even more mobile in soil and groundwater and accumulate more in plants. TFA poses a particular problem because it enters the environment primarily through the degradation of refrigerants such as R1234yf and of pesticides and pharmaceuticals containing CF₃ groups. Concentrations of the “forever chemical” TFA in the environment are increasing rapidly. Therefore, urgent measures are needed to restrict substances from which TFA can be generated.

Measures to reduce risks and ban individual PFAS cannot be a solution. The properties of PFAS make it clear that these substances are not manageable, and everything must be done to avoid them. Finally, total elimination must be the ultimate goal. Correctly, the EU intends to regulate the entire group of substances. Environmental organizations such as Friends of the Earth (FoE) Germany are calling for a phase out of all PFAS uses by 2030, with priority given to consumer-related applications [370]. The use of fluoropolymers should also be restricted as far as possible. Some applications based on the special technical properties of PFAS are essential and will not be readily substitutable. For these essential uses, best available techniques (BAT) should be used to ensure that exposure to humans and the environment is minimized. Also, product labeling could be a means to rapidly reduce the use of PFAS in near-consumer applications.

Considering that ‘legacy PFAS’ such as PFOA and PFOS are mostly replaced by less intensively studied

PFAS, the restriction of the whole group of substances is a regulatory challenge. The example of chloroperfluoropolyether carboxylates (CIPFPECAs; see “[Regulation of PFASs](#)” section) shows that many substitutes are not even known. More transparency will be essential for an effective restriction. Gold and Wagner see this case as a glaring example of regulatory deficits in the USA but also in the EU, where CIPFPECAs have not yet been registered under REACH [371].

PFAS are a worldwide problem. Regulation and reduction of PFAS applications, therefore, also require a global approach to solutions, e.g. via SAICM and the Stockholm and Basel Conventions. PFAS contribute significantly to exceeding planetary boundaries for chemical contaminants. Based on the concept of Rockström and Steffen [372, 373], Persson et al. stated that, in terms of ‘novel entities’, humanity is outside the ‘safe operating space’ [374]. Given that PFAS levels in e.g. rainwater globally exceed health-based guidance levels, Cousins et al. conclude that these fluorochemicals are an example of earth system overload [81]. They even propose an own planetary boundary for PFAS. However, it might not be the appropriate solution to combat the overload of the earth system by setting individual planetary boundaries for each problematic substance group. The exceedance of the boundary for ‘novel entities’ is also caused by the worldwide increase of material streams and chemicals production. PFAS contribute to this overload and contradict sustainability criteria. Thus, they require stringent global regulation [375].

However, reducing the use of PFAS as quickly as possible cannot be achieved just by government bans and restrictions. PFAS manufacturers and commercial users as well as trading companies are called upon to identify PFAS applications that can be dispensed with and to offer and use alternatives. The announcement of the producer 3M to stop its PFAS production and use by the end of 2025 is an encouragement that phase out PFAS might be reality in near future [376]. The identification of fluorine-free alternatives will only succeed with a joint effort of manufacturers, commercial users and research. Government recommendations and incentives can accelerate the process. Better transparency is particularly important for informing downstream users and private consumers: much information that is relevant and helpful to commercial and private users should not be considered as confidential and should be available for fact-based information.

The need for comprehensive regulation of PFAS, ideally on a global basis, arises not only from the burdens on health and the environment. Urgent action is also required from an economic point of view. This is shown by a publication of the Nordic Council of Ministers on

estimating the health and environmental costs to society associated with PFAS exposure. According to this, the annual health costs caused by PFAS are estimated to be 52–84 billion € per year in the European economic region alone [377]. Corder et al. come to a similar conclusion for the USA: their estimate is US \$37–59 billion annually in health costs alone, not counting societal costs for water treatment, remediation of legacy contaminated sites, etc. [378]. Obsekov et al. calculated health costs of at least US \$5.5 billion in 2018 for PFOA and PFOS in a differentiated analysis [379]. Thus, inaction comes at a higher cost in the medium term compared to phase out the PFAS.

Summarizing there is an obvious need for urgent action. According to current knowledge, the contamination of the environment and of humans with PFAS has already reached a level that makes adverse effects probable. PFAS will remain for decades or centuries. It will only be possible to remediate some hotspots of contaminated sites and to reduce human exposure where it is much too high. Maybe some techniques to decontaminate PFAS-containing products or to dispose them of safely will be developed in future. However, the widespread uses of PFAS and the various pathways of entry into the environment makes it necessary to phase out PFAS as quickly and as completely as possible in order to avoid further increasing contamination.

13 Reasons towards a complete phase out of PFAS

1. PFAS are a group of several thousand chemicals of multiple uses and exceptionally high persistence (“forever chemicals”).
2. PFAS are toxic to fish and amphibians in the first life stages as well as to invertebrates and to insects in the low µg/L range.
3. Accumulation of long-chain PFAS in aquatic organisms and biomagnification in terrestrial food chains lead to increasing internal PFAS exposure levels in living organisms, including humans.
4. Many PFAS bioaccumulate, some are highly mobile. These intrinsic properties have led to ubiquitous occurrence.
5. In rodent studies, PFOS and PFOA act as liver tumor promoters. Studies on human exposure to PFAS have revealed a (possible) relationship to a lot of different toxicity endpoints. Already in early pregnancy—the developmental stage with highest susceptibility—PFAS act on the developing human fetus because they virtually reach every fetal tissue. These substances with high

accumulation in kidney and liver can influence the development of organs. Long-lasting diseases of liver and kidney as well as severe immunotoxicity may be a consequence. Moreover, cancer of kidney and testes may develop years later.

6. Although the EFSA tolerable weekly intake (TWI) of 4.4 ng/kg bw for the sum of four PFAS is currently being regarded as benchmark, there are substantial gaps of knowledge. These may only be filled by applying new approaches but will not cover the whole number of PFAS. Overall, however, it must be remembered that limits or maximum levels only correspond to peak exposures. Although food and drinking water may contain PFAS at levels below these limits, they continue to be marketable and therefore continue to result in consumer exposure to PFAS.

7. PFOS and PFOA replacement by newly developed per- or polyfluorinated PFAS also pose risks because they have been shown to be persistent or transformed into persistent substances.

8. Short-chain PFAS are persistent, too. They are highly mobile in soil and groundwater and accumulate in plants. TFA enters the environment primarily through the degradation of refrigerants and of pesticides and pharmaceuticals containing CF₃ groups. Its concentration in the environment is increasing rapidly.

9. The monitoring of PFAS releases and contamination of environmental media, biota, food and humans must be significantly intensified and expanded to cope with the increasing number of persistent PFAS.

10. Current analytical methods are not sufficient to cover the variety of PFAS with a broad range of properties.

11. Remediation of legacy contaminated sites and purification of contaminated soils and waters require huge efforts, and more and more PFAS-contaminated sites with a variety of PFAS are discovered, whose properties are hardly known.

12. The current annual health costs caused by PFAS are estimated in the range of already 40–80 billion € in Europe and the USA, respectively.

13. Measures to reduce risks and ban individual PFAS is not a solution, since they will be substituted by other less investigated PFAS with similar properties. These substances are not manageable, and all efforts should be undertaken to avoid them as completely as possible.

Therefore, much more global restrictions as soon as possible are necessary with the aim of a complete phase out of the whole group of PFAS. Global research efforts are needed towards the development of alternatives for the vast number of technical applications.

Abbreviations

5H 4:1 FTOH	1H,1H,5H-Perfluoro-1-pentanol	HILIC	Hydrophilic interaction liquid chromatography
6:2 FTS	6:2 Fluorotelomer sulfonic acid	HR-CS-GFMS	High resolution-continuum source-graphite furnace molecular absorption spectrometry
6:2 FTOH	1H,1H,2H,2H-Perfluorooctanol	IARC	International Agency for Research on Cancer
8:2 FTOH	1H,1H,2H,2H-Perfluoro-1-decanol	LC-HRMS	High performance liquid chromatography coupled to high-resolution mass spectrometry
10:2 FTCA	2H,2H-Perfluorododecanoic acid	LC-MS/MS	High performance liquid chromatography coupled to tandem mass spectrometry
ADONA	Perfluoro-4,8-dioxa-3H-nonanoic acid, ammonium salt	LDL	Low density lipoprotein
ADHD	Attention deficit hyperactivity disorder	LOD	Limit of detection
ADI	Acceptable daily intake	LOQ	Limit of quantification (= limit of determination)
AFFF	Aqueous film-forming foam	MAF	Mixture assessment factor
ASD	Autism spectrum disorder	NAFLD	Non-alcoholic fatty liver disease
ALT	Alanine aminotransferase (EC 2.6.1.2)	NOAEL	No observed adverse effect level
AOF	Adsorbable organically bound fluorine	NOEC	No observed effect concentration
AOX	Adsorbable organically bound halogen	NTF2	Bis(trifluoromethylsulfonyl)-imide
ATSDR	Agency for Toxic Substances and Disease Registry at Center for Disease Control (CDC)	OECD	Organisation for Economic Cooperation and Development
BAF	Bioaccumulation factor	PAH	Polycyclic aromatic hydrocarbons
BAT	Best available techniques	di-PCB	Dioxin-like polychlorinated biphenyls
BCF	Bioconcentration factor	PBPK	Physiologically based pharmacokinetic modeling
BfR	German Federal Institute for Risk Assessment	PBT	Persistent, bioaccumulative, toxic
BMD	Benchmark dose	PCDD/PCDF	Polychlorinated dibenzo-p-dioxins and dibenzofurans
BMDL ₁₀	Benchmark dose lower limit for a 10% response	PFAS	Per- and polyfluorinated alkyl substances
bw	Body weight	PFBA	Perfluorobutanoic acid
C6O4	Perfluoro- <i>o</i> -acetic acid, 2-[(5-methoxy-1,3-dioxolan-4-yl)oxy], ammonium salt	PFBS	Perfluorobutane sulfonic acid
CBI	Confidential business information	PFCA	Perfluoroalkane carboxylic acid
CEN	Comité Européen de Normalisation (European Committee for Standardization)	PFDA	Perfluorodecanoic acid
CFC	Chlorofluorocarbon	PFDoDA	Perfluorododecanoic acid
CIC	Combustion ion chromatography	PFHpA	Perfluoroheptanoic acid
CIPFPECA	Chloro perfluoropolyether carboxylate	PFHxA	Perfluorohexanoic acid
CKD	Chronic kidney disease	PFHxS	Perfluorohexane sulfonic acid
dm	Dry matter	PFNA	Perfluorononanoic acid
ECHA	European Chemicals Agency	PFOA	Perfluorooctanoic acid
EFSA	European Food Safety Authority	PFOS	Perfluorooctane sulfonic acid
EOF	Extractable organically bound fluorine	PFPE	Perfluoropolyether
EQS	Environmental quality standard	PFPrA	Perfluoropropanoic acid
eGFR	Estimated glomerular filtration rate	PFT	Perfluorinated tensides
EtFOSA	<i>N</i> -Ethyl perfluorooctane sulfonamide	PFTeDA	Perfluorotetradecanoic acid
EtFOSE	<i>N</i> -Ethyl perfluorooctane sulfonamidoethanol	PFTrDA	Perfluorotridecanoic acid
EU	European Union	PFUnDA	Perfluoroundecanoic acid
FAP	Tris(pentafluoroethyl)-trifluorophosphate	PLC	Polymer of low concern
fm	Fresh matter	PMT	Persistent, mobile, toxic
FTA	Fluorotelomeric carboxylic acid	POP	Persistent organic pollutant
FTOH	Fluorotelomeric alcohol	PRR	Polymer requiring registration
FTS	Fluorotelomeric sulfonic acid	PPAR α	Peroxisome-proliferator-activated receptor alpha
GenX	HFPO-DA and its ammonium salt	PTFE	Polytetrafluoroethylene
GFR	Glomerular filtration rate	REACH	Registration, Evaluation, Authorization and Restriction of Chemicals (EU Regulation)
GFS	Geringfügigkeitsschwellenwerte (insignificance thresholds)	RPF	Relative potency factor
H4PFOS	Tetrahydroperfluorooctane sulfonic acid (identical with 6:2 FTS)	SAICM	Strategic Approach to an International Chemicals Management
HBM	Human biomonitoring value	Slope Factor	Cancer risk (proportion affected) per unit of dose
HBM4EU	European Human Biomonitoring Initiative	SPE	Solid phase extraction
HDPE	High-density polyethylene	SVHC	Substance of very high concern
HFC	Hydrofluorocarbon	T4	L-Thyroxin
HCFC-123	1,1,1-Trifluoro-2,2-dichloroethane	TDI	Tolerable daily intake
HFPO-DA	2,3,3,3-Tetrafluoro-2-(heptafluoropropoxy) propanoic acid	TEF	Toxicity equivalence factor
		TFA	Trifluoroacetic acid
		TFMS	Trifluoromethane sulfonic acid
		TOF	Total organically bound fluorine
		TOP	Total oxidizable precursor
		TTR	Transthyretin
		TRE	Thyroid responsive element
		TWI	Tolerable weekly intake
		UBA	Federal Environment Agency (of Germany)
		UPB	Environmental Specimen Bank (Umweltprobenbank)
		US EPA	Environmental Protection Agency (of USA)
		WHO	World Health Organization

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Author contributions

GA and HB: biological effects of PFAS on experimental animals and on humans, toxicological evaluation, human exposure from food, GR: bioconcentration and biomagnification in the food chains, ecotoxicological effects, ultra-short-chain PFAS, trifluoroacetic acid, KS: pathways into and occurrence in the environment, ultra-short-chain PFAS, trifluoroacetic acid, regulation of PFAS, coordination of the manuscript, WK: analysis of PFAS, IV: PFAS-contaminated sites, purification of PFAS-contaminated water. All authors read and approved the final manuscript.

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References

- United Nations, Environment Program (UNEP) Basel convention: annex—general technical guidelines on the environmentally sound management of wastes consisting of, containing or contaminated with persistent organic pollutants (version of 1 May 2019). UNEP/CHW.14/7/Add.1/Rev.1
- Wang Z, Cousins IT, Scheringer M, Hungerbühler K (2013) Fluorinated alternatives to long-chain perfluoroalkyl carboxylic acids (PFCAs), perfluoroalkane sulfonic acids (PFASs) and their potential precursors. *Environ Int* 60:242–248. <https://doi.org/10.1016/j.envint.2013.08.021>
- Held T (2020) Precursor! atlasten spektrum 29(6):225–231
- Glüge J, Scheringer M, Cousins IT, DeWitt JC, Goldenman G, Herzke D, Lohmann R, Ng CA, Trier X, Wang Z (2021) An overview of the uses of per- and polyfluoroalkyl substances (PFAS). *Environ Sci Process Impacts* 22(12):2345
- OECD (2018) Toward a new comprehensive global database of per- and polyfluoroalkyl substances (PFASs): summary report on updating the OECD 2007 list of per- and polyfluoroalkyl substances (PFASs). Series on risk management no. 39. ENV/JM/MONO(2018)7. p 24. [https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV-JM-MONO\(2018\)7&doclanguage=en](https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV-JM-MONO(2018)7&doclanguage=en)
- Buck RC, Korzeniowski SH, Laganis E, Adamsky F (2021) Identification and classification of commercially relevant per- and polyfluoroalkyl substances (PFAS). *Integr Environ Assess Manag* 17:1045–1055. <https://doi.org/10.1002/ieam.4450>
- US EPA (2021) PFAS master list of PFAS substances. <https://comptox.epa.gov/dashboard/chemical-lists/pfasmaster>. Accessed 27 May 2022
- Lohmann R, Cousins IT, DeWitt JC, Glüge J, Goldenman G, Herzke D, Lindstrom AB, Miller MF, Ng CA, Patton S, Scheringer M, Trier X, Wang Z (2020) Are fluoropolymers really of low concern for human and environmental health and separate from other PFAS? *Environ Sci Technol* 54:12820–12828. <https://doi.org/10.1021/acs.est.0c03244>
- Wahlström M, Pohjalainen E, Yli-Rantala E, Behringer D, Herzke D, Mudge SM, Beekman, M, de Blaeij A, Devilee J, Gabbert S, van Kuppevelt M, Zare Jeddi M, Gabrielsen P, Trier X (2021) Fluorinated polymers in a low carbon, circular and toxic-free economy. European topic centre waste and materials in a green economy. Technical report. Eionet report—ETC/WMGE 2021/9. p 151. <https://www.eionet.europa.eu/etcs/etc-cm/products/etc-cme-and-etc-wmge-report-9-2021-fluorinated-polymers-in-a-low-carbon-circular-and-toxic-free-economy>. Accessed 11 Feb 2023
- Evich MG, Davis MJB, McCord JP, Acrey B, Awkerman JA, Knappe DRU, Lindstrom AB, Speth TF, Tebes-Stevens C, Strynar M, Wang Z, Weber EJ, Henderson WM, Washington JW (2022) Per- and polyfluoroalkyl substances in the environment. *Science* 375(6850):eabg9065. <https://doi.org/10.1126/science.abg9065>
- Kwiatkowski CF, Andrews DQ, Birnbaum LS, Bruton TA, DeWitt JC, Knappe DRU, Maffini MV, Miller MF, Pelch KE, Reade A, Soehl A, Trier X, Venier M, Wagner CC, Wang Z, Blum A (2020) Scientific basis for managing PFAS as a chemical class. *Environ Sci Technol Lett* 7(8):532–543
- Interstate Technology & Regulatory Council, PFAS Team (2022) PFAS technical and regulatory guidance document. p 542. + external data tables, section 2. <https://pfas-1.itrcweb.org/>
- OECD (2022) Fact cards of major groups of per- and polyfluoroalkyl substances (PFASs) series on risk management no. 68. ENV/CBC/MONO(2022)1. p 104. https://substitution-perfluores.ineris.fr/sites/substitution-perfluores/files/documents/fact_cards_of_major_groups_of_per_and_polyfluoroalkyl_substances_pfas_ocde_2022.pdf
- ECHA (2023) Registry of restriction intentions until outcome—per- and polyfluorinated substances (PFAS). <https://echa.europa.eu/en/registry-of-restriction-intentions/-/dislist/details/0b0236e18663449b>. Accessed 08 Feb 2023
- Ritscher A et al (2018) Zürich statement on future actions on per- and polyfluoroalkyl substances (PFASs). *Environ Health Perspect* 126(8):84502. <https://doi.org/10.1289/EHP4158>
- NRDC (Natural Resources Defense Council) (2021) Engaging the textile industry as a key sector in SAICM—a review of PFAS as a chemical class in the textile sector. https://www.saicmknowledge.org/sites/default/files/publications/SAICM%20report_PFA%20in%20Textile_final_May%202021.pdf
- Straková J, Schneider J, Cingotti N (2021) Throwaway packaging, forever chemicals: European wide survey of PFAS in disposable food packaging and tableware. https://chemtrust.org/wp-content/uploads/CHE_PFAS_FCM_15July2021_Final.pdf
- von Abercron E (2021) AOF analysis by combustion IC—a sum parameter enhancing the determination of PFAS in environmental water matrices. Webinar Thermo Fisher, September 7th
- Schaidler LA, Balan SA, Blum A, Andrews DQ, Strynar M, Dickinson ME, Lunderberg DM, Lang JR, Peaslee GF (2017) Fluorinated compounds in U.S. fast food packaging. *Environ Sci Technol Lett* 4:105–111. <https://doi.org/10.1021/acs.estlett.6b00435>
- Korzeniowski SH, Buck RC, Newkold RM, El Kassmi A, van Laganis E, Matsuoaka Y, Dinelli B, Beauchet S, Adamsky F, Weilandt K, Soni VK, Kapoor D, Gunasekar P, Malvasi M, Brinati G, Musio S (2022) A critical review of the application of polymer of low concern regulatory criteria

- to fluoropolymers II: fluoroplastics and fluoroelastomers. *Integr Environ Assess Manag*. <https://doi.org/10.1002/ieam.4646>
21. Fiedler H, Kennedy T, Henry BJ (2020) A critical review of a recommended analytical and classification approach for organic fluorinated compounds with an emphasis on per- and polyfluoroalkyl substances. *Integr Environ Assess Manag* 2020:1–21. <https://doi.org/10.1002/ieam.4352>
 22. Whitehead HD, Venier M, Wu Y, Eastman E, Urbanik S, Diamond ML, Shalin A, Schwartz-Narbonne H, Bruton TA, Blum A, Wang Z, Green M, Tighe M, Wilkinson JT, McGuinness S, Peaslee GF (2021) Fluorinated compounds in North American cosmetics. *Environ Sci Technol Lett* 8:538–544. <https://doi.org/10.1021/acs.estlett.1c00240>
 23. Winkens Putz K, Namazkar S, Plassmann M, Benskin JP (2022) Are cosmetics a significant source of PFAS in Europe? Product inventories, chemical characterization and emission estimates. *Environ Sci Process Impacts*. <https://doi.org/10.1039/d2em00123c>
 24. Fernández SR, Kwiatkowski C, Bruton T (2021) Building a better world—eliminating unnecessary PFAS in building materials. Report of the Green Science Policy Institute. p 59. <https://greensciencepolicy.org/docs/pfas-building-materials-2021.pdf>
 25. Xu L, Shi Y, Li C, Song X, Qin Z, Cao D, Cai Y (2017) Discovery of a novel polyfluoroalkyl benzenesulfonic acid around oilfields in Northern China. *Environ Sci Technol* 51(24):14173–14181. <https://doi.org/10.1021/acs.est.7b04332>
 26. Neuwald IJ, Zahn D, Knepper TP (2020) Are (fluorinated) ionic liquids relevant environmental contaminants? High-resolution mass spectrometric screening for per- and polyfluoroalkyl substances in environmental water samples led to the detection of a fluorinated ionic liquid. *Anal Bioanal Chem* 412:4881–4892. <https://doi.org/10.1007/s00216-020-02606-8>
 27. Neuwald IJ, Muschkett M, Zahn D, Berger U, Seiwert B, Meier T, Kuckelkorn J, Strobel C, Knepper TP, Reemtsma T (2021) Filling the knowledge gap: a suspect screening study for 1310 potentially persistent and mobile chemicals with SFC- and HILIC-MS in two German river systems. *Water Res* 204:117256. <https://doi.org/10.1016/j.watres.2021.117645>
 28. US EPA (2022) Per- and polyfluoroalkyl substances (PFAS) in pesticide and other packaging. Last Update December 2022. <https://www.epa.gov/pesticides/pfas-packaging#packaging>. Accessed 11 Feb 2023
 29. Ogawa Y, Tokunaga E, Kobayashi O, Hirai K, Shibata N (2020) Current contributions of organofluorine compounds to the agrochemical industry. *iScience* 23:101467. <https://doi.org/10.1016/j.isci.2020.101467>
 30. Adlunger K, Anke JM, Bachem G, Banning H, Biegel-Engler A, Blondzik K, Braun U, Eckhardt A, Gildemeister D, Hilliges F, Hoffmann G, Jentzsch F, Klitzke S, Kuckelkorn J, Martens K, Müller A, Pickl C, Pirntke U, Rechenberg J, Sättler D, Schmidt U, Speichert G, Warnke I, Wehner J, Wischer R (2022) Reducing the input of chemicals into waters: trifluoroacetate (TFA) as a persistent and mobile substance with many sources—sources, input pathways, environmental contamination of TFA and regulatory approaches. Background. Umweltbundesamt (ed). Dessau-Roßlau. p 52. https://www.umweltbundesamt.de/sites/default/files/medien/3521/publikationen/2021_hg_chemiekalieneintrag_bf.pdf
 31. Rippen G (2022) Umweltchemikalien. CD-ROM und online. Landsberg: ecomed. Erstaussgabe 12/98. 57. Update, 07/2022. Data sheet on trifluoroacetic acid
 32. Müller M (2021) Sustainable pharmacy. Lecture on GDCh-Wissenschaftsforum 2021, Session “Arzneimittel der Zukunft”, 01.09.2021
 33. Inoue M, Sumii Y, Shibata N (2020) Contribution of organofluorine compounds to pharmaceuticals. *ACS Omega* 5:10633–10640. <https://doi.org/10.1021/acs.omega.0c00830>
 34. Criteria for elevation of obligations to progress SAICM issues of concern (IoCs) in the post2020 multilateral regime: the case of per and poly fluoroalkyl substances (PFASs). <http://www.saicm.org/Portals/12/documents/meetings/IP3/stakeholders/IPEN-Case-PFAS.pdf>
 35. European Commission (2020) Communication from the Commission to the European parliament, the Council, the European Economic and Social Committee and the Committee of the Regions—Chemicals strategy for sustainability. Towards a toxic-free environment. COM (2020) 667 Final. p 25. https://eur-lex.europa.eu/resource.html?uri=cellar:f815479a-0f01-11eb-bc07-01aa75ed71a1.0003.02/DOC_1&format=PDF
 36. Cousins IT, Goldenman G, Herzke D, Lohmann R, Miller M, Ng CA, Patton S, Scheringer M, Trier X, Vierke L, Wang Z, DeWitt JC (2019) The concept of essential use for determining when uses of PFASs can be phased out. *Environ Sci Process Impacts* 21:1803. <https://doi.org/10.1039/c9em00163h>
 37. Cousins IT, De Witt JC, Glüge J, Goldenman G, Herzke D, Lohmann R, Miller M, Ng CA, Patton S, Scheringer M, Trier X, Wang Z (2021) Finding essentiality feasible: common questions and misinterpretations concerning the “essential use” concept. *Environ Sci Process Impacts* 23:1079. <https://doi.org/10.1039/d1em00180a>
 38. Tickner JA, Schifano JN, Blake A, Rudisill C, Mulvihill MJ (2015) Advancing safer alternatives through functional substitution. *Environ Sci Technol* 49(2):742–749. <https://doi.org/10.1021/es503328m>
 39. Roy MA, Cousins ID, Harriman E, Scheringer M, Tickner JA, Wang Z (2022) Combined application of the essential-use and functional substitution concepts: accelerating safer alternatives. *Environ Sci Technol* 56:9842–9846. <https://doi.org/10.1021/acs.est.2c03819>
 40. Glüge J, London R, Cousins IT, DeWitt J, Goldenman G, Herzke D, Lohmann R, Miller M, Ng CA, Patton S, Trier X, Wang Z, Scheringer M (2022) Information requirements under the essential-use concept: PFAS case studies. *Environ Sci Technol* 56:2322–2624. <https://doi.org/10.1021/acs.est.1c03732>
 41. Bălan SA, Andrews DQ, Blum A, Diamond ML, Fernández SR, Harriman E, Lindstrom AB, Reade A, Richter L, Sutton R, Wang Z, Kwiatkowski CF (2023) Optimizing chemicals management in the United States and Canada through the essential-use approach. *Environ Sci Technol* 57(4):1568–1575. <https://doi.org/10.1021/acs.est.2c05932>
 42. Wood Environment & Infrastructure Solutions UK Limited (2020) The use of PFAS and fluorine-free alternatives in fire-fighting foams. Report for European Commission DG Environment and ECHA. p 534. https://echa.europa.eu/documents/10162/28801697/pfas_flourine-free_alternatives_fire_fighting_en.pdf/d5b24e2a-d027-0168-cdd8-f723c675fa98
 43. Whiting R, Nicol L, Keyte I, Kreißig J, Crookes M, Gebbink W, Potrykus A, Schöpel M (2019) The use of PFAS and fluorine-free alternatives in textiles, upholstery, carpets, leather and apparel. Report of Ramboll & Wood Environment for European Commission, Directorate General—Environment, Directorate B—circular economy and green growth, Unit B.2—sustainable chemicals, BU 9. Final report under framework contract ENV.A.3/FRA/2015/0010. Service request no 1-2019. p 531.
 44. OECD (2022) Per- and polyfluoroalkyl substances and alternatives in coatings, paints and varnishes (CPVs). Series on risk management no. 70. p 91. <https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/per-and-polyfluoroalkyl-substances-alternatives-in-coatings-paints-varnishes.pdf>
 45. OECD (2020) PFASs and alternatives in food packaging (paper and paperboard)—report on the commercial availability and current uses, OECD Series on risk management, no. 58. Environment Health and Safety, Environment Directorate, OECD. <https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/PFASs-and-alternatives-in-food-packaging-paper-and-paperboard.pdf>
 46. OECD (2022) PFAS and alternatives in food packaging (paper and paperboard): hazard profile. Series on risk management no. 69. ENV/CBC/MONO(2022)2. [https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/cbc/mono\(2022\)2&doclanguage=en](https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/cbc/mono(2022)2&doclanguage=en)
 47. Willand W, Baron Y, Blepp M, Weber R, Herold CH (2020) Best available techniques for PFOS substitution in the surface treatment of metals and plastics and analysis of alternative substances to PFOS when used in equipment for chromium plating and plastic etching. Umweltbundesamt (Ed.) Texte 211/2020. <https://www.umweltbundesamt.de/publikationen/best-available-techniques-for-pfos-substitution-in>
 48. Wang Z, Cousins IT, Scheringer M, Buck RC, Hungerbühler K (2014) Global emission inventories for C4–C14 perfluoroalkyl carboxylic acid (PFCA) homologues from 1951 to 2030, part I: production and emissions from quantifiable sources. *Environ Int* 70:62–75. <https://doi.org/10.1016/j.envint.2014.04.013>
 49. Wang Z, Cousins IT, Scheringer M, Buck RC, Hungerbühler K (2014) Global emission inventories for C4–C14 perfluoroalkyl carboxylic acid (PFCA) homologues from 1951 to 2030, part II: the remaining pieces of the puzzle. *Environ Int* 69:166–176. <https://doi.org/10.1016/j.envint.2014.04.006>

50. von Abercron E, Falk S, Stahl T, Georgii S, Hamscher G, Brunn H, Schmitz F (2019) Determination of adsorbable organically bound fluorine (AOF) and adsorbable organically bound halogens as sum parameters in aqueous environmental samples using combustion ion chromatography (CIC). *Sci Total Environ* 673:384–391. <https://doi.org/10.1016/j.scitotenv.2019.04.068>
51. Eriksson U, Haglund P, Kärrman A (2017) Contribution of precursor compounds to the release of per- and polyfluoroalkyl substances (PFASs) from wastewater treatment plants. *J Environ Sci* 61:80–90. <https://doi.org/10.1016/j.jes.2017.05.004;pmid:29191318>
52. Stahl T, Gassmann M, Falk S, Brunn H (2018) Concentrations and distribution patterns of perfluoroalkyl acids in sewage sludge and in Biowaste in Hesse, Germany. *J Agric Food Chem* 66:10147–10153. <https://doi.org/10.1021/acs.jafc.8b03063>
53. Krakau C, Stolzenberg-Hepp K, Striegel G, Teichmann R-K, Noyes D, Schmid A, Reinhard M, Schenkel C (2020) Flächenhafte PFAS-Verunreinigungen in Mittelbaden – Eine Übersicht. *altlasten spektrum* 29(6):252–256. <https://doi.org/10.37307/j.1864-8371.2020.06.07>
54. EU (2020) Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions. A new circular economy action plan for a cleaner and more competitive Europe. COM(2020) 98 final
55. Weber R, Watson A, Forter M, Ollaei F (2011) Persistent organic pollutants and landfills—a review of past experiences and future challenges. *Waste Manag Res* 29(1):107–121. <https://doi.org/10.1177/0734242X10390730>
56. Propp VR, De Silva AO, Spencer C, Brown SJ, Catingan SD, Smith JE, Roy JW (2021) Organic contaminants of emerging concern in leachate of historic municipal landfills. *Environ Pollut* 276:116474. <https://doi.org/10.1016/j.envpol.2021.116474>
57. Busch J, Ahrens L, Sturm R, Ebinghaus R (2010) Polyfluoroalkyl compounds in landfill leachates. *Environ Pollut* 158(5):1467–1471. <https://doi.org/10.1016/j.envpoll.2009.12.031>
58. US EPA (2020) Interim guidance on the destruction and disposal of perfluoroalkyl and polyfluoroalkyl substances and materials containing perfluoroalkyl and polyfluoroalkyl substances (EPA-HQ-OLEM-2020-0527-0002)
59. Yamada T, Taylor PH, Buck RC, Kaiser MA, Giraud RJ (2005) Thermal degradation of fluorotelomer treated articles and related materials. *Chemosphere* 61(7):974–984. <https://doi.org/10.1016/j.chemosphere.2005.03.025>
60. UNEP (UN Environment Programme) (2021) Guidance on best available techniques and best environmental practices for the use of perfluorooctane sulfonic acid, perfluorooctanoic acid, and their related compounds listed under the Stockholm convention. March 2021, pp 30–31. <http://chm.pops.int/implementation/nips/guidance/guidanceonbatbepfortheuseofpfos/tabid/3170/default.aspx>
61. Held T, Reinhard M (2020) Remediation management for local and wide-spread PFAS contaminations. Umweltbundesamt Texte 205/2020 (only English text without appendices). <https://www.umweltbundesamt.de/publikationen/remediation-management-for-local-wide-spread-pfas>
62. Held T, Reinhard M (2020) Sanierungsmanagement für lokale und flächenhafte PFAS-Kontaminationen. Umweltbundesamt Texte 137/2020. p 80. + 5 Appendices, here: Appendix C p 91. <https://www.umweltbundesamt.de/publikationen/sanierungsmanagement-fuer-lokale-flaechenhafte-pfas>
63. Aleksandrov K, Gehrman H-J, Hauser M, Mätzing H, Pigeon D, Stapf D, Wexler M (2019) Waste incineration of polytetrafluoroethylene (PTFE) to evaluate potential formation of per- and polyfluorinated alkyl substances (PFAS) in flue gas. *Chemosphere* 226:898–906. <https://doi.org/10.1016/j.chemosphere.2019.03.191>
64. Tsang W, Burgess DR, Babushok V (1998) On the incinerability of highly fluorinated organic compounds. *Combust Sci Technol* 139(1):385–402. <https://doi.org/10.1080/00102209808952095>
65. Bakker J, Bokkers BM, Broekman M (2021) Per- and polyfluorinated substances in waste incinerator flue gases. Report of National Institute for Public Health and the Environment, RIVM 2021-0143. p 164. <https://doi.org/10.21945/RIVM-2021-0143>
66. Sandblom O (2014) Waste incineration as a possible source of perfluoroalkyl acids to the environment—method development and screening. Master's Thesis. Stockholm University, Stockholm. <https://su.diva-portal.org/smash/get/diva2:1261025/FULLTEXT01.pdf>
67. Houben T, Boerleider R (2020) ZZS-inventarisatie AVR Duiven. Royal HaskoningDHV reference number BH2652I&BRP001F01, 2 June
68. Morales McDevitt ME, Becanova J, Blum A, Bruton T, Vojta S, Woodward M, Lohmann R (2021) The air that we breathe: neutral and volatile PFAS in indoor air. *Environ Sci Technol Lett* 8(10):897–902. <https://doi.org/10.1021/acs.estlett.1c00481>
69. Schlummer M, Gruber L, Fiedler D, Kizlasusk M, Müller J (2013) Detection of fluorotelomer alcohols in indoor environments and their relevance for human exposure. *Environ Int* 57–58:42–49. <https://doi.org/10.1016/j.envint.2013.03.010>
70. Bayerisches Landesamt für Umwelt (2022). PFC-Belastung von Böden. p 43. https://www.lfu.bayern.de/analytik_stoffe/pfc/pfc_belastung_boeden/index.htm. Accessed 10 May 2022
71. Ulman M, Sengl M, Körner W, Horst K (2012) Medienübergreifende Umweltanalytik persistenter Perfluortenside und Bestimmung (semi) flüchtiger Vorläuferverbindungen – PFC in der Umwelt. Bayerisches Landesamt für Umwelt (ed). p 95. https://www.lfu.bayern.de/analytik_stoffe/pfc/fachbeitraege/doc/abschlussbericht_semi.pdf
72. Gebbink WA, van Leeuwen SPJ (2020) Environmental contamination and human exposure to PFASs near a fluorochemical production plant: review of historic and current PFOA and GenX contamination in the Netherlands. *Environ Int*. <https://doi.org/10.1016/j.envint.2020.105583>
73. van Bentum E, Pancras T, Slenders H (2018) Aanvullend luchtdepositie onderzoek PFOA en HFPO-DA (GenX) Dordrecht en omgeving - Aanvullend onderzoek naar de invloed van luchtemissies op de kwaliteit van grond en grondwater. Expertisecentrum PFAS C05044.000267.0200/083692045. 167 pages. https://www.ozh.nl/wp-content/uploads/Expertisecentrum-maart-2018-PFOA-en-HFPO-DA_-webversie-.pdf
74. van Bentum E, Pancras T, Slenders H, van der Linden P (2018) Verkennend onderzoek naar PFOA en GenX in het milieu in Helmond - Onderzoek naar het voorkomen van PFAS in grond, grondwater, waterbodem en oppervlaktewater. Expertisecentrum PFAS C05044.000267.0200/083692045. 142 pages. <https://www.helmond.nl/Media%20Helmond.nl/Documents%20Helmond/Actueel/Nieuws/Nieuws%202018/2018-10-23%20VO%20GenX%20en%20PFOA%20Helmond%20definitief%20incl%20bijlagen.pdf>
75. Vierke L, Ahrens L, Shoeib M, Reiner EJ, Guo R, Palm W-U, Ebinghaus R, Harner T (2011) Air concentrations and particle gas partitioning of polyfluoroalkyl compounds at a wastewater treatment plant. *Environ Chem* 8(4):363–371. <https://doi.org/10.1071/EN10133>
76. Björnsdotter MK, Yeung LWY, Kärrman A, Jogsten IE (2022) Mass balance of perfluoroalkyl acids, including trifluoroacetic acid, in a freshwater lake. *Environ Sci Technol* 56:251–259. <https://doi.org/10.1021/acs.est.1c04472>
77. Yamashita N, Kannan K, Taniyasu S, Horii Y, Petrick G, Gamo T (2005) A global survey of perfluorinated acids in oceans. *Mar Pollut Bull* 51(8–12):658–668. <https://doi.org/10.1016/j.marpolbul.2005.04.026>
78. Rauert C, Shoeib M, Schuster JK, Eng A, Harner T (2018) Atmospheric concentrations and trends of poly- and perfluoroalkyl substances (PFAS) and volatile methyl siloxanes (VMS) over 7 years of sampling in the global atmospheric passive sampling (GAPS) network. *Environ Pollut* 238:94–102. <https://doi.org/10.1016/j.envpol.2018.03.017>
79. Shoeib M, Harner T, Vlahos P (2006) Perfluorinated chemicals in the arctic atmosphere. *Environ Sci Technol* 40(24):7577–7583. <https://doi.org/10.1021/es0618999>
80. Yamashita N, Taniyasu S, Petrick G, Wie S, Gamo T, Lam PKS (2008) Perfluorinated acids as novel chemical tracers of global circulation of ocean waters. *Chemosphere* 70(7):1247–1255. <https://doi.org/10.1016/j.chemosphere.2007.07.079>
81. Cousins IT, Johansson JH, Salter ME, Sha B, Scheringer M (2022) Outside the safe operating space of a new planetary boundary for per- and polyfluoroalkyl substances (PFAS). *Environ Sci Technol* 56(16):11172–11179. <https://doi.org/10.1021/acs.est.2c02765>
82. Joerss H, Xie Z, Wagner CC, von Appen W-J, Sunderland EM, Ebinghaus R (2020) Transport of legacy perfluoroalkyl substances and the replacement compound HFPO-DA through the Atlantic Gateway to the Arctic Ocean—is the Arctic a sink or a source? *Environ Sci Technol* 54(16):9958–9967. <https://doi.org/10.1021/acs.est.0c00228>

83. Johansson JH, Salter ME, Acosta Navarro JC, Leck C, Nilsson ED, Cousins IT (2019) Global transport of perfluoroalkyl acids via sea spray aerosol. *Environ Sci Process Impacts* 21:635–649
84. Sha B, Johansson JH, Benskin JP, Cousins IT, Salter ME (2021) Influence of water concentrations of perfluoroalkyl acids (PFAAs) on their size-resolved enrichment in nascent sea spray aerosols. *Environ Sci Technol* 55(14):9489–9497. <https://doi.org/10.1021/acs.est.0c03804>
85. Lesmeister L, Scheurer M, Lange FT, Schmidt CK (2019) Belastungssituation des Rheins mit Per- und Polyfluoralkylsubstanzen (PFAS). *TZW-Jahresbericht* 19:85–104
86. Li F, Duan J, Tian S, Ji H, Zhu Y, Wei Z, Zhao D (2020) Short-chain per- and polyfluoroalkyl substances in aquatic systems: occurrence, impacts and treatment. *Chem Eng J* 380:122506. <https://doi.org/10.1016/j.cej.2019.122506>
87. Kurwadkar S, Dane J, Kanel SR, Nadagouda MN, Cawdrey RW, Ambade B, Struckhoff GC, Wilkin R (2022) Per- and polyfluoroalkyl substances in water and wastewater: a critical review of their global occurrence and distribution. *Sci Total Environ* 809:151003. <https://doi.org/10.1016/j.scitotenv.2021.151003>
88. Joerss H, Menger F, Tang J, Ebinghaus R, Ahrens L (2022) Beyond the tip of the iceberg: suspect screening reveals point source-specific patterns of emerging and novel per- and polyfluoroalkyl substances in German and Chinese rivers. *Environ Sci Technol* 56:5456–5465. <https://doi.org/10.1021/acs.est.1c07987>
89. Schroers S, Mersmann M, Valentin I, Utermann J (2020) PFC in Boden und Grundwasser, Situation in Nordrhein-Westfalen, bundesweite Aktivitäten und Handlungsbedarf. Vortrag. 20. Karlsruher Altlastenseminar Altlasten 2020. 24/25 June, 2020 in Karlsruhe
90. Bierreth Ch, Dreher P, Nöltner Th, Salowsky H, Seeger AK (2021) Sachstandsbericht: PFAS—in Böden von Bodendauerbeobachtungsflächen. LUBW (Landesanstalt für Umwelt Baden-Württemberg). <https://pd.lubw.de/10215>
91. Humer M, Scheffknecht C (2021) Per- und polyfluorierte Alkylsubstanzen (PFAS) in Vorarlberg. Bericht UI-05/2021. Amt der Vorarlberger Landesregierung, Bregenz (ed). p 49. <https://vorarlberg.at/-/per-und-polyfluorierte-alkylsubstanzen-pfas-in-vorarlbergs-umwelt>
92. Washington JW, Jenkins TM, Rankin K, Naile JE (2015) Decades-scale degradation of commercial, side-chain, fluorotelomer-based polymers in soils and water. *Environ Sci Technol* 49(2):915–923. <https://doi.org/10.1021/es504347u>
93. Washington JW, Rankin K, Libelo EL, Lynch DG, Cyterski M (2019) Determining global background soil PFAS loads and the fluorotelomer-based polymer degradation rates that can account for these loads. *Sci Total Environ* 651(pt 2):2444–2449. <https://doi.org/10.1016/j.scitotenv.2018.10.071>
94. Krippner J, Falk S, Brunn H, Georgii S, Schubert S, Stahl T (2015) Accumulation potentials of perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFASs) in maize (*Zea mays*). *J Agric Food Chem* 63(14):3646–3653. <https://doi.org/10.1021/acs.jafc.5b00012>
95. Blaine AC, Rich CD, Hundal LS, Lau C, Mills MA, Harris KM, Higgins CP (2013) Uptake of perfluoroalkyl acids into edible crops via land applied biosolids: field and greenhouse studies. *Environ Sci Technol* 47(14):14062–14069
96. Blaine AC, Rich CD, Sedlacko EM, Hundal LS, Kumar K, Lau C, Mills MA, Harris KM, Higgins CP (2014) Perfluoroalkyl acid distribution in various plant compartments of edible crops grown in biosolids-amended soils. *Environ Sci Technol* 48(14):7858–7865
97. Blaine AC, Rich CD, Sedlacko EM, Hyland KC, Stushnoff C, Dickenson ER, Higgins CP (2014) Perfluoroalkyl acid uptake in lettuce (*Lactuca sativa*) and strawberry (*Fragaria ananassa*) irrigated with reclaimed water. *Environ Sci Technol* 48(24):14361–14368. <https://doi.org/10.1021/es504150h>
98. Li J, Sun J, Li P (2022) Exposure routes, bioaccumulation and toxic effects of per- and polyfluoroalkyl substances (PFASs) on plants: a critical review. *Environ Int* 158:106891. <https://doi.org/10.1016/j.envint.2021.106891>
99. Ghisi R, Vamerali T, Manzetti S (2019) Accumulation of perfluorinated alkyl substances (PFAS) in agricultural plants: a review. *Environ Res* 169:326–341. <https://doi.org/10.1016/j.envres.2018.10.023>
100. Bethke H, Budde J (2020) Ausbreitung von PFAS durch den Einsatz von AFFF-Schaumlöschmitteln. *altlasten spektrum* 29(6):245–251
101. Kotthoff M, Flidner A, Rüdell H, Göckener B, Bücking M, Biegel-Engler A, Koschorreck J (2020) Per- and polyfluoroalkyl substances in the German environment—levels and patterns in different matrices. *Sci Total Environ* 740:140116. <https://doi.org/10.1016/j.scitotenv.2020.140116>
102. Joerss H, Apel C, Ebinghaus R (2019) Emerging per- and polyfluoroalkyl substances (PFASs) in surface water and sediment of the North and Baltic Seas. *Sci Total Environ* 686:360–369. <https://doi.org/10.1016/j.scitotenv.2019.05.363>
103. Koschorreck J, Fettig I, Weber T, Göckener B, Rüdell H, Rupp J, Guckert M, Kotthoff M, Stahl T, Falk S, Wellnitz J, Dzekov T, Bandow N (2021) PFAS Daten der Umweltprobenbank des Bundes. PFAS-Seminar des Bayerischen Landesamtes für Umwelt (LfU). https://www.lfu.bayern.de/analytik_stoffe/pfc/fachtagungen/doc/pfas2021/entwicklung_umweltproben.pdf
104. Bayerisches Landesamt für Umwelt: PFOA-Problematik im Raum Gendorf. https://www.lfu.bayern.de/altlasten/pfoa_gendorf/index.htm. Accessed 11 Aug 2022
105. Falk S, Stahl T, Flidner A, Rüdell H, Tarricone K, Brunn H, Koschorreck J (2019) Levels, accumulation patterns and retrospective trends of perfluoroalkyl acids (PFAAs) in terrestrial ecosystems over the last three decades. *Environ Pollut* 246:921–931. <https://doi.org/10.1016/j.envpol.2018.12.095>
106. Byns C, Teunen L, Groffen T, Lasters R, Bervoets L (2022) Bioaccumulation and trophic transfer of perfluorinated alkyl substances (PFAS) in marine biota from the Belgian North Sea: distribution and human health risk implications. *Environ Pollut* 311:119907. <https://doi.org/10.1016/j.envpol.2022.119907>
107. Göckener B, Weber T, Rüdell H, Bücking M, Kolossa-Gehring M (2020) Human biomonitoring of per- and polyfluoroalkyl substances in German blood plasma samples from 1982 to 2019. *Environ Int* 145:106123. <https://doi.org/10.1016/j.envint.2020.106123>
108. Zheng G, Schreder E, Dempsey JC, Udine N, Chu V, Andres G, Sathyanarayana S, Salamova A (2021) Per- and polyfluoroalkyl substances (PFAS) in breast milk: concerning trends for current-use PFAS. *Environ Sci Technol* 55(11):7510–7520. <https://doi.org/10.1021/acs.est.0c06978>
109. North Carolina State University, Center for Human Health and the Environment (2022) GenX exposure study—PFAS results for blood samples collected 2020–2021. Webinar, October 18, 2022. https://genxstudy.ncsu.edu/wp-content/uploads/sites/149/2022/10/SRP_Webinar_18OCT2022_5PM-2.pdf
110. Sorg L (2021) EPA: GenX far more toxic than originally thought, could prompt NC to significantly reduce advisory goal. NC Policy Watch. <https://ncpolicywatch.com/2021/10/26/epa-genx-far-more-toxic-than-originally-thought-could-prompt-nc-to-significantly-reduce-health-advisory-goal/>. Accessed 11 Feb 2023
111. German Environmental Specimen Bank (Umweltprobenbank). <https://www.umweltprobenbank.de/en>. Accessed 30 Oct 2022
112. Koschorreck J, Environmental Specimen Bank (2021) Personal communication
113. Gassmann M, Falk S, Brunn H, Rückert H, Berthold G, Stahl T (2021) Sind PFAS eine neue Klasse von Agrarchemikalien? In: *Hydrologie: Verbindung der Umweltsphären und -disziplinen, Zusammenfassungen der Beiträge*. https://www.uni-potsdam.de/fileadmin/projects/tdh2021/TdH_2021_Abstractband_V4_.pdf
114. Göckener B, Flidner A, Rüdell H, Fettig I, Koschorreck J (2021) Exploring unknown per- and polyfluoroalkyl substances in the German environment—the total oxidizable precursor assay as helpful tool in research and regulation. *Sci Total Environ* 782:146825. <https://doi.org/10.1016/j.scitotenv.2021.146825>
115. Göckener B, Eichhorn M, Lämmer R, Kotthoff M, Kowalczyk J, Numata J, Schafft H, Lahrssen-Wiederholt M, Bücking M (2020) Transfer of per- and polyfluoroalkyl substances (PFAS) from feed into the eggs of laying hens. Part 1: analytical results including a modified total oxidizable precursor assay. *J Agric Food Chem* 68(45):12527–12538. <https://doi.org/10.1021/acs.jafc.0c04456>
116. Kowalczyk J, Göckener B, Eichhorn M, Lämmer R, Kotthoff M, Bücking M, Schafft H, Lahrssen-Wiederholt M, Numata J (2020) Transfer of per- and polyfluoroalkyl substances (PFAS) from feed into the eggs of laying hens. Part 2: toxicokinetic results including the role of precursors. *J Agric Food Chem* 68(45):12539–12548. <https://doi.org/10.1021/acs.jafc.0c04485>

117. CVUA (Chemisches und Veterinäruntersuchungsamt) Freiburg (2021) Nachweis von per- und polyfluorierten Alkylsubstanzen (PFAS) in Fischen aus dem Bodensee – Ergebnisse eines Untersuchungsprogramms aus dem Jahr 2020. https://www.ua-bw.de/pub/beitrag.asp?subid=3&Thema_ID=7&ID=3344&Pdf=No&lang=DE. Accessed 28 Feb 2022
118. Teunen L, Bervoets L, Belpaire C, De Jonge M, Groffen T (2021) PFAS accumulation in indigenous and translocated aquatic organisms from Belgium, with translation to human and ecological health risk. *Environ Sci Eur* 33:39. <https://doi.org/10.1186/s12302-021-00477-z>
119. Rüdél H, Radermacher G, Fliedner A, Lohmann N, Koschorreck J, Duffek A (2022) Tissue concentrations of per- and polyfluoroalkyl substances (PFAS) in German freshwater fish: derivation of fillet-to-whole fish conversion factors and assessment of potential risks. *Chemosphere* 292:133483. <https://doi.org/10.1016/j.chemosphere.2021.133483>
120. Stahl T, Falk S, Failing K, Berger J, Georgii S, Brunn H (2011) Perfluorooctanoic acid and perfluorooctane sulfonate in liver and muscle tissue from Wild Boar in Hesse, Germany. *Arch Environ Contam Toxicol* 62:696–703. <https://doi.org/10.1007/s00244-011-9726-3>
121. Falk S, Failing K, Georgii S, Brunn H, Stahl T (2015) Tissue specific uptake and elimination of perfluoroalkyl acids (PFAAs) in adult rainbow trout (*Oncorhynchus mykiss*) after dietary exposure. *Chemosphere* 129:150–156. <https://doi.org/10.1016/j.chemosphere.2014.06.061>
122. Umweltbundesamt (2020): What matters—PFAS—came to stay. 200922_uba_sp_1-2020_eng-web_0.pdf (umweltbundesamt.de)
123. Robuck AR, Cantwell MG, McCord JP, Addison LM, Pfohl M, Strynar MJ, McKinney R, Katz DR, Wiley DN, Lohmann R (2020) Legacy and novel per- and polyfluoroalkyl substances in juvenile seabirds from the US Atlantic Coast. *Environ Sci Technol* 54(20):12938–12948. <https://doi.org/10.1021/acs.est.0c01951>
124. Hesse State Laboratory, personal communication, 11.01.2023
125. Felder C, Trompeter L, Skutlarek D, Färber H, Mutters NT, Heinemann C (2022) Exposure of a single wild boar population in North Rhine-Westphalia (Germany) to perfluoroalkyl acids. *Environ Sci Pollut Res*. <https://doi.org/10.1007/s11356-022-23086-6>
126. Cousins JT, DeWitt JC, Glüge J, Goldenman G, Herzke D, Lohmann R, Ng CA, Scheringer M, Wang Z (2020) The high persistence of PFAS is sufficient for their management as a chemical class. *Environ Sci Process Impacts* 22:2307–2312. <https://doi.org/10.1039/d0em00355g>
127. Cousins IT, Ng CA, Wang Z, Scheringer M (2019) Why is high persistence alone a major cause of concern? *Environ Sci Process Impacts* 21:781
128. BUND (Bund für Umwelt- und Naturschutz Deutschland) (2019) Challenges for a sustainable chemicals and materials policy, BUND-position 69. Berlin. p 38. https://www.bund.net/fileadmin/user_upload_bund/publikationen/chemie/chemie_stoffpolitik-position_engl.pdf
129. Klöpffer W (1994) Environmental hazard assessment of chemicals and products. Part II. Persistence and degradability. *Environ Sci Pollut Res* 1(2):108–116. <https://doi.org/10.1007/BF02986520>
130. Scheringer M (1996) Persistence and spatial range as endpoints of an exposure-based assessment of organic chemicals. *Environ Sci Technol* 30:1652–1659. <https://doi.org/10.1021/es9506418>
131. Zhao Z, Li J, Zhang X, Wang L, Wang J, Lin T (2022) Perfluoroalkyl and polyfluoroalkyl substances (PFASs) in groundwater: current understandings and challenges to overcome. *Environ Sci Pollut Res* 29:49513–49533. <https://doi.org/10.1007/s11356-022-20755-4>
132. Johnson GR, Brusseau ML, Carroll KC, Tick GR, Duncan CM (2022) Global distributions, source-type dependencies, and concentration ranges of per- and polyfluoroalkyl substances in groundwater. *Sci Total Environ* 841:156602. <https://doi.org/10.1016/j.scitotenv.2022.156602>
133. Umweltbundesamt (2019) Protecting the sources of our drinking water: the criteria for identifying persistent, mobile and toxic (PMT) substances and very persistent and very mobile (vPvM) substances under EU Regulation REACH (EC) no. 1907/2006. Texte 127/2019. p 87. https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/2019-11-29_texte_127-2019_protecting-sources-drinking-water-pmt.pdf
134. ECHA (European Chemical Agency) Perfluoroalkyl chemicals. <https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas>. Accessed 14 June 2022
135. Miranda DA, Benskin JP, Awad R, Lepoint G, Leonel J, Hatje V (2021) Bioaccumulation of per- and polyfluoroalkyl substances (PFASs) in a tropical estuarine food web. *Sci Total Environ* 754:142146. <https://doi.org/10.1016/j.scitotenv.2020.142146>
136. Ng CA, Hungerbühler K (2013) Bioconcentration of perfluorinated alkyl acids: how important is specific binding? *Environ Sci Technol* 47:7214–7223. <https://doi.org/10.1021/es400981a>
137. Ng CA, Hungerbühler K (2014) Bioaccumulation of perfluorinated alkyl acids: observations and models. *Environ Sci Technol* 48:4637–4648. <https://doi.org/10.1021/es404008g>
138. Pan CG, Zhao JL, Liu YS, Zhang QQ, Chen ZF, Lai HJ, Peng FJ, Liu SS, Ying GG (2014) Bioaccumulation and risk assessment of per- and polyfluoroalkyl substances in wild freshwater fish from rivers in the Pearl River Delta region, South China. *Ecotox Environ Safety* 107C:192–199. <https://doi.org/10.1016/j.jecoen.2014.05.031>
139. Tal T, Vogs C (2021) Invited perspective: PFAS bioconcentration and biotransformation in early life stage Zebrafish and its implications for human health protection. *Environ Health Perspect* 129:7. <https://doi.org/10.1289/EHP9625>
140. Androulakaki A, Alygizakis N, Gkotsis G, Nika M-C, Nikolopoulou V, Bizani E, Chadwick E, Cincinelli A, Claßen D, Danielsson S, Dekker RWRJ, Duke G, Glowacka N, Jansman HAH, Krone O, Martellini T, Movalli P, Persson S, Roos A, O'Rourke E, Siebert U, Treu G, van den Brink NW, Walker LA, Deaville R, Slobodnik J, Thomaidis NS (2022) Determination of 56 per- and polyfluoroalkyl substances in top predators and their prey from Northern Europe by LC-MS/MS. *Chemosphere* 287:331775
141. Xu C, Song X, Liu Z, Ding X, Chen H, Ding D (2021) Occurrence, source apportionment, plant bioaccumulation and human exposure of legacy and emerging per- and polyfluoroalkyl substances in soil and plant leaves near a landfill in China. *Sci Total Environ* 776:145731. <https://doi.org/10.1016/j.scitotenv.2021.145731>
142. Krippner J, Brunn H, Falk S, Georgii S, Schubert S, Stahl T (2014) Effects of chain length and pH on the uptake and distribution of perfluoroalkyl substances in maize (*Zea mays*). *Chemosphere* 94:85–90. <https://doi.org/10.1016/j.chemosphere.2013.09.018>
143. Stahl T, Heyn J, Thiele H, Hübner J, Failing K, Georgii S, Brunn H (2009) Carryover of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) from soil to plants. *Arch Environ Contam Toxicol* 57:289–298. <https://doi.org/10.1007/s00244-008-9272-9>
144. Stahl T, Riebe RA, Falk S, Failing K, Brunn H (2013) A long-term lysimeter experiment to investigate the leaching of perfluoroalkyl substances (PFAAs) and the carryover from soil to plants—results of a pilot study. *J Agric Food Chem* 61:1784–1793. <https://doi.org/10.1021/jf305003h>
145. Bao J, Li C-L, Liu Y, Wang X, Yu W-J, Liu Z-Q, Shao L-X, Jin Y-H (2020) Bioaccumulation of perfluoroalkyl substances in greenhouse vegetables with long-term groundwater irrigation near fluorochemical plants in Fuxin, China. *Environ Res* 188:109751. <https://doi.org/10.1016/j.envres.2020.109751>
146. Liu Z, Lu Y, Xin S, Jones K, Sweetman AJ, Johnson AC, Zhang M, Lu X, Su C (2019) Multiple crop bioaccumulation and human exposure of perfluoroalkyl substances around a mega fluorochemical industrial park, China: implication for planting optimization and food safety. *Environ Int* 127:671–684. <https://doi.org/10.1016/j.envint.2019.04.008>
147. Lesmeister L, Lange FT, Breuer J, Biegel-Engler A, Giese E, Scheurer M (2021) Extending the knowledge about PFAS bioaccumulation factors for agricultural plants—a review. *Sci Total Environ* 766:142640. <https://doi.org/10.1016/j.scitotenv.2020.142640>
148. Surma M, Zieliński H, Piskula M (2016) Levels of contamination by perfluoroalkyl substances in honey from selected European countries. *Bull Environ Contam Toxicol* 97(1):112–118. <https://doi.org/10.1007/s00128-016-1840-5>
149. Lee JW, Choi K, Park K, Sung C, Yu SD, Kim P (2020) Adverse effects of perfluoroalkyl acids on fish and other aquatic organisms: a review. *Sci Total Environ* 707:135334. <https://doi.org/10.1016/j.scitotenv.2019.135334>
150. Schwaiger J, Ferling H, Gerst M, Römer C (2011) Auswirkungen der PFOS auf Regenbogenforellen. Abschlussbericht zum F+E-Vorhaben 76c 040100 94. 85 p. Hrsg.: Bayerisches Landesamt für Umwelt (ed), Augsburg
151. Jo A, Ji K, Choi K (2014) Endocrine disruption effects of long-term exposure to perfluorodecanoic acid (PFDA) and perfluorotridecanoic acid (PFTDA) in zebrafish (*Danio rerio*) and related mechanisms. *Chemosphere* 108:360–366. <https://doi.org/10.1016/j.chemosphere.2014.01.080>

152. Liu C, Deng J, Yu L, Ramesh M, Zhou B (2010) Endocrine disruption and reproductive impairment in zebrafish by exposure to 8:2 fluorotelomer alcohol. *Aquat Toxicol* 96(1):70–76. <https://doi.org/10.1016/j.aquatox.2009.09.012>
153. Mhadhbi L, Rial D, Perez S, Beiras R (2012) Ecological risk assessment of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) in marine environment using *Isochrysis galbana*, *Paracentrotus lividus*, *Siriella armata* and *Psetta maxima*. *J Environ Monit* 14:1375–1382. <https://doi.org/10.1039/c2em30037k>
154. Ankley GT, Cureton P, Hoke RA, Houde M, Kumar A, Kurias J, Lanno R, McCarthy C, Newsted J, Salice CJ, Sample BE, Sepúlveda MS, Steevens J, Valsecchi S (2021) Assessing the ecological risks of per- and polyfluoroalkyl substances: current state-of-the science and a proposed path forward. *Environ Toxicol Chem* 40:564–605
155. Liu CH, Chang VWC, Gin KYH, Nguyen VT (2014) Genotoxicity of perfluorinated chemicals (PFCs) to the green mussel (*Perna viridis*). *Sci Total Environ* 487:117–122. <https://doi.org/10.1016/j.scitotenv.2014.04.017>
156. Lu G, Liu J, Sun L, Yuan L (2015) Toxicity of perfluoronanoic acid and perfluorooctane sulfonate to *Daphnia magna*. *Water Sci Eng* 8:40–48. <https://doi.org/10.1016/j.wse.2015.01.001>
157. Phillips MM, Dinglasan-Panlilio MJ, Mabury SA, Solomon KR, Sibley P (2007) Fluorotelomer acids are more toxic than perfluorinated acids. *Environ Sci Technol* 41:7159–7163. <https://doi.org/10.1021/es070734c>
158. Fabbri R, Montagna M, Balbi T, Raffo E, Palumbo F, Canesi L (2014) Adaptation of the bivalve embryotoxicity assay for the high throughput screening of emerging contaminants in *Mytilus galloprovincialis*. *Mar Environ Res* 99:1–8. <https://doi.org/10.1016/j.marenvres.2014.05.007>
159. Mitchell RJ, Myers AL, Mabury SA, Solomon KR, Sibley PK (2011) Toxicity of fluorotelomer carboxylic acids to the algae *Pseudokirchneriella subcapitata* and *Chlorella vulgaris*, and the amphipod *Hyaella azteca*. *Ecotox Environ Saf* 74(8):2260–2267. <https://doi.org/10.1016/j.ecoenv.2011.07.034>
160. Marziali L, Rosignoli F, Valsecchi S, Polesello S, Stefani F (2019) Effects of perfluoroalkyl substances on a multigenerational scale: a case study with *Chironomus riparius* (Diptera, Chironomidae). *Environ Toxicol Chem* 38(5):988–999. <https://doi.org/10.1002/etc.4392>
161. Stefani F, Rusconi M, Valsecchi S, Marziali L (2014) Evolutionary ecotoxicology of perfluoroalkyl substances (PFASs) inferred from multigenerational exposure: a case study with *Chironomus riparius* (Diptera, Chironomidae). *Aquat Toxicol* 156C:41–51. <https://doi.org/10.1016/j.aquatox.2014.07.020>
162. MacDonald MM, Warne AL, Stock NL, Mabury SA, Solomon KR, Sibley PK (2004) Toxicity of perfluorooctane sulfonic acid and perfluorooctanoic acid to *Chironomus tentans*. *Environ Toxicol Chem* 23(9):2116–2123. <https://doi.org/10.1897/03-449>
163. Bots J, De Bruyn L, Snijders T, Van den Branden B, Van Gossum H (2010) Exposure to perfluorooctane sulfonic acid (PFOS) adversely affects the life-cycle of the damselfly *Enallagma cyathigerum*. *Environ Pollut* 158:101–905. <https://doi.org/10.1016/j.envpol.2009.09.016>
164. Sonter CA, Rader R, Stevenson G, Stavert JR, Wilson SC (2021) Biological and behavioral responses of European honey bee (*Apis mellifera*) colonies to perfluorooctane sulfonate exposure. *Integr Environ Assess Manag* 17(4):673–683
165. Mommaerts V, Hagenars A, Meyer J, De Coen W, Swevers L, Mosalanejad H, Guy Smagghe G (2011) Impact of a perfluorinated organic compound PFOS on the terrestrial pollinator *Bombus terrestris* (Insecta, Hymenoptera). *Ecotoxicology* 20(2):447–456
166. Hoover GM, Chislock MF, Tornabene BJ, Guffey SC, Choi YJ, De Perre C, Hoverman JT, Lee LS, Sepúlveda MS (2017) Uptake and depuration of four per/polyfluoroalkyl substances (PFASs) in northern leopard frog *Rana pipiens* tadpoles. *Environ Sci Technol Lett* 4:399–403
167. Flynn RW, Chislock MF, Gannon ME, Bauer SJ, Tornabene BJ, Hoverman JT, Sepúlveda MS (2019) Acute and chronic effects of perfluoroalkyl substance mixtures on larval American bullfrogs (*Rana catesbeiana*). *Chemosphere* 236:124350
168. Lou Q, Zhang Y, Zhou Z, Shi Y, Ge Y, Ren D, Xu H, Zhao Y, Wie W, Qin Z (2013) Effects of perfluorooctanesulfonate and perfluorobutanesulfonate on the growth and sexual development of *Xenopus laevis*. *Ecotoxicology* 22:1133–1144
169. Cheng Y, Cui Y, Chen H, Xie W (2011) Thyroid disruption effects of environmental level perfluorooctane sulfonates (PFOS) in *Xenopus laevis*. *Ecotoxicol* 20(8):2069–2078
170. Giesy JP, Naile JE, Khim JS, Jones PD, Newsted JL (2010) Aquatic toxicology of perfluorinated chemicals. *Rev Environ Contam Toxicol* 202:1–52. https://doi.org/10.1007/978-1-4419-1157-5_1
171. Ulhaq M, Carlsson G, Orn S, Norrgren L (2013) Comparison of developmental toxicity of seven perfluoroalkyl acids to zebrafish embryos. *Environ Toxicol Pharm* 36(2):423–426. <https://doi.org/10.1016/j.etap.2013.05.004>
172. Duchêne T (2015) Ableitung von Geringfügigkeitsschwellenwerten für per- und polyfluorierte Alkylsubstanzen (PFAS) im Grundwasser auf der Grundlage ausgewählter Studien zur Ökotoxizität von PFAS für aquatische Lebewesen. Abschlussarbeit M.Sc. p 108. Goethe-Universität, Frankfurt am Main
173. Cai Y, Wang O, Zhou B, Yuan R, Wang F, Chen Z, Chen H (2021) A review of responses of terrestrial organisms to perfluorinated compounds. *Sci Total Environ* 793:148565. <https://doi.org/10.1016/j.scitotenv.2021.148565>
174. Zhao S, Fan Z, Sun L, Zhou T, Xing Y, Liu L (2017) Interaction effects on uptake and toxicity of perfluoroalkyl substances and cadmium in wheat (*Triticum aestivum* L.) and rapeseed (*Brassica campestris* L.) from co-contaminated soil. *Ecotoxicol Environ Saf* 137:194–201. <https://doi.org/10.1016/j.ecoenv.2016.12.007>
175. Du W, Liu X, Zhao L, Xu Y, Yin Y, Wu J, Ji R, Sun Y, Guo H (2020) Response of cucumber (*Cucumis sativus*) to perfluorooctanoic acid in photosynthesis and metabolomics. *Sci Total Environ* 724:138257. <https://doi.org/10.1016/j.scitotenv.2020.138257>
176. C8-Panel 2020: the C8 science panel, C8 science panel website (update January 22, 2020). <http://www.c8sciencepanel.org/>. Accessed 13 Mar 2022
177. US EPA (2021) Our current understanding of the human health and environmental risks of PFAS. Per- and polyfluoroalkyl substances (PFAS) are a group of manufactured chemicals. <https://www.epa.gov/pfas/our-current-understanding-human-health-and-environmental-risks-pfas>
178. Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, Ng C, Smith JS, Roberts SM (2021) Per and polyfluoroalkyl substance toxicity and human health review: current state of knowledge and strategies for informing future research. *Environ Toxicol Chem* 40(3):606–630. <https://doi.org/10.1002/etc.4890>
179. Sunderland EM, Hu XC, Dassunacao C, Tokranov AK, Wagner CC, Allen JG (2019) A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. *J Expo Sci Environ Epidemiol* 29(2):131–147. <https://doi.org/10.1038/s41370-018-0094-1>
180. Lau C (2019) Recent animal toxicity findings on PFAS. https://superfund.berkeley.edu/wp-content/uploads/2020/01/Lau_Chris.pdf. Accessed 13 Mar 2022
181. Stahl T, Mattern D, Brunn H (2011) Toxicology of perfluorinated compounds. *Environ Sci Eur* 23:38. <https://doi.org/10.1186/2190-4715-23-38>
182. EFSA Panel on Contaminants in the Food Chain (CONTAM) (2018) Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. *EFSA J* 16(12):5194. <https://doi.org/10.2903/j.efsa.2018.5194>
183. EFSA Panel on Contaminants in the Food Chain (CONTAM) (2020) Risk to human health related to the presence of perfluoroalkyl substances in food. *EFSA J* 18(9):6223
184. EFSA (European Food Safety Authority) (2008) Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts. Scientific opinion of the panel on contaminants in the food chain. *EFSA J* 6:53:1–131
185. Boyd RI, Ahmad S, Singh R, Fazal Z, Prins GS, Erdogan ZM, Irudayaraj J, Spinella MJ (2022) Toward a mechanistic understanding of poly- and perfluoroalkylated substances and cancer. *Cancers* 14:2919. <https://doi.org/10.3390/cancers14122919>
186. Mamsen LS, Björvang RD, Mucs D, Vinnars M-T, Papadogiannakis N, Lindh CH, Andersen CY, Damdimopoulou P (2019) Concentrations of perfluoroalkyl substances (PFASs) in human embryonic and fetal organs from first, second, and third trimester pregnancies. *Environ Int* 124:482–492. <https://doi.org/10.1016/j.envint.2019.01.010>

187. Wise LA, Wesselink AK, Schildroth S, Calafat AM, Bethea TN, Geller RJ, Coleman CM, Fruh V, Claus Henn B, Botelho JC, Harmon QE, Thirkill M, Wegienka GR, Baird DD (2022) Correlates of plasma concentrations of per- and poly-fluoroalkyl substances among reproductive-aged Black women. *Environ Res* 203:111860. <https://doi.org/10.1016/j.envres.2021.111860>
188. Kawabata K, Matsuzaki H, Nukui S, Okazaki M, Sakai A, Kawashima Y, Kudo N (2017) Perfluorodecanoic acid induces cognitive deficit in adult rats. *Toxicol Sci* 157:421–428. <https://doi.org/10.1093/toxsci/kfx058>
189. Viberg H, Lee I, Eriksson P (2013) Adult dose-dependent behavioral and cognitive disturbances after a single neonatal PFHxS dose. *Toxicology* 304:185–191. <https://doi.org/10.1016/j.tox.2012.12.013>
190. Beans C (2021) How “forever chemicals” might impair the immune system. *PNAS* 118(15):e2105018118. <https://doi.org/10.1073/pnas.2105018118>
191. Grandjean P, Andersen EW, Budtz-Jørgensen E, Nielsen F, Mølbak K, Weihe P, Heilmann C (2012) Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA* 307:391–397. <https://doi.org/10.1001/jama.2011.2034>
192. Abraham K, Mielke H, Fromme H, Völkel W, Menze J, Peiser M, Zepp F, Willich SN, Weikert C (2020) Internal exposure to perfluoroalkyl substances (PFASs) and biological markers in 101 healthy 1-year-old children: associations between levels of perfluorooctanoic acid (PFOA) and vaccine response. *Arch Toxicol* 94(6):2131–2147. <https://doi.org/10.1007/s00204-020-02715-4>
193. Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA, Woodruff TJ (2014) The navigation guide—evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environ Health Perspect* 122(10):1028–1039. <https://doi.org/10.1289/ehp.1307893>
194. Xiao C, Grandjean P, Valvi D, Nielsen F, Jensen TK, Weihe P, Oulhote Y (2020) Associations of exposure to perfluoroalkyl substances with thyroid hormone concentrations and birth size. *J Clin Endocrinol Metab* 105(3):735–745. <https://doi.org/10.1210/clinem/dgz147>
195. Darrow LA, Stein CR, Steenland K (2013) Serum perfluorooctanoic acid and perfluorooctane sulfonate concentrations in relation to birth outcomes in the Mid-Ohio Valley, 2005–2010. *Environ Health Perspect* 121(10):1207–1213. <https://doi.org/10.1289/ehp.1206372>
196. Washino N, Saijo Y, Sasaki S, Kato S, Ban S, Konishi K, Ito R, Nakata A, Iwasaki Y, Saito K, Nakazawa H, Kishi R (2009) Correlations between prenatal exposure to perfluorinated chemicals and reduced fetal growth. *Environ Health Perspect* 117(4):660–667. <https://doi.org/10.1289/ehp.11681>
197. Kashino I, Sasaki S, Okada E, Matsuura H, Goudarzi H, Miyashita C, Okada E, Ito YM, Araki A, Kishi R (2020) Prenatal exposure to 11 perfluoroalkyl substances and fetal growth: a large-scale, prospective birth cohort study. *Environ Int* 136:105355. <https://doi.org/10.1016/j.envint.2019.105355>
198. Jin R, McConnell R, Catherine C, Xu S, Walker DI, Stratakis N, Jones DP, Miller GW, Peng C, Conti DV, Vos MB, Chatzi L (2020) Perfluoroalkyl substances and severity of nonalcoholic fatty liver in children: an untargeted metabolomics approach. *Environ Int* 134:105220. <https://doi.org/10.1016/j.envint.2019.105220>
199. Chatzi L (2022) PFAS and liver disease—translating the knowledge into humans and preventive practices. Webinar “exposure to PFAS and liver injury—a systematic review and meta-analysis”. <https://www.healthenvironment.org/webinars/96609>. Accessed 14 Sept 2022
200. Stratakis N, Conti DV, Jin R, Margetaki K, Valvi D, Siskos AP, Maitre L, Garcia E, Varo N, Zhao Y, Roumeliotaki T, Vafeiadi M, Urquiza J, Fernández-Barrés S, Heude B, Basagana X, Casas M, Fossati S, Gražulevičienė R, Andrušaitytė S, Uppal K, McEachan RRC, Papadopoulou E, Robinson O, Haug LS, Wright J, Vos MB, Keun HC, Vrijheid M, Berhane KT, McConnell R, Chatzi L (2020) Prenatal exposure to perfluoroalkyl substances associated with increased susceptibility to liver injury in children. *Hepatology* 72:1758–1770. <https://doi.org/10.1002/hep.31483>
201. Goodrich JA, Walker D, Lin X, Wang H, Lim T, McConnell R, Conti DV, Chatzi L, Setiawan VW (2022) Exposure to perfluoroalkyl substances and risk of hepatocellular carcinoma in a multiethnic cohort. *JHEP Rep*. <https://doi.org/10.1016/j.jhepr.2022.100550>
202. Cao H, Zhou Z, Hu Z, Wei C, Li J, Wang L, Liu G, Zhang J, Wang Y, Wang T, Liang Y (2022) Effect of enterohepatic circulation on the accumulation of per- and polyfluoroalkyl substances: evidence from experimental and computational studies. *Environ Sci Technol* 56:3214–3224. <https://doi.org/10.1021/acs.est.1c07176>
203. Brück K, Stel VS, Gambaro G, Hallan S, Völzke H, Ärnlöv J, Kastarinen M, Guessous I, Vinhas J, Stengel B, Brenner H, Chudek J, Romundstad S, Tomson C, Gonzalez AO, Bello AK, Ferrieres J, Palmieri L, Browne G, Capuano V, van Biesen W, Zoccali C, Gansevoort R, Navis G, Rothenbacher D, Ferraro PM, Nitsch D, Wanner C, Jager KJ (2016) CKD prevalence varies across the European general population. *J Am Soc Nephrol* 27:2135–2147. <https://doi.org/10.1681/ASN.2015050542>
204. Kataria A, Trachtman H, Malaga-Dieguez L, Trasande L (2015) Association between perfluoroalkyl acids and kidney function in a cross-sectional study of adolescents. *Environ Health*. <https://doi.org/10.1186/s12940-015-0077-9>
205. Wen LL, Chen YT, Lee YCG, Ko TL, Chou HC, Juan SH (2021) Perfluorooctane sulfonate induces autophagy-associated apoptosis through oxidative stress and the activation of extracellular signal-regulated kinases in renal tubular cells. *PLoS ONE* 16(1):e0245442. <https://doi.org/10.1371/journal.pone.0245442>
206. International Agency of Research on Cancer (IARC) (2018) Perfluorooctanoic acid. In: Some chemicals used as solvents and in polymer manufacture. IARC-Monographs on the evaluation of cancerogenic risks to humans. 110:37–110. <https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono110-01.pdf>
207. Shearer JJ, Callahan CL, Calafat AM, Huang WY, Jones RR, Sabbiseti VS, Freedman ND, Sampson JN, Silverman DT, Purdue MP, Hofmann JN (2021) Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma. *J Natl Cancer Inst* 113:580–587. <https://doi.org/10.1093/jnci/djaa143>
208. Steenland K, Hofmann JN, Silverman DT, Bartell SM (2022) Risk assessment for PFOA and kidney cancer based on a pooled analysis of two studies. *Environ Int* 167:107425. <https://doi.org/10.1016/j.envint.2022.107425>
209. US Department of Health and Human Services, ATSDR (Agency for Toxic Substances and Disease Registry) (2021) Toxicological profile for perfluoroalkyls. p 993. <https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf>. Accessed 3 Apr 2022
210. Rodgers KM, Udesky JO, Rudel RA, Brody JG (2018) Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. *Environ Res* 160:152–182. <https://doi.org/10.1016/j.envres.2017.08.045>
211. Zeinomar N, Oskar S, Kehm RD, Sahebzada S, Terry MB (2020) Environmental exposures and breast cancer risk in the context of underlying susceptibility: a systematic review of the epidemiological literature. *Environ Res* 187:109346. <https://doi.org/10.1016/j.envres.2020.109346>
212. Ghisari M, Long M, Røge DM, Olsen J, Bonefeld-Jørgensen EC (2017) Polymorphism in xenobiotic and estrogen metabolizing genes, exposure to perfluorinated compounds and subsequent breast cancer risk: a nested case-control study in the Danish national birth cohort. *Environ Res* 154:325–333. <https://doi.org/10.1016/j.envres.2017.01.020>
213. Birru RL, Liang H-W, Farooq F, Bedi M, Feghali M, Haggerty CL, Mendez DD, Catov JM, Ng CA, Adibi JJ (2021) A pathway level analysis of PFAS exposure and risk of gestational diabetes mellitus. *Environ Health* 20:63. <https://doi.org/10.1186/s12940-021-00740-z>
214. Rickard BP, Rizvi I, Fenton SE (2022) Per- and poly-fluoroalkyl substances (PFAS) and female reproductive outcomes: PFAS elimination, endocrine-mediated effects, and disease. *Toxicology* 465:153031. <https://doi.org/10.1016/j.tox.2021.153031>
215. NIH (National Institute of Environmental Health Sciences). Endocrine disruptors. <https://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm>. Accessed 8 Mar 2022
216. Gonsioroski A, Mourikes VE, Flaws JA (2020) Endocrine disruptors in water and their effects on the reproductive system. *Int J Mol Sci* 21(6):1929. <https://doi.org/10.3390/ijms21061929>
217. Caporale N et al (2022) From cohorts to molecules: adverse impacts of endocrine disrupting mixtures. *Science* 375(6582):eabe8244. <https://doi.org/10.1126/science.abe8244>

218. HBM4EU (European Human Biomonitoring Initiative) (2022) Policy brief PFAS. https://www.hbm4eu.eu/wp-content/uploads/2022/06/HBM4EU_Policy-Brief-PFAS.pdf
219. EFSA Scientific Committee (2017) Update: use of the benchmark dose approach in risk assessment. *EFSA J* 15(1):4658. <https://doi.org/10.2903/j.efsa.2017.4658>
220. EFSA Panel on Contaminants in The Food Chain (CONTAM) (2018) Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. *EFSA J* 16(11):5333. <https://doi.org/10.2903/j.efsa.2018.5333>
221. EFSA (2019) Mixtures methodology equips EFSA for multiple chemicals. <https://www.efsa.europa.eu/en/press/news/190325>
222. US EPA (Environmental Protection Agency) (2018) Physiologically-based pharmacokinetic (PBPK) models. Scientific models to help evaluate health effects of chemicals. https://www.epa.gov/sites/default/files/2018-02/documents/pbpb_factsheet_feb2018_0.pdf
223. WHO (2022) PFOS and PFOA in drinking-water—background document for development of WHO guidelines for drinking-water quality. Version for public review. WHO/SDE/WSH/XXX. https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/pfos-pfoa-gdwq-bd-working-draft-for-public-review-29.9.22.pdf?sfvrsn=eac28c23_3
224. Bil W, Zeilmaker M, Fragki S, Lijzen J, Verbruggen E, Bokkers B (2020) Risk assessment of per- and polyfluoroalkyl substance mixtures: a relative potency factor approach. *Environ Toxicol Chem* 40(3):859–870
225. Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) (2022) Scientific Opinion on “Draft Environmental Quality Standards for Priority Substances under the Water Framework Directive”—PFAS. https://health.ec.europa.eu/publications/scheer-scientific-opinion-draft-environmental-quality-standards-priority-substances-under-water_en
226. Amstutz VH, Cengo A, Gehres F, Sijm DTHM, Vrolijk MF (2022) Investigating the cytotoxicity of per- and polyfluoroalkyl substances in HepG2 cells: a structure-activity relationship approach. *Toxicology* 480:153312. <https://doi.org/10.1016/j.tox.2022.153312>
227. Behnisch PA, Besselink H, Weber R, Willand W, Huang J, Brouwer A (2021) Developing potency factors for thyroid hormone disruption by PFASs using TTR-TRb CALUX[®] bioassay and assessment of PFASs mixtures in technical products. *Environ Int* 157:106791. <https://doi.org/10.1016/j.envint.2021.106791>
228. US EPA (United States Environmental Protection Agency), Office of Water (2021) Fact sheet: human health toxicity assessment for GenX chemicals. EPA 822-F-21-006. https://www.epa.gov/system/files/documents/2021-10/genx-final-tox-assessment-general_factsheet-2021.pdf
229. Science Advisory Board (SAB) (2022) Review of EPA’s analysis to support EPA’s national primary drinking water rulemaking for PFAS. EPA-SAB-22-008. August 22/2022. p 147. <https://sab.epa.gov/ords/sab/f?p=100:12:7379831650123:::12>
230. Duffek A, Conrad A, Kolossa-Gehring M, Lange R, Rucic E, Schulte C, Wellmütz J (2020) Per- and polyfluoroalkyl substances in blood plasma—results of the German environmental survey for children and adolescents 2014–2017 (GerES V). *Int J Hyg Environ Health* 228:113549. <https://doi.org/10.1016/j.ijheh.2020.113549>
231. Abraham K, Monien B (2022) Transdermal absorption of 13C4-perfluorooctanoic acid (13C4-PFOA) from a sunscreen in a male volunteer—what could be the contribution of cosmetics to the internal exposure of perfluoroalkyl substances (PFAS)? *Environ Int* 169:107549. <https://doi.org/10.1016/j.envint.2022.107549>
232. Colles A, Bruckers L, Den Hond E, Govarts E, Morrens B, Schettgen T, Buekers J, Coertjens D, Nawrot T, Loots I, Nelen V, De Henauw S, Schoeters G, Baeyens W, van Larebeke N (2020) Perfluorinated substances in the Flemish population (Belgium): levels and determinants of variability in exposure. *Chemosphere* 242:125250. <https://doi.org/10.1016/j.chemosphere.2019.125250>
233. Richterova D, Govarts E, Fabelova L, Rausova K, Rodriguez Martin L, Gilles L, Remy S, Colles A, Rambaud L, Riou M, Gabriel C, Sarigiannis D, Pedraza-Diaz S, Ramos JJ, Kosjek T, Snoj Tratnik J, Lignell S, Gyllenhammar I, Thomsen C, Haug LS, Kolossa-Gehring M, Vogel N, Franken C, Vanlarebeke N, Bruckers L, Stewart L, Sepai O, Schoeters G, Uhl M, Castano A, Esteban Lopez M, Göen T, Palkovicova Murinova L (2023) PFAS levels and determinants of variability in exposure in European teenagers—results from the HBM4EU aligned studies (2014–2021). *Int J Hyg Environ Health* 247:114057. <https://doi.org/10.1016/j.ijheh.2022.114057>
234. Fromme H, Mosch C, Morovitz M, Alba-Alejandre I, Boehmer S, Kiranoglu M, Faber F, Hannibal I, Genzel-Boroviczeny O, Koletzko B, Völkel W (2010) Pre- and postnatal exposure to perfluorinated compounds (PFCs). *Environ Sci Technol* 44(18):7123–7129
235. BfR (Bundesinstitut für Risikobewertung) (2021) PFAS in food: BfR confirms critical exposure to industrial chemicals. BfR opinion no. 020/2021 issued 28 June, 2021. <https://doi.org/10.17590/20210914-121236>
236. Rippen G (2021) Leserbrief zu “PFAS - Flächenhafte Verunreinigungen in Mittelbaden – Eine Übersicht” in altlasten spektrum 6/2020, 252–256. altlasten spektrum 30:31
237. Georgii S (2022) Hessian state laboratory, personal communication
238. EU (2022) Commission recommendation (EU) 2022/1431 of 24 August 2022 on the monitoring of perfluoroalkyl substances in food. *Off J Eur Union L* 221/105, 26.08.2022. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32022H1431>. Accessed 11 Feb 2023
239. EU (2022) Commission Regulation (EU) 2022/2388 of 7 December 2022 amending regulation (EC) no. 1881/2006 as regards maximum levels of perfluoroalkyl substances in certain foodstuffs. *Off J Eur Union L* 316/38, December 8th, 2022. <https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32022R2388&from=IT>. Accessed 11 Feb 2023
240. Andrews DO, Naidenko OV (2020) Population-wide exposure to per- and polyfluoroalkyl substances from drinking water in the United States. *Environ Sci Technol Lett* 7:931–936. <https://doi.org/10.1021/acs.estlett.0c00713>
241. Liu L, Qu Y, Huang J, Weber R (2021) Per- and polyfluoroalkyl substances (PFASs) in Chinese drinking water: risk assessment and geographical distribution. *Environ Sci Eur* 33:6. <https://doi.org/10.1186/s12302-020-00425-3>
242. Yeung LWY, Stacey C, Mabur SA (2017) Simultaneous analysis of perfluoroalkyl and polyfluoroalkyl substances including ultrashort-chain C2 and C3 compounds in rain and river water samples by ultra performance convergence chromatography. *J Chromatogr A* 1522:78–85. <https://doi.org/10.1016/j.chroma.2017.09.049>
243. Neuwald IJ, Hübner D, Wiegand HL, Valkov V, Borchers U, Nödler K, Scheurer M, Hale SE, Arp HPH, Zahn D (2022) Ultra-short-chain PFASs in the sources of German drinking water: prevalent, overlooked, difficult to remove, and unregulated. *Environ Sci Technol* 56(10):6380–6390. <https://doi.org/10.1021/acs.est.1c07949>
244. ECHA: substance info card—trifluoromethanesulphonic acid. <https://echa.europa.eu/de/substance-information/-/substanceinfo/100.014.625>
245. WorldTimes (2022): Durch Zufall entdeckt: Verunreinigtes Trinkwasser bei Bad Wimpfen. <https://www.worldtimes-online.com/news/402-durch-zufall-entdeckt-verunreinigtes-trinkwasser-bei-bad-wimpfen.html>. Accessed 09 May 2022
246. Zhai Z, Wu J, Hu X, Li L, Guo J, Zhang B, Hu J, Zhang J (2015) A 17-fold increase of trifluoroacetic acid in landscape waters of Beijing, China during the last decade. *Chemosphere* 129:110–117. <https://doi.org/10.1016/j.chemosphere.2014.09.033>
247. Scheurer M, Nödler K, Freeling F, Janda J, Happel O, Riegel M, Müller U, Storck FR, Fleig M, Lange FT, Brunsch A, Brauch HJ (2017) Small, mobile, persistent: trifluoroacetate in the water cycle—overlooked sources, pathways, and consequences for drinking water supply. *Water Res* 126:460–471. <https://doi.org/10.1016/j.watres.2017.09.045>
248. Behringer D, Heydel F, Gschrey B, Osterheld S, Schwarz W, Warncke K, Freeling F, Nödler K, Blepp M, Jörß W, Liu R, Ludig S, Rüdener I, Garterer S (2021) Persistent degradation products of halogenated refrigerants and blowing agents in the environment: type, environmental concentrations, and fate with particular regard to new halogenated substitutes with low global warming potential. *Texte* 73/2021. Umweltbundesamt (ed). p 259. <https://www.umweltbundesamt.de/publikationen/persistent-degradation-products-of-halogenated>
249. Joudan S, De Silva AO, Young CJ (2021) Insufficient evidence for the existence of natural trifluoroacetic acid. *Environ Sci Process Impacts* 23:1641–1649
250. Nödler K, Freeling F, Sandholzer A, Schaffer M, Schmid R, Scheurer M (2019) Untersuchungen zum „Vorkommen und Bildungspotential von Trifluoacetat (TFA) in niedersächsischen Oberflächengewässern.

- Landesweiter Überblick und Identifikation von Belastungsschwerpunkten. p 19. Niedersächsischer Landesbetrieb für Wasserwirtschaft, Küsten- und Naturschutz (ed.). https://www.nlwkn.niedersachsen.de/startseite/service/veroeffentlichungen_webshop/schriften_zum_download/downloads_gewaessergute/veroeffentlichungen-zum-thema-gewaessergute-107788.html
251. Ellis DA, Mabury SA, Martin JW, Muir DC (2001) Thermolysis of fluoropolymers as a potential source of halogenated organic acids in the environment. *Nature* 412(6844):321–324. <https://doi.org/10.1038/35085548>
 252. Banning H (2021) Welche Rolle spielen Rückstände von Pflanzenschutzmitteln für die TFA-Belastung? Vortrag beim DUH-Fachgespräch "TFA-Belastung in Gewässern". 18.05.2021
 253. Freeling F, Behringer D, Heydel F, Scheurer M, Ternes TA, Nödler K (2020) Trifluoroacetate in precipitation: deriving a benchmark data set. *Environ Sci Technol* 54(18):11210–11219. <https://doi.org/10.1021/acs.est.0c02910>
 254. Umweltbundesamt (2021) Trifluoressigsäure aus fluorierten Kältemitteln belastet Regenwasser – Umstieg auf natürliche Kältemittel schnell nötig. Pressemitteilung 22/2021 vom 25.05.2021. <https://www.umweltbundesamt.de/presse/pressemitteilungen/trifluoressigsaeure-aus-fluorierten-kaeltemitteln>
 255. Freeling F, Scheurer M, Koschorreck J, Hoffmann G, Ternes TA, Nödler K (2022) Levels and temporal trends of trifluoroacetate (TFA) in archived plants: evidence for increasing emissions of gaseous TFA precursors over the last decades. *Environ Sci Technol Lett* 9:400–405. <https://doi.org/10.1021/acs.estlett.2c00164>
 256. Freeling F, Scheurer M (2021) Langzeitrends für Trifluoressigsäure in terrestrischen Umweltproben - Untersuchung von Pflanzenproben der Umweltprobenbank des Bundes (UPB) auf Trifluoressigsäure. Bericht des Technologiezentrums Wasser (TZW) an das Umweltbundesamt. UBA-Texte 177/2021. p 31. Karlsruhe. <https://www.umweltbundesamt.de/publikationen/langzeitrends-fuer-trifluoressigsaeure-in-uba-texte-177-2021>
 257. Boutonnet JC, Bingham P, Calamari D, de Rooij C, Franklin J, Kawano T, Libre J-M, McCulloch A, Malinverno G, Odom JM, Rusch GM, Smythe K, Sobolev I, Thompson R, Tiedje JM (1999) Environmental risk assessment of trifluoroacetic acid. *Hum Ecol Risk Assess* 5:59–124. <https://doi.org/10.1080/10807039991289644>
 258. Benesch JA, Gustin MS, Cramer G, Cahill TM (2002) Investigation of effects of trifluoroacetate on vernal pool ecosystems. *Environ Toxicol Chem* 21:640–647. <https://doi.org/10.1002/etc.5620210325>
 259. Zhang L, Sun H, Wang Q, Chen H, Yao Y, Zhao Z, Alder AC (2019) Uptake mechanisms of perfluoroalkyl acids with different carbon chain lengths (C2–C8) by wheat (*Triticum aestivum* L.). *Sci Total Environ* 654:19–27. <https://doi.org/10.1016/j.scitotenv.2018.10.443>
 260. Duan Y, Sun H, Yao Y, Meng Y, Li Y (2020) Distribution of novel and legacy per-/polyfluoroalkyl substances in serum and its associations with two glycemic biomarkers among Chinese adult men and women with normal blood glucose levels. *Environ Int* 134:105295. <https://doi.org/10.1016/j.envint.2019.105295>
 261. European Chemicals Agency (ECHA): registration dossier trifluoroacetic acid. March 03, 2011. Last modified November 29, 2022. <https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/5203>. Accessed 11 Feb 2023
 262. Umweltbundesamt (2020) Trifluoressigsäure (TFA) – Gewässerschutz im Spannungsfeld von toxikologischem Leitwert, Trinkwasserhygiene und Eintragsminimierung – Erläuterungen zur Einordnung des neuen Trinkwasserleitwerts von 60 µg/L. https://www.umweltbundesamt.de/sites/default/files/medien/362/dokumente/2020_10_20_uba_einordnung_tfa_leitwert.pdf
 263. Umweltbundesamt (2020) Ableitung eines gesundheitlichen Leitwertes für Trifluoressigsäure (TFA). https://www.umweltbundesamt.de/sites/default/files/medien/421/dokumente/ableitung_eines_gesundheitlichen_leitwertes_fuer_trifluoressigsaeure_fuer_uba-homepage.pdf
 264. Ghantous H, Parnerud I, Danielsson BRG, Dencker L (1986) Distribution of halothane and the metabolites trifluoroacetic acid and bromide in the conceptus after halothane inhalation by pregnant mice. *Acta Pharmacol Toxicol* 59(5):370–376. <https://doi.org/10.1111/j.1600-0773.1986.tb00186.x>. (Abstract)
 265. Cappon GD, Keller DA, Brock WJ, Slauter RW, Hurtt ME (2002) Effects of HCFC-123 exposure to maternal and infant rhesus monkeys on hepatic biochemistry, lactational parameters and postnatal growth. *Drug Chem Toxicol* 25:481–496. <https://doi.org/10.1081/DCT-120014798>. (Abstract)
 266. US EPA (Environmental Protection Agency) (2021) Other test method 45 (OTM-45). Measurement of selected per- and polyfluorinated alkyl substances from stationary sources. <https://www.epa.gov/water-research/pfas-analytical-methods-development-and-sampling-research>
 267. DIN 38407-42:2011-03 (2011) Deutsche Einheitsverfahren zur Wasser-, Abwasser- und Schlammuntersuchung – Gemeinsam erfassbare Stoffgruppen (Gruppe F) – Teil 42: Bestimmung ausgewählter polyfluorierter Verbindungen (PFC) in Wasser – Verfahren mittels Hochleistungs-Flüssigkeitschromatographie und massenspektrometrischer Detektion (HPLC-MS/MS) nach Fest-Flüssig-Extraktion (F42). Beuth, Berlin
 268. ISO 21675 (2019) Water quality—determination of perfluoroalkyl and polyfluoroalkyl substances (PFAS) in water—method using solid phase extraction and liquid chromatography-tandem mass spectrometry (LC-MS/MS). ISO (International Organization for Standardization) 2019–10. <https://www.iso.org/standard/71338.html>
 269. Directive (EU) 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the quality of water intended for human consumption (recast). Off J Eur Union, L435/1–62. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020L2184&from=EN>. Accessed 23 Dec 2020
 270. prEN 17892 (2022) Water quality—determination of the sum of perfluorinated substances (sum of PFAS) in drinking water—method using liquid chromatography/mass spectrometry (LC/MS). CEN, European Committee for Standardization. August 25, 2022
 271. DIN 38414-14:2011-08 (2011) Deutsche Einheitsverfahren zur Wasser-, Abwasser- und Schlammuntersuchung – Schlamm und Sedimente (Gruppe S) – Teil 14: Bestimmung ausgewählter polyfluorierter Verbindungen (PFC) in Schlamm, Kompost und Boden – Verfahren mittels Hochleistungs-Flüssigkeitschromatographie und massenspektrometrischer Detektion (HPLC-MS/MS) (S14). Beuth, Berlin
 272. Aßhoff N (2022) Entwicklung einer Methode zur Bestimmung per- und polyfluorierter Alkylsubstanzen (PFAS) in ng/kg-Bereich mittels LC-MS/MS. *Lebensmittelchemie* 76(S1):S1–114–S1115
 273. European Committee for Standardization (CEN) (2010) CEN/TS 15968:2010 Determination of extractable perfluoroctanesulfonate (PFOS) in coated and impregnated solid articles, liquids and fire fighting foams—method for sampling, extraction and analysis by LC-qMS or LC-tandem/MS. <https://standards.iteh.ai/catalog/standards/cen/eb019682-5765-4ae0-9b89-2697e94b9532/cen-ts-15968-2010>. Accessed 11 Feb 2023
 274. Barber JL, Berger U, Chaemfa C, Huber S, Jahnke A, Temme C, Jones KC (2007) Analysis of per- and polyfluorinated alkyl substances in air samples from Northwest Europe. *J Environ Monit* 9(6):530–541. <https://doi.org/10.1039/b701417a>
 275. Jahnke A, Ahrens L, Ebinghaus R, Temme C (2007) Urban vs. remote air concentrations of fluorotelomer alcohols and other polyfluorinated alkyl substances in Germany. *Environ Sci Technol* 41(3):745–752. <https://doi.org/10.1021/es0619861>
 276. Müller CE, Gerecke AC, Bogdal C, Wang Z, Scheringer M, Hungerbühler K (2012) Atmospheric fate of poly- and perfluorinated alkyl substances (PFASs): I. Day–night patterns of air concentrations in summer in Zürich, Switzerland. *Environ Pollut* 169:196–203. <https://doi.org/10.1016/j.envpol.2012.04.010>
 277. Wang Z, Xie Z, Möller A, Mi W, Wolschke H, Ebinghaus R (2014) Atmospheric concentrations and gas/particle partitioning of neutral poly- and perfluoroalkyl substances in northern German coast. *Atmos Environ* 95:207–213. <https://doi.org/10.1016/j.atmosenv.2014.06.036>
 278. Wu R, Lin H, Yamazaki E, Taniyasu S, Söregard M, Ahrens L, Lam PKS, Eun H, Yamashita N (2021) Simultaneous analysis of neutral and ionizable per- and polyfluoroalkyl substances in air. *Chemosphere* 280:130607. <https://doi.org/10.1016/j.chemosphere.2021.130607>
 279. Bayerisches Landesamt für Umwelt (2010) Bestimmung persistenter bioakkumulierender Perfluoroalkylverbindungen in verschiedenen Umweltmatrices. *Bestimmung persistenter, bioakkumulierender Perfluoroalkylverbindungen in verschiedenen Umweltmatrices - Bioakkumulieren de Perfluoroalkylverbindungen - Publikationsshop der Bayerischen Staatsregierung (bayern.de)*

280. VDI Guideline 3498 Part2 (2002) Ambient air measurement—indoor air measurement. Measurement of polychlorinated dibenzo-p-dioxins and dibenzofurans. Method using small filters. Beuth, Berlin
281. VDI Guideline 2464 Part 3 (2012) Ambient air measurement—indoor air measurement. Measurement of polybrominated diphenyl ethers, hexabromocyclododecane and hexabromobenzene with GC/MS. Beuth, Berlin
282. VDI Guideline 2464 Part2 (2009) Ambient air measurement—indoor air measurement. Measurement of polychlorinated biphenyls (PCBs). HR-GC/HR-MS method for coplanar PCBs. Beuth, Berlin
283. Kunkel U, Bavarian Environment Agency (2022) unpublished results
284. Schulz W, Lucke T et al (2019) Non-target screening in water analysis. Guideline for the application of LC-ESI-HRMS for screening. https://www.wasserchemische-gesellschaft.de/images/HALL/NTS-Guideline_EN_s.pdf
285. Hollender J, van Bavel B, Dulio V, Eivind Farmen E, Furtmann K, Koschorreck J, Kunkel U, Krauss M, Munthe J, Schlabach M, Slobodnik J, Stroomberg G, Ternes T, Thomaidis NS, Togola A, Tornero A (2019) High resolution mass spectrometry-based non-target screening can support regulatory environmental monitoring and chemicals management. *Environ Sci Eur* 31:42. <https://doi.org/10.1186/s12302-019-0225-x>
286. Consumer Reports (2020) Solvay impedes research into unknown PFAS by threatening testing lab with legal action. <https://www.consumerreports.org/toxic-chemicals-substances/solvay-impedes-research-into-new-pfas-chemicals-by-threatening-testing-lab-with-legal-action-a5034074563/>
287. Young RB, Pica NE, Sharifan H, Chen H, Roth HK, Blakney GT, Borch T, Higgins CP, Kornuc JJ, McKenna AM, Blotevogel J (2022) PFAS analysis with ultrahigh resolution 21T FT-ICR MS: suspect and nontargeted screening with unrivaled mass resolving power and accuracy. *Environ Sci Technol* 56:2455–2465. <https://doi.org/10.1021/acs.est.1c08143>
288. Wischer R, Bartz J, Lange FT (2022) Minimierung der Fluoridstörung und Optimierung der Wiederfindungen per- und polyfluorierter Alkylsubstanzen (PFAS) bei der Bestimmung des adsorbierbaren organisch gebundenen Fluors (AOF). *Vom Wasser* 120(3):56–64. <https://doi.org/10.1002/vomw.202200011>
289. Han Y, Pulikkal VF, Sun M (2021) Comprehensive validation of the adsorbable organic fluorine analysis and performance comparison of current methods for total per- and polyfluoroalkyl substances in water samples. *Environ Sci Technol Water* 1:1474–1482. <https://doi.org/10.1021/acestwater.1c00047>
290. DIN 38409-59:2022-10 (2020) Deutsche Einheitsverfahren zur Wasser-, Abwasser- und Schlammuntersuchung – Summarische Wirkungs- und Stoffkenngrößen (Gruppe H) – Teil 59: Bestimmung von adsorbierbarem organisch gebundenem Fluor, Chlor, Brom und Iod (AOF, AOCl, AOBr, AOI) mittels Verbrennung und nachfolgender ionenchromatographischer Messung (H59). Beuth, Berlin
291. ISO (2022) Water quality—determination of adsorbable organically bound fluorine, chlorine, bromine and iodine (AOF, AOCl, AOBr, AOI)—method using combustion and subsequent ion chromatographic measurement. FORM 4—new work item proposal (NP) version 01/2022. Draft standard ISO/WD 18127:2022(E). 2022-06-08
292. Metzger M, Ley P, Sturm M, Meermann B (2019) Screening method for extractable organically bound fluorine (EOF) in river water samples by means of high-resolution-continuum source graphite furnace molecular absorption spectrometry (HR-CS GF MAS). *Anal Bioanal Chem* 411:4647–4660. <https://doi.org/10.1007/s00216-019-01698-1>
293. Gehrenkemper L, Simon F, Roesch P, Fischer E, von der Au M, Pfeifer J, Cossmer A, Wittwer P, Vogel C, Simon F-G, Meermann B (2021) Determination of organically bound fluorine sum parameters in river water samples—comparison of combustion ion chromatography (CIC) and high resolution-continuum source-graphite furnace molecular absorption spectrometry (HR-CS-GFMS). *Anal Bioanal Chem* 413:103–115
294. Simon F, Gehrenkemper L, von der Au M, Wittwer P, Roesch P, Pfeifer J, Cossmer A, Meermann B (2022) A fast and simple PFAS extraction method utilizing HR-CS-GFMS for soil samples. *Chemosphere* 295:133922. <https://doi.org/10.1016/j.chemosphere.2022.133922>
295. DIN 38414-17:2017-01 (2017) Deutsche Einheitsverfahren zur Wasser-, Abwasser- und Schlammuntersuchung – Schlamm und Sedimente (Gruppe S) – Teil 17: Bestimmung von extrahierbaren organisch gebundenen Halogenen (EOX) (S17). Beuth, Berlin
296. Houtz EF, Sedlak DL (2012) Oxidative conversion as a means of detecting precursors to perfluoroalkyl acids in urban runoff. *Environ Sci Technol* 46(17):9342–9349. <https://doi.org/10.1021/es302274g>
297. Zhang C, Hopkins ZR, McCord J, Strynar MJ, Knappe DRU (2019) Fate of per- and polyfluoroalkyl ether acids in the total oxidizable precursor assay and implications for the analysis of impacted water. *Environ Sci Technol Lett* 6:662–668. <https://doi.org/10.1021/acs.estlett.9b00525>
298. Janda J, Nödler K, Scheurer M, Happel O, Nürenberg G, Zwiener C, Lange FT (2019) Closing the gap—inclusion of ultrashort-chain perfluoroalkyl carboxylic acids in the total oxidizable precursor (TOP) assay protocol. *Environ Sci Process Impacts* 21:1926–1935. <https://doi.org/10.1039/C9EM00169G>
299. Gökçener B, Lange FT, Lesmeister L, Gökçe E, Dahme HU, Bandow N, Biegel-Engler A (2022) Digging deep—implementation, standardisation and interpretation of a total oxidisable precursor (TOP) assay within the regulatory context of per- and polyfluoroalkyl substances (PFASs) in soil. *Environ Sci Eur* 34:52. <https://doi.org/10.1186/s12302-022-00631-1>
300. Nickerson A, Maizel AC, Kulkarni P, Adamson DT, Kotnuc JJ, Higgins CP (2020) Enhanced extraction of AFFF-associated PFASs from source zone soils. *Environ Sci Technol* 54:4952–4962. <https://doi.org/10.1021/acs.est.0c00792>
301. DIN 51723:2002-06 (2002) Prüfung fester Brennstoffe – Bestimmung des Fluorgehaltes. Beuth, Berlin
302. ISO 10304-1 (2007) Water quality—determination of dissolved anions by liquid chromatography of ions—part 1: determination of bromide, chloride, fluoride, nitrate, nitrite, phosphate and sulfate. ISO (International Organization for Standardization) 2007–08. <https://www.iso.org/standard/46004.html>
303. Weiss JM, Andersson PL, Lamoree MH, Leonards PEG, van Leeuwen SPJ, Hamers T (2009) Competitive binding of poly- and perfluorinated compounds to the thyroid hormone transport protein transthyretin. *Toxicol Sci* 109(2):206–216
304. Stockholm Convention on Persistent Organic Pollutants (2017) Guidance for the inventory of perfluorooctane sulfonic acid (PFOS) and related chemicals listed under the Stockholm convention on persistent organic pollutants. <http://chm.pops.int/Implementation/IndustrialPOPs/PFAS/Guidance/tabid/5225/Default.aspx>. Accessed 11 Feb 2023
305. ECHA (European Chemicals Agency) (2022) Annex XV restriction report, proposal for a restriction (of) Per- and polyfluoroalkyl substances (PFASs) in firefighting foams, version number 2.0, Date 23 March 2022. p 211. https://echa.europa.eu/documents/10162/0/rest_pfas_ff_axvreport_en.pdf/5ee6f85d-8339-cf1c-34c8-cfcb2861bde7?t=1645608390512
306. Mersmann M (2021) PFAS-Situation in NRW: Bestandsaufnahme punktueller Fälle und Hintergrundbelastungen. Fälle mit PFAS-Belastungen im Boden und Grundwasser in Nordrhein-Westfalen (Stand: Mai 2021). BEW-Seminar PFAS in Boden und Grundwasser. Duisburg. https://www.lanuv.nrw.de/fileadmin/lanuv/boden/uploads/PFAS-Bestandsaufnahme_Bericht_f%C3%BCr_Homepage.pdf
307. Held T (2015) Länderfinanzierungsprogramm Wasser, Boden, Abfall: Projekte B 4.14 und 4.15 LABO. <http://www.laenderfinanzierungsprogramm.de/projektberichte/labob/>
308. Bantz I, Valentin I (2019) Stand der Erfassung und Sanierung von PFC-Verunreinigungen in Düsseldorf. *Mitt Umweltchem Ökotox* 25(1):2–7
309. Freie Hansestadt Bremen: Verunreinigungen durch Schaumlöschmittel im Bereich Bremer Flughafen und Grolland. https://www.bauumwelt.bremen.de/umwelt/boden_und_altlasten/verunreinigungen_durch_schaumloeschmittel_im_bereich_bremer_flughafen_und_grolland-98443
310. Klatt P (2022) Zehn Jahre PFAS-Belastung in Mittelbaden: Ein "Freilandexperiment" mit unbekanntem Ausgang? *Mitt Umweltchem Ökotox* 28(2):47–52
311. Klatt P (2021) PFAS/PFC in Mittelbaden – Globale Umweltgifte werden zum regionalen Problem. p 45. <https://pfas-dilemma.info/images/PFAS-Broschuere.pdf>
312. Ministerium für Ernährung, ländlichen Raum und Verbraucherschutz Baden-Württemberg (2017) Erlass vom 01.03.2017. Lebensmittelüberwachung; Fortschreibung der Bewertung von kurzkettigen perfluorierten Verbindungen (PFC) in Lebensmitteln, Az. 36-5477.10-71
313. Ministerium für Ernährung, ländlichen Raum und Verbraucherschutz Baden-Württemberg (2021) Erlass vom 28.06.2021.

- PFAS-Kontaminationen in Lebensmitteln; Anwendung des EFSA-TWI-Werts bei der Lebensmittelüberwachung und beim Vor-Ernte-monitoring. https://rp.baden-wuerttemberg.de/fileadmin/RP-Internet/Karlsruhe/Abteilung_5/Referat_54.1/Stabsstelle_PFC/_DocumentLibraries/Documents/pfc_lebensmittelueberw_MLR-Erlass_210628.pdf
314. arpav: Sostanze perfluoro alchiliche (PFAS). <https://www.arpav.veneto.it/+api++/temi-ambientali/acque-interne/sostanze-perfluoro-alchiliche-pfas>. Accessed 20 Jan 2023
 315. Pitter G, da Re F, Canova C, Barbieri G, Zare Jeddi M, Daprà F, Manea F, Zolin R, Bettega AM, Stopazzolo G, Vittorii S, Zambelli L, Martuzzi M, Mantoan D, Russo F (2020) Serum levels of perfluoroalkyl substances (PFAS) in adolescents and young adults exposed to contaminated drinking water in the Veneto Region, Italy: a cross-sectional study based on a health surveillance program. *Environ Health Perspect* 128(2):027007. <https://doi.org/10.1289/EHP5337>
 316. Washington JW, Rosal CG, McCord JP, Strynar MJ, Lindstrom AB, Bergman EL, Goodrow SM, Tadesse HK, Pilant AN, Washington BJ, Davis MJ, Stuart BG, Jenkins TM (2020) Nontargeted mass-spectral detection of chloroperfluoropolyether carboxylates in New Jersey soils. *Science* 368:1103–1107. <https://doi.org/10.1126/science.aba7127>
 317. Oliaei F, Kriens D, Weber R, Watson A (2013) PFOS and PFC releases and associated pollution from a PFC production plant in Minnesota (USA). *Environ Sci Pollut Res Int* 20:1977–1992. <https://doi.org/10.1007/s11356-012-1275-4>
 318. EU (2022) Regulation (EU) 2022/2400 of the European parliament and of the council of 23 November 2022 amending Annexes IV and V to regulation (EU) 2019/1021 on persistent organic pollutants. <http://data.europa.eu/eli/reg/2022/2400/oj>. Accessed 11 Feb 2023
 319. Bundesministerium für Umwelt, Naturschutz, nukleare Sicherheit und Verbraucherschutz (2022) Guidelines for PFAS assessment. Recommendations for the uniform nationwide assessment of soil and water contamination and for the disposal of soil material containing PFA. Last Update February 21, 2022. https://www.bmu.de/fileadmin/Daten_BMU/Download_PDF/Bodenschutz/pfas_leitfaden_2022_en_bf.pdf; <https://www.bmu.de/download/leitfaden-zur-pfas-bewertung>
 320. Bund/Länder-Arbeitsgemeinschaft Wasser (2017) Ableitung von Geringfügigkeitsschwellenwerten für das Grundwasser – Per- und polyfluorierte Chemikalien (PFC); mit Datenblättern zu human- und ökotoxischen Wirkungen von 14 PFAS. <https://www.lawa.de/Publikationen-363-Grundwasser.html>
 321. Bundesministerium für Umwelt, Naturschutz, nukleare Sicherheit und Verbraucherschutz (2021) Neufassung der Bundes-Bodenschutz- und Altlastenverordnung (BBodSchV) vom. <https://www.bmu.de/themen/wasser-ressourcen-abfall/boden-und-altlasten/die-neue-bundes-bodenschutz-und-altlastenverordnung>. Accessed 16 July 2021
 322. Scheurer M, Lesmeister L, Breuer J, Boeddinghaus R, Schultheiß M, Mechler M, Dobslaw D, Engesser K-H, Kuch B (2022) Erarbeitung von fachlichen Grundlagen für die Ableitung von Bewertungsmaßstäben für weitere bodenrelevante, bisher nicht in der BBodSchV enthaltene Schadstoffe und Schadstoffgruppen in Böden (Schwerpunkt PFAS) im Wirkungspfad Boden – Pflanze, Umweltbundesamt Texte 77/2022. p 227. <https://www.umweltbundesamt.de/publikationen/erarbeitung-von-fachlichen-grundlagen-fuer-die>
 323. Weber R, Bell L, Watson A, Petrlik J, Paun MC, Vijgen J (2019) Assessment of POPs contaminated sites and the need for stringent soil standards for food safety for the protection of human health. *Environ Pollut* 249:703–715. <https://doi.org/10.1016/j.envpol.2019.03.066>
 324. Winkler J (2015) High levels of dioxin-like PCBs found in organic-farmed eggs caused by coating materials of asbestos-cement fiber plates: a case study. *Environ Intern* 80:72–78. <https://doi.org/10.1016/j.envint.2015.03.005>
 325. PFAS found in organic eggs in Denmark. <https://www.food.dtu.dk/english/news/pfas-found-in-organic-eggs-in-denmark?id=789f9ba1-bdfc-4a7d-908b-fc6ccff4742>. Accessed 06 Feb 2023
 326. Granby K, DTU Fødevareinstituttet (2023) Indhold af PFAS i fiskemel og via indhold i økologisk foder i økologiske æg. 9 pages. <https://www.food.dtu.dk/english/-/media/institutter/foedevareinstituttet/publikationer/pub-2023/pfas-i-oekologiske-aeg-og-foder-jan-2023.pdf?la=en&hash=17AC563D804FF35B1A97FDF6C71EE99E3B01F819>. Accessed 06 Feb 2023
 327. Brambilla G, D'Hollander W, Oliaei F, Stahl T, Weber R (2015) Pathways and factors for food safety and food security at PFOS contaminated sites within a problem based learning approach. *Chemosphere* 129:192–202. <https://doi.org/10.1016/j.chemosphere.2014.09.050>
 328. US EPA (2022) Proposed designation of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) as CERCLA hazardous substances. <https://www.epa.gov/superfund/proposed-designation-perfluorooctanoic-acid-pfoa-and-perfluorooctanesulfonic-acid-pfos>. Accessed 10 Sept 2022
 329. Bloomberg Law (2022) Companies face billions in damages as PFAS lawsuits flood courts. <https://news.bloomberglaw.com/pfas-project/companies-face-billions-in-damages-as-pfas-lawsuits-flood-courts>. Accessed 25 Jan 2023
 330. DW (2022) US company 3M agrees to pay for Belgium chemical leak. <https://www.dw.com/en/belgium-us-company-3m-agrees-to-massive-payout-for-chemical-leak/a-62385891>. Accessed 25 Jan 2023
 331. 3M (2022) Agreement reached between the Flemish government and 3M Belgium to support the people of Flanders. <https://pfas.3m.com/2022-07-06-Agreement-Reached-Between-the-Flemish-Government-and-3M-Belgium-to-Support-the-People-of-Flanders>. Accessed 25 Jan 2023
 332. Riegel M (2022) Entfernung (kurzketziger) PFAS mit einem neuen Ansatz aus Aktivkohle und Ionenaustauscher. *Vom Wasser* 120(1):4–16. <https://doi.org/10.1002/vomw.202200001>
 333. Bayer. Landesamt für Umwelt (2014) Entwicklung von Aufbereitungsverfahren für PFC-haltige Grundwässer am Beispiel des Flughafens Nürnberg. https://www.lfu.bayern.de/analytik_stoffe/pfc/fachbeitraege/doc/kurzfassung_lfu.pdf
 334. Rohn A (2021) PFAS: Technologische Ansätze zu Elimination & Management von Konzentraten. Per- und polyfluorierte Alkylverbindungen (PFAS). *IWW J* 54:10–11.
 335. Cornelsen M, Weber R, Panglisch S (2021) Minimizing the environmental impact of PFAS by using specialized coagulants for the treatment of PFAS polluted waters and for the decontamination of firefighting equipment. *Emerg Contam* 7:63–76. <https://doi.org/10.1016/j.emcon.2021.02.001>
 336. Cornelsen M (2022) Untersuchungen zur Anwendung von Aktivkohlen, Ionenaustauschern und eines funktionellen Fällmittels für die Elimination von Per- und Polyfluoralkyl-Substanzen (PFAS) aus hoch belasteten Wässern. Dissertation zum Dr.-Ing., Fakultät für Ingenieurwissenschaften, Abteilung Maschinenbau und Verfahrenstechnik, Universität Duisburg-Essen. <https://doi.org/10.17185/dupublico/75897>
 337. Roest K, ter Laak TL, Huiting H, Siegers W, Meekel N, de Jong C, de Jong M, van Houten M, Pancras T, Plaisier W, Dalmijn J (2021) Performance of water treatment systems for PFAS removal. CONCAWE report no. 5/21. p 119. https://www.concawe.eu/wp-content/uploads/Rpt_21-5.pdf
 338. US EPA (Environ Protection Agency) (2021) Potential PFAS destruction technology: electrochemical oxidation—research BRIEF. <https://www.epa.gov/chemical-research/research-brief-potential-pfas-destruction-technology-electrochemical-oxidation>
 339. Wang Y, Pierce RD Jr, Shia H, Lia C, Huang Q (2020) Electrochemical degradation of perfluoroalkyl acids by titanium suboxide anodes. *Environ Sci Water Res Technol* 6:144–152. <https://doi.org/10.1039/C9EW00759H>
 340. Krause M, Thoma E, Sahle-Demessie B, Crone A, Whitehill A, Shields E, Gullett B (2022) Supercritical water oxidation as an innovative technology for PFAS destruction. *Int J Environ Eng*. [https://doi.org/10.1061/\(ASCE\)EE.1943-7870.0001957](https://doi.org/10.1061/(ASCE)EE.1943-7870.0001957)
 341. Singh RK, Brown E, Mededovic Thagard S, Holsen TM (2021) Treatment of PFAS containing landfill leachate using an enhanced contact plasma reactor. *J Haz Mat* 408:124452. <https://doi.org/10.1016/j.jhazmat.2020.124452>
 342. Grabda M, Zawadzki M, Oleszek S, Matsumoto M, Królkowski M, Tahara Y (2022) Removal of perfluorooctanoic acid from water using a hydrophobic ionic liquid selected using the conductor-like screening model for realistic solvents. *Environ Sci Technol* 56(10):6445–6454. <https://doi.org/10.1021/acs.est.1c08537>
 343. Liu Z, Chen Z, Gao J, Yu Y, Men Y, Gu C, Liu J (2022) Accelerated degradation of perfluorosulfonates and perfluorocarboxylates by UV/sulfite + iodide: reaction mechanisms and system efficiencies. *Environ Sci Technol* 56:3699–3709. <https://doi.org/10.1021/acs.est.1c07608>

344. Chen G, Liu S, Shi Q, Gan J, Jin B, Men Y, Liu H (2022) Hydrogen-polarized vacuum ultraviolet photolysis system for enhanced destruction of perfluoroalkyl substances. *J Hazard Mater Lett* 3:100072. <https://doi.org/10.1016/j.hazl.2022.100072>
345. Quian L, Kopinke FD, Scherzer T, Griebel J, Georgi A (2022) Enhanced degradation of perfluorooctanoic acid by heat-activated persulfate in the presence of zeolites. *Chem Eng J* 429:132500. <https://doi.org/10.1016/j.cej.2021.132500>
346. Georgi A, Mackenzie K (2022) PFAS – Eine Herausforderung für die Umwelttechnologie. *Mitt Umweltchem Ökotox* 28(2):53–57
347. EFCTC (European FluoroCarbons Technical Committee) (2022) What is the Kigali amendment? <https://www.fluorocarbons.org/environment/climate-change/kigali-amendment/>
348. Stockholm Convention on Persistent Organic Pollutants (2022) Proposal to list long-chain perfluorocarboxylic acids, their salts and related compounds in Annexes A, B and/or C to the Stockholm convention on persistent organic pollutants, UNEP/POPS/POPRC.17/7. <https://chm.pops.int>
349. SAICM (Strategic Approach to an International Chemicals Management) (2022) Perfluorinated chemicals. <https://saicmknowledge.org/program/perfluorinated-chemicals>. Accessed 10 Feb 2023
350. European Chemical Agency (ECHA) (2022) Candidate list of substances of very high concern for authorisation. 233 results. <https://echa.europa.eu/en/candidate-list-table>. Accessed 24 Jan 2023
351. Henry BJ, Carlin JP, Hammerschmidt JA, Buck RS, Buxton LW, Fiedler H, Seed J, Hernandez O (2018) A critical review of the application of polymer of low concern and regulatory criteria to fluoropolymers. *Integr Environ Assess Manag* 14:316–334. <https://doi.org/10.1002/ieam.4035>
352. Wood (2020) Scientific and technical support for the development of criteria to identify and group polymers for registration/evaluation under REACH and their impact assessment. Final report. European Commission, ENV.B.2—sustainable chemicals. p 352. <https://op.europa.eu/de/publication-detail/-/publication/1cc811ff-d5fc-11ea-adf7-01aa75ed71a1>
353. OECD (2022) Synthesis report on understanding side-chain fluorinated polymers and their life cycle. OECD series on risk management no. 73. Environment, health and safety, environment directorate, OECD. <https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/synthesis-report-on-understanding-side-chain-fluorinated-polymers-and-their-life-cycle.pdf>. Accessed 11 Feb 2023
354. Gardella J (2021) Vermont PFAS legislation passes—businesses feel impact. *The National Law Review*, Vol XI, No 221. <https://www.natlawreview.com/article/vermont-pfas-legislation-passes-businesses-feel-impact>
355. Chemical Watch (2021) Maine lawmakers pass unprecedented bill to ban PFASs in products. July 02. <https://chemicalwatch.com/294168/maine-lawmakers-pass-unprecedented-bill-to-ban-pfass-in-products>
356. Ministry of Environment and Food Denmark, Danish Veterinary and Food Administration (2020) Ban on fluorinated substances in paper and board food contact materials (FCM). Fact sheet June 2020. <https://www.foedevarestyrelsen.dk/english/SiteCollectionDocuments/Kemi%20og%20foedevarekvalitet/UK-Fact-sheet-fluorinated-substances.pdf>
357. Ministère de la Transition Écologique et de la Cohésion des Territoires (2023) Plan d'Action Ministériel sur les PFAS. <https://www.ecologie.gouv.fr/plan-d-action-ministeriel-sur-pfas>. Accessed 11 Feb 2023
358. Borchers U, Kämpfe A, Knapp H, Sacher F, Suchenwirth R (2022) PFAS im Trinkwasser: Erster Überblick über Befunde und Herausforderungen für die Wasserversorgung. *bbr* 07/08:32–37
359. Bundesministerium für Gesundheit und Bundesministerium für Ernährung und Landwirtschaft (2022) Referentenentwurf: Zweite Verordnung zur Novellierung der Trinkwasserverordnung. https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Gesetze_und_Verordnungen/GuV/Tr/2022-07-22_Zweite_VO_Nov_TrinkwV_RefE.pdf
360. Miljøministeriet Miljøstyrelsen Denmark: tightened requirements for PFAS substances in drinking water. https://mst-dk.translate.google.com/serve/nyheder/nyhedsarkiv/2021/jun/skaerpede-krav-til-pfas-stoffer-i-drikkevand/?x_tr_sl=auto&x_tr_tl=en&x_tr_hl=de
361. US Environmental Protection Agency, Office of Water (2022) Lifetime drinking water health advisories for four perfluoroalkyl substances [FRL 9855–01–OW]. Federal Register 87(118):36848–36849. <https://www.govinfo.gov/content/pkg/FR-2022-06-21/pdf/2022-13221.pdf>
362. Bundesgesetzblatt (2017) Verordnung über das Inverkehrbringen von Düngemitteln, Bodenhilfsstoffen, Kultursubstraten und Pflanzhilfsmitteln (Düngemittelverordnung - DüMV), Annex 2 Table 1.4. https://www.gesetze-im-internet.de/d_mv_2012/BJNR248200012.html
363. Verordnung zur Einführung einer Ersatzbaustoffverordnung, zur Neufassung der Bundes-Bodenschutz- und Altlastenverordnung und zur Änderung der Deponieverordnung und der Gewerbeabfallverordnung vom 09.07.2021. BGBl. I Nr. 43 vom 16.07.2021, S. 2598–2752. Inkrafttreten 01.08.2023
364. EU Commission (2022) PFOS EQS dossier 2011. p 27. <https://circabc.europa.eu/d/a/workspace/SpacesStore/027ff47c-038b-4929-a84c-da3359acecee/PFOS%20EQS%20dossier%202011.pdf>
365. EU (2022) Commission proposal for a directive of the European parliament and of the council amending directive 2000/60/EC establishing a framework for community action in the field of water policy, directive 2006/118/EC on the protection of groundwater against pollution and deterioration and directive 2008/105/EC on environmental quality standards in the field of water policy—Annex V, COM(2022)final. <https://ec.europa.eu/environment/water/water-pollutants/>
366. Wang Y, Chang W, Wang L, Zhang Y, Wang M, Wang Y, Li P (2019) A review of sources, multimedia distribution and health risks of novel fluorinated alternatives. *Ecotoxicol Environ Saf* 182:109402. <https://doi.org/10.1016/j.ecoenv.2019.109402>
367. New Jersey Department of Environmental Protection (2022) Ground water quality standard for chloroperfluoropolyether carboxylates (ClPFPEAs). <https://www.nj.gov/dep/wms/bears/docs/ClPFPEAs-factsheet2021Final.pdf>
368. Mazzoni M, Polesello S, Rusconi M, Valsecchi S (2015) Investigating the occurrence of C8-based perfluorinated substitutes in Italian waters. *Norman Bulletin* | Issue 4 | March 2015. https://www.norman-network.net/sites/default/files/files/bulletins/NORMAN%20Bulletin_n4March2015_vfinal.pdf
369. Kortenkamp A, Backhaus T, Faust M (2009) State of the art report on mixture toxicity. Report for the Directorate General for the environment of the European Commission. p 391. https://ec.europa.eu/environment/chemicals/effects/pdf/report_mixture_toxicity.pdf
370. BUND (2021) Fluorochemicals—persistent, dangerous, avoidable. Background paper. https://www.bund.net/fileadmin/user_upload_bund/publikationen/chemie/Background_Fluorochemicals_Web_EN.pdf. Accessed 28 Jan 2022
371. Gold SC, Wagner WE (2020) Filling gaps in science exposes gaps in chemical regulation examination of US and EU regulatory systems raises more questions than answers. *Science* 368(6495):1066–1068. <https://doi.org/10.1126/science.abc1250>
372. Rockström J, Steffen W, Noone K, Persson A, Chapin FSI, Lambin EF, Lenton TM, Scheffer M, Folke C, Schellnhuber H-J, Nykvist B, de Wit CA, Hughes T, van der Leeuw S, Rodhe H, Sörlin S, Snyder PK, Costanza R, Svedin U, Falkenmark M, Karlberg L, Corell RW, Fabry VJ, Hansen J, Walker B, Liverman D, Richardson K, Crutzen P, Foley J (2009) A safe operating space for humanity. *Nature* 461:472–475. <https://doi.org/10.1038/461472a>
373. Steffen W, Richardson K, Rockström J, Cornell SE, Fetzer I, Bennett EM, Biggs R, Carpenter SR, de Vries W, de Wit CA, Folke C, Gerten D, Heinke J, Mace GM, Persson LM, Ramanathan V, Rayers B, Sörlin S (2015) Planetary boundaries: guiding human development on a changing planet. *Science* 347(6223):1259855. <https://doi.org/10.1126/science.1259855>
374. Persson L, Carney Almoth BM, Collins CD, Cornell S, de Wit CA, Diamond ML, Fantke P, Hasselöv M, MacLeod M, Ryberg MW, Søgaard Jørgensen P, Villarubia-Gómez P, Wang Z, Hauschild MZ (2022) Outside the safe operating space of the planetary boundary for novel entities. *Environ Sci Technol* 56:1510–1521. <https://doi.org/10.1021/acs.est.1c04158>
375. Steinhäuser KG, von Gleich A, Große Ophoff M, Körner W (2022) The necessity of a global binding framework for sustainable management of chemicals and materials—interactions with climate and biodiversity. *Sustain Chem* 3:205–237. <https://doi.org/10.3390/suschem3020014>

376. 3M News Center (2022) 3M to exit PFAS manufacturing by the end of 2025. Press release December 20, 2022. <https://news.3m.com/2022-12-20-3M-to-Exit-PFAS-Manufacturing-by-the-End-of-2025>. Accessed 10 Jan 2023
377. Goldenman G, Fernandes M, Holland M, Tugran T, Nordin A, Schoumacher C, McNeill A (2019) The cost of inaction: a socioeconomic analysis of environmental and health impacts linked to exposure to PFAS. Nordic Council of Ministers, Copenhagen, p 194. <https://doi.org/10.6027/TN2019-516>
378. Cordner A, Goldenman G, Birnbaum LS, Brown P, Miller MF, Mueller R, Patton S, Salvatore DH, Trasande L (2021) The true cost of PFAS and the benefits of acting now. *Environ Sci Technol* 55(14):9630–9633. <https://doi.org/10.1021/acs.est.1c03565>
379. Obsekov V, Kahn LG, Trasande L (2022) Leveraging systematic reviews to explore disease burden and costs of per- and polyfluoroalkyl substance exposures in the United States. *Expo Health*. <https://doi.org/10.1007/s12403-022-00496-y>
380. Kato K, Wong LY, Jia LT, Kuklencyk Z, Calafat AM (2011) Trends in exposure to polyfluoroalkyl chemicals in the U.S. population: 1999–2008. *Environ Sci Technol* 45:8037–8045. <https://doi.org/10.1021/es1043613>
381. Lopez-Espinosa MJ, Mondal D, Armstrong B, Bloom MS, Fletcher T (2012) Thyroid function and perfluoroalkyl acids in children living near a chemical plant. *Environ Health Perspect* 120:1036–1041. <https://doi.org/10.1289/ehp.1104370>
382. Domazet SL, Grøntved A, Timmermann AG, Nielsen F, Jensen TK (2016) Longitudinal associations of exposure to perfluoroalkylated substances in childhood and adolescence and indicators of adiposity and glucose metabolism 6 and 12 years later: the European Youth heart study. *Diabetes Care* 39:1745–1751. <https://doi.org/10.2337/dci16-0269>
383. Papadopoulou E, Sabaredzovic A, Namork E, Nygaard UC, Granum B, Haug LS (2016) Exposure of Norwegian toddlers to perfluoroalkyl substances (PFAS) the association with breastfeeding and maternal PFAS concentrations. *Environ Int* 94:687–694. <https://doi.org/10.1016/j.envint.2016.07.006>
384. Ballesteros V, Costa O, Iñiguez C, Fletcher T, Ballester F, Lopez-Espinosa MJ (2017) Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: a systematic review of epidemiologic studies. *Environ Int* 99:15–28. <https://doi.org/10.1016/j.envint.2016.10.015>
385. Costello E, Rock S, Stratakis N, Eckel SP, Walker DI, Valvi D, Cserbik D, Jenkins T, Xanthakos SA, Kohli R, Sisley S, Vasilio V, La Merrill MA, Rosen H, Conti DV, McConnell R, Chatzi L (2022) Exposure to per- and polyfluoroalkyl substances and markers of liver injury: a systematic review and meta-analysis. *Environ Health Perspect* 130:46001. <https://doi.org/10.1289/EHP10092>
386. Salihovic S, Stubleski J, Kärrman A, Larsson A, Fall T, Lind L, Lind PM (2018) Changes in markers of liver function in relation to changes in perfluoroalkyl substances—a longitudinal study. *Environ Int* 117:196–203. <https://doi.org/10.1016/j.envint.2018.04.052>
387. Sinisalu L, Yeung LWY, Wang J, Pan Y, Dai J, Hyötyläinen T (2021) Prenatal exposure to poly-/per-fluoroalkyl substances is associated with alteration of lipid profiles in cord-blood. *Metabolomics* 17:103. <https://doi.org/10.1007/s11306-021-01853-9>
388. Bassler J, Ducatman A, Elliott M, Wen S, Wahlang B, Barnett J, Cave MC (2019) Environmental perfluoroalkyl acid exposures are associated with liver disease characterized by apoptosis and altered serum adipocytokines. *Environ Pollut* 247:1055–1063. <https://doi.org/10.1016/j.envpol.2019.01.064>
389. Stanifer JW, Stapleton HM, Souma T, Wittmer A, Zhao X, Boulware LE (2018) Perfluorinated chemicals as emerging environmental threats to kidney health: a scoping review. *Clin J Am Soc Nephrol* 13:1479–1492. <https://doi.org/10.2215/CJN.04670418>
390. Wang J, Zeng XW, Bloom MS, Qian Z, Hinyard LJ, Belue R, Lin S, Wang SQ, Tian YP, Yang M, Chu C, Gurrain N, Hu L-W, Liu KK, Yang BY, Feng D, Liu RQ, Dong GH (2019) Renal function and isomers of perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS): isomers of C8 health project in China. *Chemosphere* 218:1042–1049. <https://doi.org/10.1016/j.chemosphere.2018.11.191>
391. Shankar A, Xiao J, Ducatman A (2011) Perfluoroalkyl chemicals and chronic kidney disease in US adults. *Am J Epidemiol* 174:893–900. <https://doi.org/10.1093/aje/kwr171>
392. Wang P, Liu D, Yan S, Liang Y, Cui J, Guo L, Ren S, Chen P (2022) The role of ferroptosis in the damage of human proximal tubule epithelial cells caused by perfluorooctane sulfonate. *Toxics* 10:436. <https://doi.org/10.3390/toxics10080436>
393. Dong GH, Tung KY, Tsai CH, Liu MM, Wang D, Liu W, Jin YH, Hsieh WS, Lee YL, Chen PC (2013) Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children. *Environ Health Perspect* 121:507–513. <https://doi.org/10.1289/ehp.1205351>
394. Aimuzi R, Luo K, Huang R, Huo X, Nian M, Ouyang F, Du Y, Feng L, Wang W, Zhang J, Shanghai Birth Cohort Study (2020) Perfluoroalkyl and polyfluoroalkyl substances and maternal thyroid hormones in early pregnancy. *Environ Pollut* 264:114557. <https://doi.org/10.1016/j.envpol.2020.114557>
395. Preston EV, Webster TF, Claus Henn B, McClean MD, Gennings C, Oken E, Rifas-Shiman SL, Pearce EN, Calafat AM, Fleisch AF, Sagiv SK (2020) Prenatal exposure to per- and polyfluoroalkyl substances and maternal and neonatal thyroid function in the project viva cohort: a mixtures approach. *Environ Int* 139:105728. <https://doi.org/10.1016/j.envint.2020.105728>
396. Sun M, Cao X, Wu Y, Shen L, Wei G (2022) Prenatal exposure to endocrine-disrupting chemicals and thyroid function in neonates: a systematic review and meta-analysis. *Ecotoxicol Environ Saf* 231:113215. <https://doi.org/10.1016/j.ecoenv.2022.113215>
397. Eick SM, Goin DE, Cushing L, DeMicco E, Smith S, Park JS, Padula AM, Woodruff TJ, Morello-Frosch R (2021) Joint effects of prenatal exposure to per- and poly-fluoroalkyl substances and psychosocial stressors on cotropin-releasing hormone during pregnancy. *J Expo Sci Environ Epidemiol* 32:27–36. <https://doi.org/10.1038/s41370-021-00322-8>
398. Goudarzi H, Araki A, Itoh S, Sasaki S, Miyashita C, Mitsui T, Nakazawa H, Nonomura K, Kishi R (2017) The association of prenatal exposure to perfluorinated chemicals with glucocorticoid and androgenic hormones in cord blood samples: the Hokkaido study. *Environ Health Perspect* 125:111–118. <https://doi.org/10.1289/EHP142>
399. Harris MH, Oken E, Rifas-Shiman SL, Calafat AM, Ye X, Bellinger DC, Webster TF, White RF, Sagiv SK (2018) Prenatal and childhood exposure to per- and polyfluoroalkyl substances (PFASs) and child cognition. *Environ Int* 115:358–369. <https://doi.org/10.1016/j.envint.2018.03.025>
400. Tachachartvanich P, Singam ERA, Durkin KA, Furlow JD, Smith MT, La Merrill MA (2022) *In Vitro* characterization of the endocrine disrupting effects of per- and poly-fluoroalkyl substances (PFASs) on the human androgen receptor. *J Hazard Mat* 429:128243. <https://doi.org/10.1016/j.jhazmat.2022.128243>
401. Nitsche EM, Arnold G (2022) Endokrine Disruptoren – Sind hormonwirksame Substanzen in der Nahrung bedenklich? Teil 1. *Kinder-Jugendarzt* 53:584–590
402. Schillemans T, Shi L, Donat-Vargas C, Hanhineva K, Tornevi A, Johansson I, Koponen J, Kiviranta H, Rolandsson O, Bergdahl IA, Landberg R, Åkesson A, Brunius C (2021) Plasma metabolites associated with exposure to perfluoroalkyl substances and risk of type 2 diabetes—a nested case-control study. *Environ Int* 146:106180. <https://doi.org/10.1016/j.envint.2020.106180>
403. Alderete TL, Jin R, Walker DI, Valvi D, Chen Z, Jones DP, Peng C, Gilliland FD, Berhane K, Conti DV, Goran MI, Chatzi L (2019) Perfluoroalkyl substances, metabolomic profiling, and alterations in glucose homeostasis among overweight and obese Hispanic children: a proof-of-concept analysis. *Environ Int* 126:445–453. <https://doi.org/10.1016/j.envint.2019.02.04>
404. Park SK, Wang X, Ding N, Karvonen-Gutierrez CA, Calafat AM, Herman WH, Mukherjee B, Harlow SD (2022) Per- and polyfluoroalkyl substances and incident diabetes in midlife women: the Study of women's health across the nation (SWAN). *Diabetologia* 65:1157–1168. <https://doi.org/10.1007/s00125-022-05695-5>
405. Donat-Vargas C, Bergdahl IA, Tornevi A, Wennberg M, Sommar J, Kiviranta H, Koponen J, Rolandsson O, Åkesson A (2019) Perfluoroalkyl substances and risk of type II diabetes: a prospective nested case-control study. *Environ Int* 123:390–398. <https://doi.org/10.1016/j.envint.2018.12.026>
406. Sun Q, Zong G, Valvi D, Nielsen F, Coull B, Grandjean P (2018) Plasma concentrations of perfluoroalkyl substances and risk of type 2 diabetes:

- a prospective investigation among US women. *Environ Health Perspect* 126:037001. <https://doi.org/10.1289/EHP2619>
407. Spratlen MJ, Perera FP, Lederman SA, Rauh VA, Robinson M, Kannan K, Trasande L, Herbstman J (2020) The association between prenatal exposure to perfluoroalkyl substances and childhood neurodevelopment. *Environ Pollut* 263:114444. <https://doi.org/10.1016/j.envpol.2020.114444>
 408. Li Y, Barregard L, Xu Y, Scott K, Pineda D, Lindh CH, Jakobsson K, Fletcher T (2020) Associations between perfluoroalkyl substances and serum lipids in a Swedish adult population with contaminated drinking water. *Environ Health* 19:33. <https://doi.org/10.1186/s12940-020-00588-9>
 409. Guo P, Furnary T, Vasilou V, Yan Q, Nyhan K, Jones DP, Johnson CH, Liew Z (2022) Non-targeted metabolomics and associations with per- and polyfluoroalkyl substances (PFAS) exposure in humans: a scoping review. *Environ Int* 162:107159. <https://doi.org/10.1016/j.envint.2022.107159>
 410. Khalil N, Ebert JR, Honda M, Lee M, Ramzi W, Nahhas RW, Koskela A, Hangartner T, Kannan K (2018) Perfluoroalkyl substances, bone density, and cardio-metabolic risk factors in obese 8–12 year old children: a pilot study. *Environ Res* 160:314–321. <https://doi.org/10.1016/j.envres.2017.10.014>
 411. Schillemans T, Donat-Vargas C, Lindh CH, de Faire U, Wolk A, Leander K, Åkesson A (2022) Per- and polyfluoroalkyl substances and risk of myocardial infarction and stroke: a nested case-control study in Sweden. *Environ Health Perspect* 130:37007. <https://doi.org/10.1289/EHP9791>
 412. Rosen EM, Kotlarz N, Knappe DRU, Lea S, Collier DN, Richardson DB, Hoppin JA (2021) Drinking water-associated PFAS and fluoroethers and lipid outcomes in the GenX exposure study. *Environ Health Perspect*. <https://doi.org/10.1289/EHP11033>
 413. Di Nisio A, Rocca MS, Sabovic I, De RoccoPonce M, Corsini C, Guidolin D, Zanon C, Acquasaliente L, Carosso AR, De Toni L, Foresta C (2020) Perfluorooctanoic acid alters progesterone activity in human endometrial cells and induces reproductive alterations in young women. *Chemosphere* 242:125208. <https://doi.org/10.1016/j.chemosphere.2019.125208>
 414. Di Nisio A, Sabovic I, Valente U, Tesca S, Santa Rocca M, Guidolin D, Dall'Acqua S, Acquasaliente L, Pozzi N, Plebani M, Garolla A, Foresta C (2019) Endocrine disruption of androgenic activity by perfluoroalkyl substances: clinical and experimental evidence. *J Clin Endocrinol Metab* 104:1259–1271. <https://doi.org/10.1210/je.2018-01855>
 415. Liew Z, Luo J, Nohr EA, Hammer Bech B, Bossi R, Arah OA, Olsen J (2020) Maternal plasma perfluoroalkyl substances and miscarriage: a nested case-control study in the Danish national birth cohort. *Environ Health Perspect* 128:47007. <https://doi.org/10.1289/EHP6202>
 416. Rappazzo KM, Coffman E, Hines EP (2017) Exposure to perfluorinated alkyl substances and health outcomes in children: a systematic review of the epidemiologic literature. *Int J Environ Res Public Health* 14:691. <https://doi.org/10.3390/ijerph14070691>
 417. Breton CV, Marsit CJ, Faustman E, Nadeau K, Goodrich JM, Dolinoy DC, Herbstman J, Holland N, LaSalle JM, Schmidt R, Yousefi P, Perera F, Joubert BR, Wiemels J, Taylor M, Yang IV, Chen R, Hew KM, Freeland DMH, Miller R, Murphy SK (2017) Small-magnitude effect sizes in epigenetic end points are important in children's environmental health studies: the children's environmental health and disease prevention research center's epigenetics working group. *Environ Health Perspect* 125:511–526. <https://doi.org/10.1289/EHP595>
 418. Kishi R, Ikeda-Araki A, Miyashita C, Itoh S, Kobayashi S, Bamai YA, Yamazaki K, Tamura N, Minatoya M, Mesfin Ketema R, Poudel K, Miura R, Masuda H, Itoh M, Yamaguchi T, Fukunaga H, Ito K, Goudarzi H, Members of the Hokkaido Study on Environment and Children's Health (2021) Hokkaido birth cohort study on environment and children's health: cohort profile 2021. *Environ Health Prev Med* 26:59. <https://doi.org/10.1186/s12199-021-00980-y>
 419. Oulhote Y, Steuerwald U, Debes F, Weihe P, Grandjean P (2016) Behavioral difficulties in 7-year old children in relation to developmental exposure to perfluorinated alkyl substances. *Environ Int* 97:237–245. <https://doi.org/10.1016/j.envint.2016.09.015>
 420. Ghassabian A, Bell EM, Ma WL, Sundaram R, Kannan K, Louis GMB, Yeung E (2018) Concentrations of perfluoroalkyl substances and bisphenol A in newborn dried blood spots and the association with child behavior. *Environ Pollut* 243(Pt B):1629–1636. <https://doi.org/10.1016/j.envpol.2018.09.107>
 421. Sharpe RM (2018) Fetal life shapes adult male reproductive function. *Lancet Child Adolesc* 2:695–696. [https://doi.org/10.1016/S2352-4642\(18\)30276-1](https://doi.org/10.1016/S2352-4642(18)30276-1)
 422. Petersen KU, Larsen JR, Deen L, Flachs EM, Hærvig KK, Hull SD, Bonde JPE, Tøttenborg SS (2020) Per- and polyfluoroalkyl substances and male reproductive health: a systematic review of the epidemiological evidence. *J Toxicol Environ Health B Crit Rev* 23:276–291. <https://doi.org/10.1080/10937404.2020.1798315>
 423. Huang R, Chen Q, Zhang L, Luo K, Chen L, Zhao S, Feng L, Zhang J (2019) Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy. *Environ Health* 18:5. <https://doi.org/10.1186/s12940-018-0445-3>
 424. Kahn LG, Trasande L (2018) Environmental toxicant exposure and hypertensive disorders of pregnancy: recent findings. *Curr Hypertens Rep* 20:87. <https://doi.org/10.1007/s11906-018-0888-5>
 425. Chambers WS, Hopkins JG, Richards SM (2021) A review of per- and polyfluorinated alkyl substance impairment of reproduction. *Front Toxicol* 3:732436. <https://doi.org/10.3389/ftox.2021.732436>
 426. Jensen TK, Andersen LB, Kyhl HB, Nielsen F, Christesen HT, Grandjean P (2015) Association between perfluorinated compound exposure and miscarriage in Danish pregnant women. *PLoS ONE* 10:e0123496. <https://doi.org/10.1371/journal.pone.0123496>
 427. Wikström S, Hussein G, Karlsson AL, Lindh CH, Bornehag C-G (2021) Exposure to perfluoroalkyl substances in early pregnancy and risk of sporadic first trimester miscarriage. *Sci Rep* 11:3568
 428. Hall SM, Zhang S, Hoffman K, Miranda ML, Stapleton HM (2022) Concentrations of per- and polyfluoroalkyl substances (PFAS) in human placental tissues and associations with birth outcomes. *Chemosphere* 295:133873. <https://doi.org/10.1016/j.chemosphere.2022.133873>
 429. Ashley-Martin J, Dodds L, Arbuckle TE, Bouchard MF, Fisher M, Morriset AS, Monnier P, Shapiro GD, Ettinger AS, Dallaire R, Taback S, Fraser W, Platt RW (2017) Maternal concentrations of perfluoroalkyl substances and fetal markers of metabolic function and birth weight. The maternal-infant research on environmental chemicals (MIREC) Study. *Am J Epidemiol* 185:185–193. <https://doi.org/10.1093/aje/kww213>
 430. Lauritzen HB, Larose TL, Øien T, Sandanger TM, Odland JØ, van de Bor M, Jacobsen GW (2017) Maternal serum levels of perfluoroalkyl substances and organochlorines and indices of fetal growth: a Scandinavian case-cohort study. *Pediatr Res* 81:33–42. <https://doi.org/10.1038/pr.2016.187>
 431. Manzano-Salgado CB, Casas M, Lopez-Espinosa MJ, Ballester F, Iñiguez C, Martinez D, Costa O, Santa-Marina L, Pereda-Pereda E, Schettgen T, Sunyer J, Vrijheid M (2017) Prenatal exposure to perfluoroalkyl substances and birth outcomes in a Spanish birth cohort. *Environ Int* 108:278–284. <https://doi.org/10.1016/j.envint.2017.09.006>
 432. Shi Y, Yang L, Li J, Lai J, Wang Y, Zhao Y, Wu Y (2017) Occurrence of perfluoroalkyl substances in cord serum and association with growth indicators in newborns from Beijing. *Chemosphere* 169:396–402. <https://doi.org/10.1016/j.chemosphere.2016.11.050>
 433. Olsen GW, Butenhoff JL, Zobel LR (2009) Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. *Reprod Toxicol* 27:212–230. <https://doi.org/10.1016/j.reprotox.2009.02.001>
 434. Apelberg BJ, Witter FR, Herbstman JB, Calafat AM, Halden RU, Larry L, Needham LI, Goldman LR (2007) Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. *Environ Health Perspect* 115:1670–1676. <https://doi.org/10.1289/ehp.10334>
 435. Fei C, McLaughlin JK, Tarone RE, Olsen J (2008) Fetal growth indicators and perfluorinated chemicals: a study in the Danish national birth cohort. *Am J Epidemiol* 168:66–72. <https://doi.org/10.1093/aje/kwn095>
 436. Kalloo G, Wellenius GA, McCandless L, Calafat AM, Sjodin A, Romano ME, Karagas MR, Chen A, Yolton K, Lanphear BP, Braun JM (2020) Exposures to chemical mixtures during pregnancy and neonatal outcomes: the HOME study. *Environ Int* 134:105219. <https://doi.org/10.1016/j.envint.2019.105219>
 437. Gardener H, Sun Q, Grandjean P (2021) PFAS concentration during pregnancy in relation to cardiometabolic health and birth outcomes. *Environ Res* 192:110287. <https://doi.org/10.1016/j.envres.2020.110287>

438. Street ME, Bernasconi S (2020) Endocrine-disrupting chemicals in human fetal growth. *Int J Mol Sci* 21:1430. <https://doi.org/10.3390/ijms21041430>
439. Reardon AJF, Khodayari Moez E, Dinu I, Goruk S, Field CJ, Kinniburgh DW, MacDonald AM, Martin JW (2019) Longitudinal analysis reveals early-pregnancy associations between perfluoroalkyl sulfonates and thyroid hormone status in a Canadian prospective birth cohort. *Environ Int* 129:389–399. <https://doi.org/10.1016/j.envint.2019.04.023>
440. Foguth RM, Flynn RW, de Perre C, Iacchetta M, Lee LS, Sepúlveda MS, Cannon JR (2019) Developmental exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) selectively decreases brain dopamine levels in Northern leopard frogs. *Toxicol Appl Pharmacol* 377:114623. <https://doi.org/10.1016/j.taap.2019.114623>
441. Hoffman K, Webster TF, Weiskopf MG, Weinberg J, Vieira VM (2010) Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in U.S. children 12–15 years of age. *Environ Health Perspect* 118:1762–1767. <https://doi.org/10.1289/ehp.1001898>
442. Luo J, Xiao J, Gao Y, Ramlau-Hansen CH, Toft G, Li J, Obel C, Linding Andersen S, Deziel NC, Tseng WL, Inoue K, Bonefeld-Jørgensen EC, Olsen J, Liew Z (2020) Prenatal exposure to perfluoroalkyl substances and behavioral difficulties in childhood at 7 and 11 years. *Environ Res* 191:110111. <https://doi.org/10.1016/j.envres.2020.110111>
443. Fornis J, Verner MA, Iszatt N, Nowack N, BaLch CC, Vrijheid M, Costa O, Andiarrena A, Sovcikova E, Høyer BB, Wittsiepe J, Lopez-Espinosa MJ, Ibarluzea J, Hertz-Picciotto I, Toft G, Stigum H, Guxens M, Liew Z, Eggesbø M (2020) Early life exposure to perfluoroalkyl substances (PFAS) and ADHD: a meta-analysis of nine European population-based studies. *Environ Health Perspect* 128:57002. <https://doi.org/10.1289/EHP5444>
444. Vuong AM, Webster GM, Yolton K, Calafat AM, Muckle G, Lanphear BP, Chen A (2021) Prenatal exposure to per- and polyfluoroalkyl substances (PFAS) and neurobehavior in US children through 8 years of age: the HOME study. *Environ Res* 195:110825. <https://doi.org/10.1016/j.envres.2021.110825>
445. Harris MH, Oken E, Rifas-Shiman SL, Calafat AM, Bellinger DC, Webster TF, White RF, Sagiv SK (2021) Prenatal and childhood exposure to per- and polyfluoroalkyl substances (PFAS) and child executive function and behavioral problems. *Environ Res* 202:111621. <https://doi.org/10.1016/j.envres.2021.111621>
446. Skogheim TS, Weyde KVF, Aase H, Engel SM, Surén P, Øie MG, Biele G, Reichborn-Kjennerud T, Brantsæter AL, Haug LS, Sabaredzovic A, Auyeung B, Villanger GD (2021) Prenatal exposure to per- and polyfluoroalkyl substances (PFAS) and associations with attention-deficit/hyperactivity disorder and autism spectrum disorder in children. *Environ Res* 202:111692. <https://doi.org/10.1016/j.envres.2021.111692>
447. Grønnestad R, Modahl Johanson S, Müller MHB, Schlenk D, Tanabe P, Krøkje Å, Jaspers VLB, Munro Jenssen B, Ræder EM, Lyche JL, Shi O, Arukwe A (2021) Effects of an environmentally relevant PFAS mixture on dopamine and steroid hormone levels in exposed mice. *Toxicol Appl Pharmacol* 428:115670. <https://doi.org/10.1016/j.taap.2021.115670>
448. Høyer BB, Ramlau-Hansen CH, Obel C, Pedersen HS, Hernik A, Ogniev V, Jönsson BAG, Lindh CH, Rylander L, Rignell-Hydbom A, Bonde JP, Toft G (2015) Pregnancy serum concentrations of perfluorinated alkyl substances and offspring behaviour and motor development at age 5–9 years—a prospective study. *Environ Health* 14:2. <https://doi.org/10.1186/1476-069X-14-2>
449. Lenters V, Iszatt N, Fornis J, Čechová E, Kočan A, Legler J, Leonardis P, Stigum H, Eggesbø M (2019) Early-life exposure to persistent organic pollutants (OCPs, PBDEs, PCBs, PFASs) and attention-deficit/hyperactivity disorder: a multi-pollutant analysis of a Norwegian birth cohort. *Environ Int* 125:33–42. <https://doi.org/10.1016/j.envint.2019.01.020>
450. Lien GW, Huang CC, Shiu JS, Chen MH, Hsieh WS, Guo YL, Chen PH (2016) Perfluoroalkyl substances in cord blood and attention deficit/hyperactivity disorder symptoms in seven-year-old children. *Chemosphere* 156:118–127. <https://doi.org/10.1016/j.chemosphere.2016.04.102>
451. Stein CR, Savitz DA (2011) Serum perfluorinated compound concentration and attention deficit/hyperactivity disorder in children 5–18 years of age. *Environ Health Perspect* 119:1466–1471. <https://doi.org/10.1289/ehp.1003538>
452. Stein CR, Savitz DA, Bellinger DC (2014) Perfluorooctanoate exposure in a highly exposed community and parent and teacher reports of behaviour in 6–12-year-old children. *Paediatr Perinat Epidemiol* 28:146–156. <https://doi.org/10.1111/ppe.12097>
453. Park SK, Ding N, Han D (2021) Perfluoroalkyl substances and cognitive function in older adults: should we consider non-monotonic dose-responses and chronic kidney disease? *Environ Res* 192:10346. <https://doi.org/10.1016/j.envres.2020.110346>
454. Mastrantonio M, Bai E, Uccelli R, Cordiano V, Screpanti A, Crosignani P (2018) Drinking water contamination from perfluoroalkyl substances (PFAS): an ecological mortality study in the Veneto Region, Italy. *Eur J Public Health* 28:180–185. <https://doi.org/10.1093/eurpub/ckx066>
455. Xu Y, Jurkovic-Mlakar S, Li Y, Wahlberg K, Scott K, Pineda D, Lindh CH, Jakobsson K, Engström K (2020) Association between serum concentrations of perfluoroalkyl substances (PFAS) and expression of serum microRNAs in a cohort highly exposed to PFAS from drinking water. *Environ Int* 136:105446. <https://doi.org/10.1016/j.envint.2019.105446>
456. Panieri E, Katarina Baralic K, Djukic-Cosic D, Buha Djordjevic A, Saso L (2022) PFAS molecules: a major concern for the human health and the environment. *Toxics* 10:44. <https://doi.org/10.3390/toxics10020044>
457. Shin H-M, Bennett DH, Calafat AM, Tancredi D, Hertz-Picciotto I (2020) Modeled prenatal exposure to per- and polyfluoroalkyl substances in association with child autism spectrum disorder: a case-control study. *Environ Res* 186:109514. <https://doi.org/10.1016/j.envres.2020.109514>
458. Oh J, Bennett DH, Calafat AM, Tancredi D, Roa DL, Schmidt RJ, Hertz-Picciotto I, Shin HM (2021) Prenatal exposure to per- and polyfluoroalkyl substances in association with autism spectrum disorder in the MARBLES study. *Environ Int* 147:106328. <https://doi.org/10.1016/j.envint.2020.106328>
459. Lyall K, Yau VM, Hansen R, Kharrazi M, Yoshida CK, Calafat AM, Windham G, Croen LA (2018) Prenatal maternal serum concentrations of per- and polyfluoroalkyl substances in association with autism spectrum disorder and intellectual disability. *Environ Health Perspect* 126:017001. <https://doi.org/10.1289/EHP1830>
460. Di Nisio A, Pannella M, Vogiatzis S, Sut S, Dall'Acqua S, Santa Rocca M, Antonini A, Porzionato A, De Caro R, Bertolozzi M, De Toni L, Foresta C (2022) Impairment of human dopaminergic neurons at different developmental stages by perfluoro-octanoic acid (PFOA) and differential human brain areas accumulation of perfluoroalkyl chemicals. *Environ Int* 158:106982. <https://doi.org/10.1016/j.envint.2021.106982>
461. Shen C-Y, Weng JC, Tsai JD, Su PH, Chou MC, Wang SL (2021) Prenatal exposure to endocrine-disrupting chemicals and subsequent brain structure changes revealed by voxel-based morphometry and generalized Q-sampling MRI. *Int J Environ Res Public Health* 18:4798. <https://doi.org/10.3390/ijerph18094798>
462. Ding N, Park SK (2020) Perfluoroalkyl substances exposure and hearing impairment in US adults. *Environ Res* 187:109686. <https://doi.org/10.1016/j.envres.2020.109686>
463. Wang Y, Rogan WJ, Chen HY, Chende PC, Su PH, Chen HY, Wang SL (2015) Prenatal exposure to perfluoroalkyl substances and children's IQ: the Taiwan maternal and infant cohort study. *Int J Hyg Environ Health* 218:639–644. <https://doi.org/10.1016/j.ijheh.2015.07.002>
464. Stein CR, Savitz DA, Bellinger DC (2013) Perfluorooctanoate and neuropsychological outcomes in children. *Epidemiol* 24:590–599. <https://doi.org/10.1097/EDE.0b013e3182944432>
465. Gallo V, Leonardi G, Brayne C, Armstrong B, Fletcher T (2013) Serum perfluoroalkyl acids concentrations and memory impairment in a large cross-sectional study. *BMJ Open* 3:e002414. <https://doi.org/10.1136/bmjopen-2012-002414>
466. Brown-Leung JM, Cannon JR (2022) Neurotransmission targets of per- and polyfluoroalkyl substance neurotoxicity: mechanisms and potential implications for adverse neurological outcomes. *Chem Res Toxicol* 35:1312–1333. <https://doi.org/10.1021/acs.chemrestox.2c00072>
467. Oh J, Schmidt RJ, Tancredi D, Calafat AM, Roa DL, Hertz-Picciotto I, Shin HM (2021) Prenatal exposure to per- and polyfluoroalkyl substances and cognitive development in infancy and toddlerhood. *Environ Res* 196:110939. <https://doi.org/10.1016/j.envres.2021.110939>
468. Wang Y, Wang L, Chang W, Zhang Y, Zhang Y, Liu W (2019) Neurotoxic effects of perfluoroalkyl acids: neurobehavioral deficit and its molecular mechanism. *Toxicol Lett* 305:65–72. <https://doi.org/10.1016/j.toxlet.2019.01.012>

469. Gump BB, Wu Q, Dumas AK, Kannan K (2011) Perfluorochemical (PFC) exposure in children: associations with impaired response inhibition. *Environ Sci Technol* 45:8151–8159. <https://doi.org/10.1021/es103712g>
470. Liew Z, Ritz B, Bonefeld-Jørgensen EC, Brink Henriksen T, Aagaard Nohr E, Hammer Bech B, Fei C, Bossi R, von Ehrenstein OS, Streja E, Uldall P, Olsen J (2014) Prenatal exposure to perfluoroalkyl substances and the risk of congenital cerebral palsy in children. *Am J Epidemiol* 180:574–581. <https://doi.org/10.1093/aje/kwu179>
471. Hutcheson R, Innes K, Conway B (2020) Perfluoroalkyl substances and likelihood of stroke in persons with and without diabetes. *Diab Vasc Dis Res* 17:1479164119892223. <https://doi.org/10.1177/1479164119892223>
472. Piekarski DJ, Diaz KR, McNeerney MW (2020) Perfluoroalkyl chemicals in neurological health and disease: human concerns and animal models. *Neurotoxicol* 77:155–168. <https://doi.org/10.1016/j.neuro.2020.01.001>
473. Starnes HM, Rock KD, Jackson TW, Belcher SM (2022) A critical review and meta-analysis of impacts of per- and polyfluorinated substances on the brain and behavior. *Front Toxicol* 4:881584. <https://doi.org/10.3389/ftox.2022.881584>
474. Xie Z, Tan J, Fang G, Ji H, Miao M, Tian Y, Hu H, Cao W, Liang H, Yuan W (2022) Associations between prenatal exposure to perfluoroalkyl substances and neurobehavioral development in early childhood: a prospective cohort study. *Ecotoxicol Environ Saf* 241:113818. <https://doi.org/10.1016/j.ecoenv.2022.113818>
475. Larebeke N, Koppen G, Decraemer S, Colles A, Bruckers L, Den Hond E, Govarts E, Morrens B, Schettgen Th, Remy S, Coertjens D, Nawrot T, Nelen V, Baeyens W, Schoeters G (2022) Per- and polyfluoroalkyl substances (PFAS) and neurobehavioral function and cognition in adolescents (2010–2011) and elderly people (2014): results from the Flanders environment and health studies (FLEHS). *Environ Sci Eur* 34:98. <https://doi.org/10.1186/s12302-022-00675-3>
476. Tukker AM, Bouwman LMS, van Kleef RGDM, Hendriks HS, Legler J, Westerlin RHS (2020) Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) acutely affect human $\alpha_2\beta_2\gamma_{2L}$ GABA_A receptor and spontaneous neuronal network function *in vitro*. *Sci Rep* 10:5311. <https://doi.org/10.1038/s41598-020-62152-2>
477. Khalil N, Chen A, Lee M, Czerwinski SA, Ebert JR, DeWitt JC, Kannan K (2016) Association of perfluoroalkyl substances, bone mineral density, and osteoporosis in the U.S. population in NHANES 2009–2010. *Environ Health Perspect* 124:81–87. <https://doi.org/10.1289/ehp.1307909>
478. Di Nisio A, De Rocco PM, Giadone A, Rocca MS, Guidolin D, Foresta C (2020) Perfluoroalkyl substances and bone health in young men: a pilot study. *Endocrine* 67:678–684. <https://doi.org/10.1007/s12020-019-02096-4>
479. Banjabi AA, Li AJ, Kumosani TA, Yousef JM, Kannan K (2020) Serum concentrations of perfluoroalkyl substances and their association with osteoporosis in a population in Jeddah, Saudi Arabia. *Environ Res* 187:109676. <https://doi.org/10.1016/j.envres.2020.109676>
480. Buckley JP, Kuiper JR, Lanphear BP, Calafat AM, Cecil KM, Chen A, Xu Y, Yolton K, Kalkwarf HJ, Braun JM (2021) Associations of maternal serum perfluoroalkyl substances concentrations with early adolescent bone mineral content and density: the health outcomes and measures of the environment (HOME) study. *Environ Health Perspect* 129:97011. <https://doi.org/10.1289/EHP9424>
481. Schmidt CW (2021) A measure of strength: developmental PFAS exposures and bone mineral content in adolescence. *Environ Health Perspect* 129:124002–124011. <https://doi.org/10.1289/EHP10551>
482. Koskela A, Koponen J, Lehenkari P, Viluksela M, Korkalainen M, Tuukkanen J (2017) Perfluoroalkyl substances in human bone: concentrations in bones and effects on bone cell differentiation. *Sci Rep* 7:6841
483. Cluett R, Seshasayee SM, Rokoff LB, Rifas-Shiman SL, Ye X, Calafat AM, Gold DR, Coull B, Gordon CM, Rosen CJ, Oken E, Sagiv SK, Fleisch AF (2019) Per- and polyfluoroalkyl substance plasma concentrations and bone mineral density in midchildhood: a cross-sectional study (project viva, United States). *Environ Health Perspect* 127:87006. <https://doi.org/10.1289/EHP4918>
484. Xiong X, Chen B, Wang Z, Ma L, Li S, Gao Y (2022) Association between perfluoroalkyl substances concentration and bone mineral density in the US adolescents aged 12–19 years in NHANES 2005–2010. *Front Endocrinol* 13:980608. <https://doi.org/10.3389/fendo.2022.980608>
485. Granum B, Haug LS, Namork E, Stølevik SB, Thomsen C, Aaberge IS, van Loveren H, Løvik M, Nygaard UC (2013) Prenatal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. *J Immunotoxicol* 10:373–379. <https://doi.org/10.3109/1547691X.2012.755580>
486. Dalsager L, Christensen N, Husby S, Kyhl H, Nielsen F, Høst A, Grandjean P, Kold Jensen T (2016) Association between prenatal exposure to perfluorinated compounds and symptoms of infections at age 1–4 years among 359 children in the Odense child cohort. *Environ Int* 96:48–64. <https://doi.org/10.1016/j.envint.2016.08.026>
487. Steenland K, Zhao L, Winquist A, Parks C (2013) Ulcerative colitis and perfluorooctanoic acid (PFOA) in a highly exposed population of community residents and workers in the mid-Ohio valley. *Environ Health Perspect* 121:900–905. <https://doi.org/10.1289/ehp.1206449>
488. Bao WW, Qian Z, Geiger SD, Liu E, Liu Y, Wang SQ, Lawrence WR, Yang BY, Hu LW, Zeng XW, Dong GH (2017) Gender-specific associations between serum isomers of perfluoroalkyl substances and blood pressure among Chinese: isomers of C8 health project in China. *Sci Total Environ* 607–608:1304–1312. <https://doi.org/10.1016/j.scitotenv.2017.07.124>
489. Huang M, Jiao J, Zhuang P, Chen X, Wang J, Zhang Y (2018) Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population. *Environ Int* 119:37–46. <https://doi.org/10.1016/j.envint.2018.05.051>
490. Mitro SD, Sagiv SK, Fleisch AF, Jaacks LM, Williams PL, Rifas-Shiman SL, Calafat AM, Hivert MF, Oken E, James-Todd TM (2020) Pregnancy per- and polyfluoroalkyl substance concentrations and postpartum health in project viva: a prospective cohort. *J Clin Endocrinol Metab* 105:e3415–e3426. <https://doi.org/10.1210/clinem/dgaa431>
491. De Toni L, Radu CM, Sabovic I, Di Nisio A, Dall'Acqua S, Guidolin D, Spampinato S, Campello E, Simioni P, Foresta C (2020) Increased cardiovascular risk associated with chemical sensitivity to perfluoro-octanoic acid: role of impaired platelet aggregation. *Int J Mol Sci* 21:399. <https://doi.org/10.3390/ijms21020399>
492. Li N, Liu Y, Papandonatos GD, Calafat AM, Eaton CB, Kelsey KT, Cecil KM, Kalkwarf HJ, Yolton K, Lanphear BP, Chen A, Braun JM (2021) Gestational and childhood exposure to per- and polyfluoro-alkyl substances and cardiometabolic risk at age 12 years. *Environ Int* 147:106344. <https://doi.org/10.1016/j.envint.2020.106344>
493. Ding N, Karvonen-Gutierrez CA, Mukherjee B, Calafat AM, Harlow SD, Park SK (2022) Per- and polyfluoroalkyl substances and incident hypertension in multi-racial/ethnic women: the study of women's health across the nation. *Hypertension* 79:1876–1886. <https://doi.org/10.1161/hypertensionaha.121.18809>
494. Preston EV, Hivert MF, Fleisch AF, Calafat AM, Sagiv SK, Perrig W, Rifas-Shiman SL, Chavarro JE, Oken E, Zota AR, James-Todd T (2022) Early-pregnancy plasma per- and polyfluoroalkyl substance (PFAS) concentrations and hypertensive disorders of pregnancy in the project viva cohort. *Environ Int* 165:107335. <https://doi.org/10.1016/j.envint.2022.107335>
495. Guerrero-Preston R, Ili-Gangas C, LeBron C, Witter FR, Apelberg BJ, Hernández-Roystacher M, Jaffe A, Halden RU, Sidransky D (2010) Global DNA hypomethylation is associated with *in utero* exposure to cotinine and perfluorinated alkyl compounds. *Epigenetics* 5:539–546. <https://doi.org/10.4161/epi.5.6.12378>
496. Liu CY, Chen PC, Lien PC, Liao YP (2018) Prenatal perfluorooctyl sulfonate exposure and Alu DNA hypomethylation in cord blood. *Int J Environ Res Public Health* 15:1066. <https://doi.org/10.3390/ijerph15061066>
497. Starling AP, Liu C, Shen G, Yang IV, Kechris K, Borengasser SJ, Boyle KE, Zhang W, Smith HA, Calafat AM, Hamman RF, Adgate JL, Dabelea D (2020) Prenatal exposure to per- and polyfluoroalkyl substances, umbilical cord blood DNA methylation, and cardio-metabolic indicators in newborns: the healthy start study. *Environ Health Perspect* 128:127014. <https://doi.org/10.1289/EHP6888>
498. Kim S, Thapar I, Brooks BW (2021) Epigenetic changes by per- and polyfluoroalkyl substances (PFAS). *Environ Pollut* 279:116929. <https://doi.org/10.1016/j.envpol.2021.116929>
499. Goodrich JM, Calkins MM, Caban-Martinez AJ, Stueckle T, Grant C, Calafat AM, Nematollahi A, Jung AM, Graber JM, Jenkins T, Slitt AL, Dewald A, Cook Botelho J, Beitel S, Littau S, Gulotta J, Wallentine D, Hughes J, Popp C, Burgess JL (2021) Per- and polyfluoroalkyl substances,

- epigenetic age and DNA methylation: a cross-sectional study of firefighters. *Epigenomics* 13:1619–1636. <https://doi.org/10.2217/epi-2021-0225>
500. Steenland K, Winquist A (2021) PFAS and cancer, a scoping review of the epidemiologic evidence. *Environ Res* 194:110690. <https://doi.org/10.1016/j.envres.2020.110690>
501. US EPA (United States Environmental Protection Agency) (2021) Our current understanding of the human health and environmental risks of PFAS. Per- and polyfluoroalkyl substances (PFAS) are a group of manufactured chemicals. <https://www.epa.gov/pfas/our-current-understanding-human-health-and-environmental-risks-pfas>. Last Update March 16, 2022
502. Barry V, Winquist A, Steenland K (2013) Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ Health Perspect* 121:1313–1318. <https://doi.org/10.1289/ehp.1306615>
503. Consonni D, Straif K, Symons JM, Tomenson JA, van Amelsvoort LGPM, Sleguwoenhoek A, Cherrie JW, Bonetti P, Colombo I, Farrar DG, Bertazzi PA (2013) Cancer risk among tetrafluoroethylene synthesis and polymerization workers. *Am J Epidemiol* 178:350–358. <https://doi.org/10.1093/aje/kws588>
504. Bartell SM, Vieira VM (2021) Critical review on PFOA, kidney cancer, and testicular cancer. *J Air Waste Manag Assoc* 71:663–679. <https://doi.org/10.1080/10962247.2021.1909668>
505. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Coglian VJ, Straif K (2016) Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect* 124:713–721. <https://doi.org/10.1289/ehp.1509912>
506. Li H, Hammarstrand S, Midberg B, Xu Y, Li Y, Olsson DS, Fletcher T, Jakobsson K, Andersson EM (2022) Cancer incidence in a Swedish cohort with high exposure to perfluoroalkyl substances in drinking water. *Environ Res* 204:112217. <https://doi.org/10.1016/j.envres.2021.112217>
507. Cohen JC, Horton JD, Hobbs HH (2011) Human fatty liver disease: old questions and new insights. *Science* 332:1519–1523. <https://doi.org/10.1126/science.1204265>
508. Itoh H, Harada KH, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, Yokoyama K, Zhu J, Sassa MH, Tsugane S, Iwasaki M (2021) Serum perfluoroalkyl substances and breast cancer risk in Japanese women: a case-control study. *Sci Total Environ* 800:149316. <https://doi.org/10.1016/j.scitotenv.2021.149316>

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