



A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects

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Abstract

Here, we review present understanding of sources and trends in human exposure to poly- and perfluoroalkyl substances (PFASs) and epidemiologic evidence for impacts on cancer, immune function, metabolic outcomes, and neurodevelopment. More than 4000 PFASs have been manufactured by humans and hundreds have been detected in environmental samples. Direct exposures due to use in products can be quickly phased out by shifts in chemical production but exposures driven by PFAS accumulation in the ocean and marine food chains and contamination of groundwater persist over long timescales. Serum concentrations of legacy PFASs in humans are declining globally but total exposures to newer PFASs and precursor compounds have not been well characterized. Human exposures to legacy PFASs from seafood and drinking water are stable or increasing in many regions, suggesting observed declines reflect phase-outs in legacy PFAS use in consumer products. Many regions globally are continuing to discover PFAS contaminated sites from aqueous film forming foam (AFFF) use, particularly next to airports and military bases. Exposures from food packaging and indoor environments are uncertain due to a rapidly changing chemical landscape where legacy PFASs have been replaced by diverse precursors and custom molecules that are difficult to detect. Multiple studies find significant associations between PFAS exposure and adverse immune outcomes in children. Dyslipidemia is the strongest metabolic outcome associated with PFAS exposure. Evidence for cancer is limited to manufacturing locations with extremely high exposures and insufficient data are available to characterize impacts of PFAS exposures on neurodevelopment. Preliminary evidence suggests significant health effects associated with exposures to emerging PFASs. Lessons learned from legacy PFASs indicate that limited data should not be used as a justification to delay risk mitigation actions for replacement PFASs.

Introduction

Poly- and perfluoroalkyl substances (PFASs) are a family of more than 4000 highly fluorinated aliphatic compounds manufactured for diverse applications [1]. They have been

widely used for their hydrophobic and oleophobic properties in consumer products such as disposable food packaging, cookware, outdoor gear, furniture, and carpet. They are also one of the main components (1–5% w/w) [2] of aqueous film forming foams (AFFF) used frequently at airports and military bases for firefighting and training activities [3]. AFFF contamination of groundwater is a major source of drinking water contamination and has been identified as a nationally significant challenge in countries such as the US and Sweden [4, 5]. Releases of PFASs to the environment can occur next to chemical manufacturing locations, at industrial sites where PFASs are used, and at various stages of product use and disposal. The carbon–fluorine bond in these compounds is extremely strong and thus many PFASs are not appreciably degraded under environmental conditions

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[6]. This has resulted in their accumulation in the environment since the onset of production in the late 1940s [7].

International concern regarding potential health effects associated with PFAS exposure began in the early 2000s when perfluorooctanesulfonate (PFOS) was detected in the blood of polar bears in the Arctic and wildlife in other remote regions [8]. Early data on PFOS bioaccumulation in aquatic food webs indicated the propensity for human exposure to these compounds through seafood [9]. The U.S. Centers for Disease Control and Prevention (CDC) later reported these compounds are detectable in the blood of virtually all Americans (98%) [10–12]. Between 2000 and 2002, the main global manufacturer of PFASs (3M) voluntarily discontinued manufacturing of the parent chemical used to produce PFOS and its precursors [13]. The US introduced a variety of programs to curb the use of the most abundant environmental PFASs, including the PFOA Stewardship Program enacted in 2006 to end production of the longest chained compounds by 2015. PFOS was added to the Stockholm Convention's list of globally restricted Persistent Organic Pollutants (POPs) in 2009.

Human exposures to PFOS and PFOA have been declining in western countries and Japan over the last decade [14–16] due to these regulatory interventions while understanding of their adverse effects on human health has been rapidly advancing [17]. At the same time, a proliferation of new PFASs has been reported in the environmental literature as the industry has rapidly replaced PFOS and PFOA with shorter chain length PFASs and new chemicals that are difficult to detect using standard methods [3]. Emerging evidence from animal experiments suggests some of these alternative PFASs can be equally hazardous [18]. Environmental health scientists thus face a considerable challenge in understanding the relative importance of diverse exposure pathways to PFASs in different human populations and their potential effects on human health in a rapidly changing chemical landscape.

Here we review current understanding of: (1) the predominant exposure pathways for PFASs for different populations, (2) health impacts associated with exposure, and (3) critical research needs for the future. We focus on four health effects: cancer, immune effects, metabolic effects, and neurodevelopment. We use this review to summarize key knowledge gaps and future research needs.

PFAS nomenclature

All PFASs contain at least one perfluoroalkyl moiety (C_nF_{2n+1}) [19]. Fully fluorinated aliphatic carbon chains are known as perfluoroalkyl substances while those with the incomplete replacement of hydrogen atoms by fluorine are referred to as polyfluoroalkyl substances. Perfluoroalkyl

acids (PFAAs) include perfluoroalkyl carboxylic, sulfonic, phosphonic, and phosphinic acids, which are differentiated by their functional groups. Most research has focused on perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) with between four and sixteen (C4–C16) carbons. Long-chain PFASs are defined as PFCAs with seven or more perfluorinated carbons and PFSAs with six or more perfluorinated carbons. The fluorinated carbon chain of these chemicals is both hydrophobic and oleophobic but the head group for many PFASs is easily deprotonated, resulting in high stability in solution. High water solubility of some PFASs has led to their accumulation in groundwater, rivers, and the ocean and contamination of drinking water resources, fish and marine mammals.

PFAA precursors, hereon referred to as “precursors”, are compounds that can biotically, and sometimes abiotically, degrade to PFAAs [6, 20]. Volatile precursors can be transported long distances in the atmosphere prior to deposition in regions remote from pollution sources [21, 22]. Precursors are often not measured during standard PFAA analysis, which can result in an underestimate of human exposure because they can be metabolized to terminal PFAAs in the human body [23, 24].

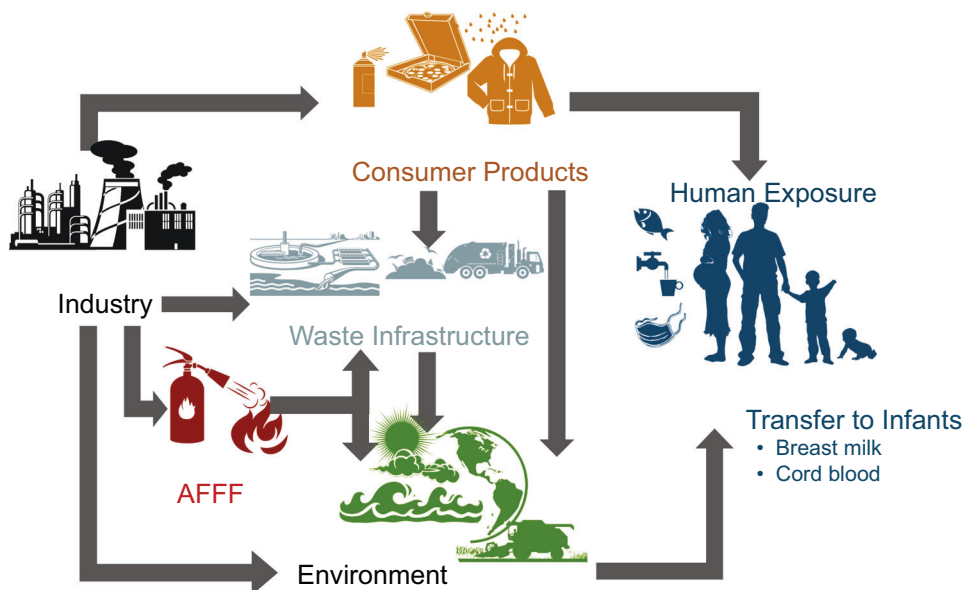
Human exposure pathways

Figure 1 provides an overview of the pathways for human exposure to PFASs. Human exposure to PFASs occurs through ingestion of contaminated drinking water and seafood, inhalation of indoor air, and contact with other contaminated media [25]. PFASs are often used for their “non-stick” and surface-tension lowering properties, which makes them useful for repelling oil and water (preventing stains) and modifying surface chemistry. The latter includes applications such as AFFF, processing aids for fluoropolymer manufacture, metal plating, and the production of semiconductors [26, 27]. Direct exposures due to use in products can be quickly phased out by shifts in chemical production but exposures driven by PFAS accumulation in the ocean and marine food chains and AFFF contamination of groundwater persist over long timescales [28, 29]. Understanding the relative importance of these different exposure pathways is thus critical for interpreting drivers of temporal differences in serum PFAS concentrations measured in biomonitoring studies [28, 30], and for anticipating future exposure risks.

Consumer products, indoor air, and dust

PFASs have been detected in jackets, upholstery, carpets, papers, building materials, food contact materials, impregnation agents, cleansers, polishes, paints, and ski waxes,

Fig. 1 Overview of PFAS exposure pathways for different human populations outside of occupational settings



among many other items commonly found in offices, households, and cars [31–40]. PFASs can migrate from fluorochemical-treated food contact papers into food-simulants such as butter, water, vinegar, and water/ethanol mixtures, indicating a direct exposure route to humans [36, 41, 42]. Dermal exposure to PFOS and PFOA from products is thought to be low [25]. In a study of 41 Norwegian women, Haug et al. [23] reported that food is typically the dominant exposure pathway, although the indoor environment (dust, air) could account for up to ~50% of the total PFAS intake.

Precursor compounds in many consumer products can be biotransformed in the human body to PFAAs, leading to additional uncertainty regarding the significance of exposures from this source [23, 24]. Inhalation of volatile precursors is known to occur and these precursors have been measured in indoor environments where PFAS containing products are used [43, 44]. The phase-out of PFOS and PFOA and their precursors has led to the increased production of short-chain compounds and structurally similar alternative compounds [3, 6], requiring a more holistic approach to determining human exposure from fluorinated compounds. To address this challenge, Robel et al. [32] measured total fluorine concentrations and determined the fraction of fluorine that can migrate from a select group of consumer products and is available for human exposure. The authors reported that typical measurement techniques for PFASs only account for up to 16% of the total fluorine measured using particle-induced gamma ray emission (PIGE) [32]. Additional research is thus needed to establish the link between the PFAS concentrations in products and the concentrations in dust, air, and food and their overall

contributions to human exposure in populations with diverse product use patterns.

Drinking water

Drinking water has been identified as a substantial source of PFAS exposure for many populations, particularly those living near contaminated sites [4, 5]. The United States Environmental Protection Agency (U.S. EPA) proposed a lifetime health advisory level for PFOS+PFOA of 70 ng/L in drinking water in 2016 [45]. In 2018, the Agency for Toxic Substances and Disease Registry (ATSDR) in the US further lowered the Minimum Risk Levels (MRLs) for PFOS and PFOA by approximately an order of magnitude compared to the reference dose (RfD) used by the U.S. EPA to develop the 2016 lifetime advisory [46]. Drinking water advisory levels corresponding to the MRLs used by ATSDR would be 11 ng/L for PFOA and 7 ng/L for PFOS. Some lifetime drinking water advisories proposed by other state and international agencies include up to 11 or 12 PFASs (Sweden and Denmark) and range from less than 10 ng/L up to hundreds to thousands of ng/L for different PFASs in Canada [47]. Notably, Grandjean and Budtz-Jørgensen [48] estimated the lifetime drinking water advisory level should be less than 1 ng/L based on the benchmark dose for immunotoxicity associated with PFAS exposure for children in the Faroe Islands.

Figure 2 shows the growth in the identification of sites contaminated by PFASs across the US between 1999 and 2017. PFAS contamination of drinking water was first reported in the US in public and private drinking water supplies near a fluoropolymer manufacturing facility in Washington, WV in 1999 [49]. The average PFOA

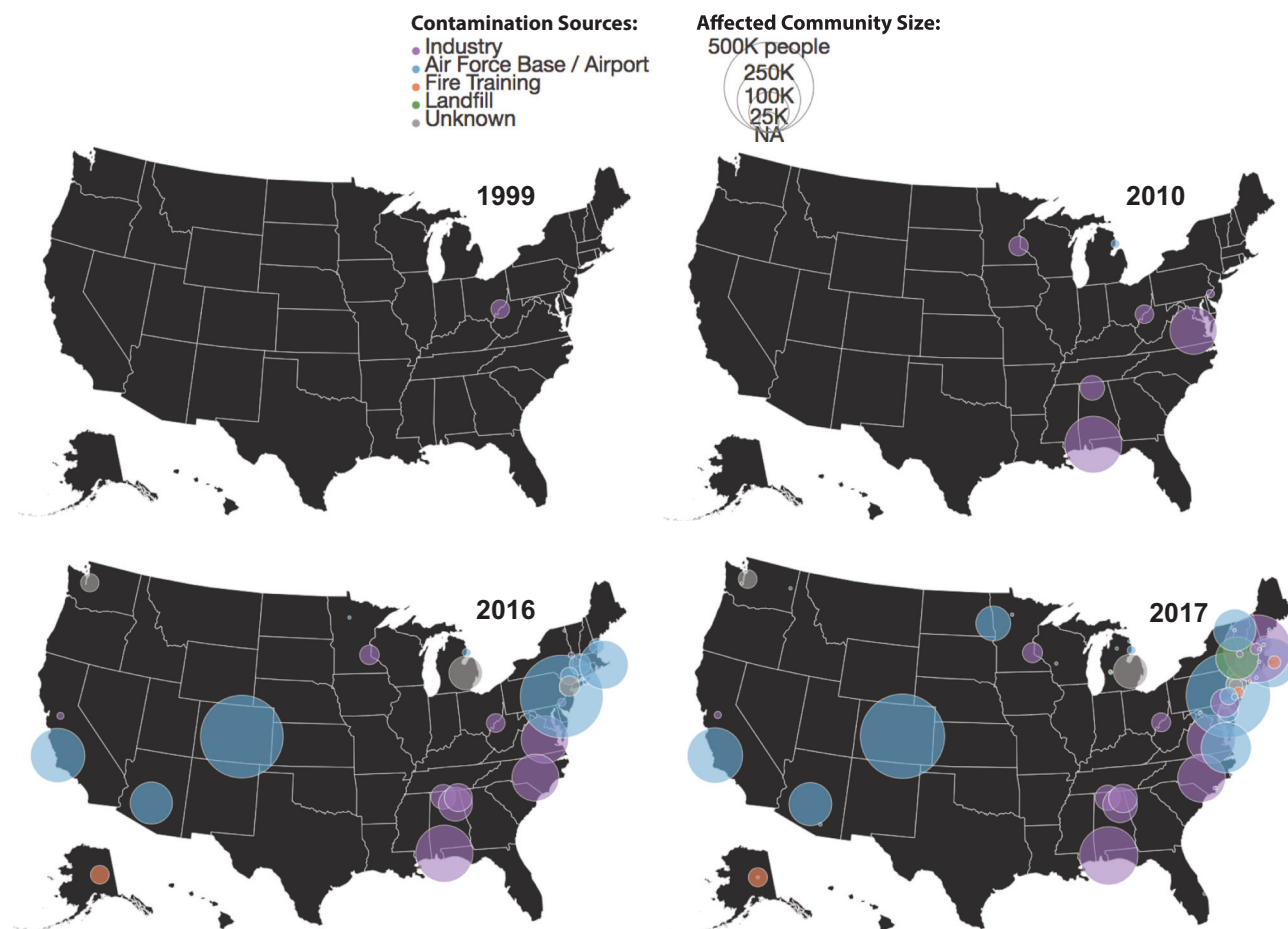


Fig. 2 Discovery of sites contaminated by PFASs leading to elevated concentrations in drinking water across the US. Figure adapted from data compiled by Northeastern University's Social Science

Environmental Health Research Institute (SSEHRI) that was last updated 12/17/17 [162]. Colors of circles represent different types of pollution source, and magnitudes indicate sizes of local communities

concentration of in one public water supply, the Little Hocking water system, was 3550 ng L^{-1} (range $1500\text{--}7200 \text{ ng L}^{-1}$) between 2002 and 2005. Drinking water contamination near a military base was first discovered in Michigan in 2010. Many additional cases of high concentrations of PFASs in finished drinking water across the US have since been reported (Fig. 2).

Most of these cases focus on single communities or small areas with a known point source of contamination. The first statewide study of PFAS occurrence in the US drinking water was conducted by New Jersey, where PFOA was detected in 59% of the public water supplies and maximum concentrations reached 190 ng L^{-1} [50]. The first nationwide occurrence survey of PFASs in public water supplies was conducted between 2013 and 2015 by the U.S. EPA under the third Unregulated Contaminant Monitoring Rule (UMCR3) [51]. Hu et al. [4] noted that drinking water concentrations of PFOS and/or PFOA exceeding the U.S. EPA 2016 health advisory levels were detected in large public water supplies serving approximately six million Americans. Further, there are no data for approximately 100

million Americans who obtain their water from small public water supplies serving less than 10,000 individuals and private wells, representing a critical research need for the future.

Following the shift in PFAS production away from PFOS, PFOA and their precursors, different PFASs may now be accumulating in drinking water and become relevant for human exposure. Newer PFASs, such as GenX, have been detected at high concentration (hundreds of ng L^{-1}) in the Cape Fear River watershed in North Carolina, downstream of a PFAS manufacturing plant [52]. The large-scale implications of such findings have yet to be evaluated and knowledge of the international significance of drinking water contamination by PFASs continues to advance at a rapid pace.

Seafood

Elevated serum concentrations of PFASs have been reported for a number of seafood consuming populations, including Inuit men in Greenland who frequently consume

seafood and marine mammals [53], whaling men in the Faroe Islands [54], and commercial fishery employees in China [55]. Seafood PFAS concentrations vary considerably with highest concentrations measured next to contaminated sites [56, 57]. Environmental concentrations of long-chain compounds appear to be the main driver of variability in tissue concentrations across sites and species [56, 58, 59]. Long-chained compounds and PFASs bioaccumulate to a greater degree than shorter chain length compounds and PFCAs [60, 61]. However, early studies of bioaccumulation potential were based on assays designed for highly lipophilic substances and therefore do not provide comprehensive information on all PFASs presently in use [58].

There is considerable variability in the contribution of seafood to the overall exposure of humans to PFASs. Cooking has been shown to reduce concentrations of some PFASs such as PFOS [59]. Christensen et al. [62] found higher concentrations of serum PFASs among high-frequency fish consumers in the U.S. National Health and Nutrition Exam Survey between 2007 and 2014. The European Food Safety Authority (EFSA) recently estimated that “fish and other seafood” account for up to 86% of dietary PFAS exposure in adults [57]. Hu et al. [63] showed that the presence of elevated serum concentrations of PFASs with $C \geq 9$ chain-length in humans is useful for identifying when seafood is a dominant exposure source. Birth cohort data from the Faroe Islands confirmed this observation by showing strong associations between serum concentrations of perfluoroundecanoic acid (PFUnDA, C11) and hair mercury concentrations, which are a strong tracer of seafood consumption [30]. Concentrations of legacy PFASs in marine biota have lagged shifts in production away from these compounds, resulting in increased significance of seafood as an exposure source [30].

Biosolids and agriculture

Many PFASs used in products or in industry enter the waste stream and are channeled to wastewater treatment plants. Wastewater treatment plants themselves are thus point sources for PFAS pollution [57]. The presence of greater than three treatment plants within a catchment has been associated with increased likelihood of PFAS detection in drinking water [4]. Data on the full suite of PFASs present in wastewater plumes are limited and this is expected to change temporally as chemical production and use in products shifts.

Figure 3 shows temporal changes in catchment level discharges of PFOS from wastewater treatment plants across the US between 1995 and 2005 [29]. PFOS discharges were modeled based on wastewater flow rates ($m^3 \text{ day}^{-1}$) from the Clean Watersheds Needs Survey (CWNS)

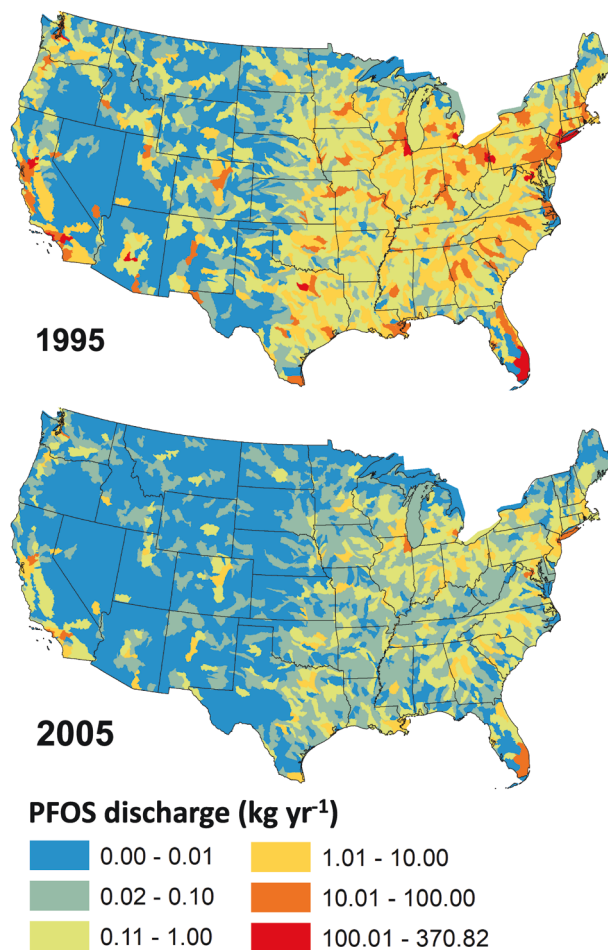


Fig. 3 PFOS discharges from wastewater treatment plants into streams and rivers across the US in 1995 and 2005. Adapted from data presented in Zhang et al. [29] and PFOS production estimates Wang et al. [166]

2008 Report to Congress and an empirical relationship between population served by wastewater treatment plants and PFOS concentrations, as described in Zhang et al. [29]. Higher levels of PFOS discharges from wastewater treatment plants are apparent in 1995 prior to the phase-out between 2000 and 2002 [26, 29]. Discharges from wastewater enter regional river networks and ultimately result in large inputs to marine ecosystems as the terminal sink. For PFOS, wastewater was thought to account for approximately 85% of releases on a continental scale, while industrial sites can be most significant at the local scale [64, 65].

Sewage sludge from wastewater treatment plants is often used for fertilizer in agriculture, presenting another potential vector for human exposure. Several studies have detected PFASs in such biosolids [66–68]. The 2001 U.S. EPA National Sewage Sludge Survey suggested that the load of PFASs in the US biosolids was $2749\text{--}3450 \text{ kg year}^{-1}$ based on the 13 PFASs measured. Of this total US load, an estimated $1375\text{--}2070 \text{ kg year}^{-1}$ was applied for agriculture and

467–587 kg year⁻¹ was transported to landfills [68]. Several studies have also investigated the uptake of PFASs into crops and earthworms from biosolids application [69–71]. In one study, concentration factors for roots relative to soil up to 4.7 and 10.3 were found for PFOS and PFOA, respectively, and all seven plants investigated displayed root concentration factors greater than one [71]. Elevated PFAS concentrations in meat and dairy products have also been reported [57, 72], suggesting PFAS uptake from biosolids contaminated agriculture is a source of dietary exposure for farm animals. Additional research on the significance of human exposures to PFASs originating from biosolids and agriculture is needed.

Approaches for quantifying exposure sources

Table 1 presents some literature estimates of source contributions to overall PFAS exposures for adults. There is general agreement that dietary intake is the largest source of PFAS exposure rather than inhalation or dermal contact. However, the relative importance of different source categories varies dramatically across demographic groups and populations (Table 1). Next to contaminated sites, drinking water has been reported to account for up to 75% of total PFAS exposure [73, 74]. Using a compilation of numerous

food samples, dietary survey data and toxicokinetic modeling, EFSA estimated that fish and other seafood dominate the chronic dietary exposure of adults to PFOS (up to 86% of total exposure). For the elderly, EFSA estimated meat and meat products account for up to 52% of PFOS exposure, while eggs and egg products account for up to 42% of infant exposure [57]. For PFOA, EFSA suggested the most important sources of chronic exposure were milk and dairy products for toddlers (up to 86% of exposure), drinking water (up to 60% for infants), and fish and other seafood (up to 56% in elderly).

Human exposures to PFASs (blood PFAS concentrations) are typically estimated using data on measured concentrations in exposure media, contact frequency, and toxicokinetic parameters [23, 25, 74–76]. The reliability of this approach depends on the accuracy of data needed to convert an external dose to internal concentrations. Many of these parameters for PFASs are poorly understood or hard to measure, resulting in large uncertainties about exposure sources (Table 1). For example, Vestergren and Cousins [74] relied on exposure estimates from multiple geographic regions to estimate total PFAS intake from the combination of dietary sources (German data), dust (data from the US and Spain) and inhalation (northwest Europe). Trudel et al. [25] tested a series of scenarios for chemical concentrations and contact frequencies across populations in Europe and

Table 1 Literature estimates of sources contributions (%) to adult PFAS exposures

PFAS	Diet	Dust	Tap water	Food Pkg.	Inhalation	Dermal	Other	Reference
PFOA	16	11		56	14		2 ^a	Trudel et al. [25]
PFOA	85	6	1	3 ^b			4 ^c	Vestergren and Cousins [74]
PFOA	77	8	11		4			Haug et al. [23]
PFOA	66	9	24		<1	<1		Lorber and Egeghy [76]
PFOA	41		37				22 ^d	Tian et al. [163]
PFOA	99		<1					Shan et al. [164]
PFOS	66	10	7		2		16 ^d	Gebbink et al. [165]
PFOS	72	6	22		<1	<1		Egeghy and Lorber [75]
PFOS	96	1	1		2			Haug et al. [23]
PFOS	81	15					4 ^a	Trudel et al. [25]
PFOS	93		4				3 ^d	Tian et al. [163]
PFOS	100		<1					Shan et al. [164]
PFBA		4	96					Gebbink et al. [165]
PFHxA	38	4	38		8		12 ^d	Gebbink et al. [165]
PFOA	47	8	12		6		27 ^d	Gebbink et al. [165]
PFDA	51	2	4		15		28 ^d	Gebbink et al. [165]
PFDoDA	86	2	2		4		5 ^d	Gebbink et al. [165]

^aCarpet

^bConsumer goods

^cPrecursors

^dIndirect

North America and found plausible ranges in PFAS exposures spanned two orders of magnitude.

Uncertainty in such estimates motivates an alternative solution that uses measured serum concentrations to identify predominant exposure sources. The ratio between two chemical homologues and the correlation among multiple chemical homologues in environmental samples, including human serum, contains information on their origin. This process is referred to as “chemometrics” and has been applied to polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons (PAHs) [77, 78]. Applying such techniques to PFASs is complicated by dramatic shifts in production over time and the complex metabolism of PFAS precursors. In prior work, researchers have used PFAS isomer profiles to assess the relative contributions from electrochemical fluorination (ECF) and telomere manufacturing to measured PFOA concentrations in the environment [79, 80]. Zhang et al. [81] showed that the measured PFAS composition in surface water provides useful information on sources of environmental pollution. Hu et al. [63] extended this approach to human biomarkers by comparing human serum samples collected at similar time periods and controlling for physiological differences. Using cohort data from the Faroe Islands and the U.S. National Health and Nutrition Examination Survey (NHANES), the authors showed that elevated C9–C12 PFCAs were associated with predominant exposures through seafood consumption. Further, PFHxS and N-EtFOSAA were linked to exposure from consumer products such as carpet and food packaging [63].

Serum samples are routinely collected during epidemiological studies, but environmental samples pertinent to multiple exposure pathways such as drinking water, diet, air, and dust samples are not [82]. Information on contact frequency is often collected using self-reported questionnaires with known recall bias [83]. In addition, there are limited data on chemical half-lives in the human body ($t_{1/2}$) and distribution volumes (V_D) for PFASs other than PFOS, PFOA, and PFHxS. This means that traditional exposure modeling is limited to only a few relatively well-characterized individual PFASs and cannot be easily applied to the PFAS mixtures that are more relevant for human exposures.

The results presented in Hu et al. [63] are mostly qualitative and cannot quantify the percentage of PFAS exposure from different exposure pathways. This preliminary approach can be enhanced by expanding the list of PFAS analytes. Regular epidemiological studies usually report six legacy PFASs (branched and linear PFOS, PFOA, PFHxS, PFNA, PFDA) but exposure analyses would be enhanced by including additional PFASs that are increasingly relevant to current production patterns. In addition, a total mass balance is needed to provide quantitative assessments of the

relative importance of different exposure sources [84]. Routine measurements of extractable organic fluorine (EOF) in human sera would thus complement data on individual PFASs and allow such quantitative inferences from the chemometric approach [85, 86].

Temporal trends in human exposure to PFASs

The presence of organic fluorine in human blood was first detected by Taves [87] in the 1960s. Data on specific forms of organic fluorine such as PFOS and PFOA in human sera were not published until 1990 [88]. Grandjean [89] pointed out that there has been a lag of more than two decades between industry information on exposures and health effects of PFASs and academic research and regulatory action.

Declines in serum concentrations of PFASs following the phase-out in the production of the parent chemical to PFOS and its precursors between 2000 and 2002 have been reported across diverse populations worldwide and provide a success story for the effectiveness of industrial shifts and regulatory actions. These include children from the Faroe Islands [30] and the eastern US [90], adult women from the western US [91] and Sweden [92], the general Australian population [93], and Norwegian men [94]. However, declines in PFOS and PFOA have primarily driven decreasing legacy PFAS concentrations. Concentrations of total PFASs or EOF in human serum that include newer PFASs in production and precursors have not been measured for most populations. One study that examined EOF in human serum in China found the legacy PFASs measured in standard epidemiologic studies only comprised between 30 and 70% of the total fluorine [95]. These results suggest unquantified PFASs may be exhibiting different trends than legacy compounds.

Following the phase-outs in use of PFOS and PFOA in many products, C6-based fluorocarbons (including perfluorohexanesulfonic acid: PFHxS and perfluorohexanoic acid: PFHxA) were used as an initial replacement [96, 97]. Concentrations of PFHxS and PFCAs with 9–14 carbons in human serum have not decreased concomitantly with PFOS, PFOA and their precursors. No change and some increases in exposures to these compounds have been observed across populations. For example, significant increases in PFNA, PFDA, and PFUnDA and no change in PFHxS was observed in Swedish and Danish women through 2015 [92, 98]. Blood concentrations of PFNA, PFDA, PFUnDA, and PFDoDA from multiple countries show no significant change [13]. Similarly, PFHxS concentrations in the blood of Mexican American NHANES participants showed no

significant trend between 1999 and 2004 and increased from 2005 to 2008 [12, 99].

Increasing trends in concentrations of PFHxS and long-chain PFCAs are noteworthy since they significantly contribute to the overall body burden of PFASs and have longer half-lives than both PFOS and PFOA. Additionally, exposures to the C9–C11 PFCAs for some individuals are primarily from seafood consumption [30, 62, 63]. C9–C11 PFCAs exhibit different temporal patterns than PFOS and PFOA. They are bioaccumulative and concentrations in some seafood have been increasing, as discussed in Dasuncao et al. [30]. This suggests that while exposures to PFOS and PFOA have been successfully reduced by product phase-outs for many populations, exposures to C9–C11 PFCAs have not followed the same trends.

Health effects associated with exposure to PFASs

The 3M Company was the major global manufacturer of PFASs in the 1990s and conducted most of the early studies on the health effects of PFAS exposures in animals and humans [26, 100]. Many of these studies were not published in the peer-reviewed literature but can be found in the U.S. EPA public docket AR-226, and are reviewed in the section below.

Early industry studies

Before 1980, 3M conducted multiple studies of acute animal toxicity associated with exposure to legacy PFASs [101]. Serum PFAS concentrations measured as organic fluorine in 3M workers were ten times higher than the general population in 1980 [102]. Shortly after this, 3M carried out a series of subacute and chronic studies in various animal models such as rats, mice, and monkeys [103–105]. Results showed N-ethyl perfluorooctane sulfonamidoethanol (N-EtFOSE) was carcinogenic in rats after a 2-year chronic study concluded in 1988. However, the results were first misinterpreted as a null finding and only corrected a decade later [106, 107]. In a 90-day rhesus monkey study, all monkeys in all treatment groups died after 20 days and the study had to be aborted [104]. In later monkey studies with lower doses, reductions in total cholesterol, increased liver weight, and toxicity on the reticuloendothelial system (immune system) were observed [103].

Health surveillance of 3M workers produced inconsistent results, mainly due to small sample sizes and a scenario known in epidemiology literature as the “healthy worker effect” [108]. A doctoral thesis that focused on a cohort of 3M workers reported in 1992 that PFOA exposure may significantly alter male reproductive hormones and

leukocyte counts [109]. Later investigations published by 3M did not find the same associations [110]. Differences between these findings may be caused by the exposure assessment methods used: Gilliland [109] measured serum total organic fluorine while Olsen [110] measured serum PFOA concentrations. This suggests adverse effects observed in Gilliland’s work [109] may have result from exposures to fluorochemicals other than PFOA.

Academic studies

Most academic research on PFASs was initiated in the early 2000s after the voluntary phase-out in the production of the parent chemical to PFOS and its precursors by 3M, the major global manufacturer at the time. Results from experimental studies in rodents can be challenging to translate directly to human health impacts because of differences in peroxisome proliferation expression, which is one of the main mechanisms of PFASs toxicity [111]. The most comprehensive longitudinal evidence for adverse health effects associated with PFAS exposure (C8 Health Project) is from the population living near the West Virginia DuPont Washington Works fluorotelomer plant. Probable links between PFOA exposure and six diseases have been identified: high cholesterol, thyroid disease, pregnancy-induced hypertension, ulcerative colitis, and kidney and testicular cancer [112–115].

Children may be more vulnerable to PFAS exposures because they often have higher body burdens than adults and are going through sensitive windows for development. A recent systematic review of the children’s health literature identified positive associations between PFAS exposures and dyslipidemia, immunity, renal function, and age at menarche [116]. Some health effects such as immunotoxicity can be detected at lower exposure levels than others. For example, Grandjean et al. [117] examined the impact of serum PFAS concentrations on serum antibody production in children at ages 5 and 7 years following routine vaccinations for tetanus and diphtheria. A doubling of serum PFOS, PFOA, and PFHxS concentrations at age 5 was associated with a 50% decline in antibody concentrations at age 7. If this effect is causal, average serum concentrations in the general population of most countries with biomonitoring data greatly exceed the benchmark doses of 1.3 ng/mL for PFOS and 0.3 ng/mL for PFOA calculated based on immunotoxicity in children [48].

Cancer

Numerous studies have investigated PFAS carcinogenicity, mainly focusing on PFOA and PFOS. PFHxA is the only other PFAS that has been investigated in an animal study and null findings were reported [118]. Human studies for

PFOS and PFOA include chemical workers, communities with contaminated drinking water, and the general population. A 3.3-fold increase (95% CI, 1.02–10.6) in prostate cancer mortality was reported for each month spent in the chemical division with PFOA production was observed among occupationally exposed workers, but the number of cases was small [119]. Later data from this occupational cohort did not support an association between occupational exposure and cancer mortality or incidence [120]. The strongest evidence for increased cancer risk has been reported by studies among community members whose drinking water was contaminated by PFOA. Barry et al. [112] and Vieira et al. [121] showed a positive association between PFOA levels and kidney and testicular cancers among participants in the C8 Health Project. These studies form the foundation of the overall conclusion from the C8 Health Project. Results among studies conducted in general population are inconsistent. Eriksen et al. [122] were the first to examine PFOA exposure and cancer in the general population and they did not find an association between plasma PFOA or PFOS concentration and prostate, bladder, pancreatic, or liver cancer. The International Agency for Research on Cancer (IARC) classified PFOA as a possibly carcinogenic to humans (Group 2B). No IARC evaluation is available for PFOS.

Immune effects

Immunotoxicity of PFASs has been demonstrated in multiple animal models, including rodents, birds, reptiles and other mammalian and non-mammalian wildlife. Epidemiological data is relatively sparse but mounting evidence suggests that the immunotoxic effects in laboratory animal

models occur at serum concentrations that are comparable to body burden of highly exposed humans and wildlife [123].

Table 2 shows findings from a review of 25 epidemiological studies published between 2008 and 2018. Cohort data were from China, Denmark, the Faroe Islands, Japan, Norway, Taiwan, and the US and 14 out of the 25 studies reviewed were longitudinal. Two studies focused on occupational exposures and the remaining 23 were based on environmental exposures. Infants and children were the most studied demographic group for this health endpoint and accounted for 16 out of the 25 studies. Three studies considered data from teenagers in the U.S. NHANES survey. Six studies were based on either residents or workers from the C8 health project near a fluorotelomer plant in West Virginia. One study examined a group of healthy adults who received vaccination. Serum PFAS concentration measurements were the most widely used exposure assessment method, accounting for 22 out of 25 studies. Four studies from the C8 health project used job-exposure matrix or residential history to estimate lifetime cumulative exposures.

The health outcomes related to PFAS immunotoxicity include both molecular-level (i.e., antibody concentrations) and organ/system-level (i.e., infection of the respiratory system). In general, more consistent results across different studies were reported for molecular-level health endpoints such as vaccine antibody or other immune markers such as immunoglobulin (Table 1).

Five studies examined the association between PFAS exposure and suppression of antibody response to vaccination among children, adolescents or adults. Four out of the five found statistically significant associations between

Table 2 Summary of the epidemiologic literature on PFAS exposures and metabolic outcomes

Outcome	# of total studies	# of studies by results				Other PFASs
		PFOA	PFNA	PFHxS	PFOS	
Lipid profile ^a	39	21/10/1 ^b	8/1/2	4/4/2	20/9/3	Inconsistent results for PFDA, PFUnDA, PFTeDA
Insulin resistance and diabetes	18	6/9/1	3/5/0	1/2/1	7/4/1	Mostly null for PFDA, PFUnDA, PFDoDA, N-EtFOSAA, N-MeFOSAA; One positive finding for PFDoDA and insulin resistance
Hypertension, vascular disease and stroke	10	3/5/1	3/0/1	0/3/1	1/3/1	Only one study reported null for PFDA and PFUnDA
Thyroid disease	8	4/3/0	1/2/0	1/2/0	1/3/0	Positive finding for PFDA and PFUnDA in two studies. Null for PFTeDA
Cardiovascular disease	6	1/4/1	1/0/0	0/1/0	0/1/0	No other PFASs have been investigated
Uric acid	5	4/0/0	0/0/0	0/1/0	2/2/0	No other PFASs have been investigated
Overweight and obese	4	1/3/0	1/1/0	1/1/0	3/1/0	Positive finding for PFDA in only one study (Liu et al. [134])

Details of the studies examined are provided in the Supporting Information Table S1

^aLipid profile includes low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides

^bNumber of studies with adverse/null/protective results

higher PFAS exposure and suppressed immune response. Grandjean et al. [117] were the first to link PFAS exposure in children to deficits in immune function. The authors reported a 2-fold increase of major PFASs in child serum was associated with a $-49%$ (95% confidence interval (CI), $-67%$ to $-23%$) decline in tetanus and diphtheria antibody concentrations. This effect size is larger than later studies and can be attributed to different exposure levels, different vaccine strains, and different times elapsed since vaccination (peak antibodies vs. residual antibodies). Other studies have not examined tetanus and diphtheria, but similar associations have been found in PFAS exposure and other childhood vaccinations such as rubella and mumps [124, 125], and adult influenza vaccination such as FluMist [126] and anti-H3N2 [127].

Five out of seven studies that examined associations between PFAS exposure and immune markers found statistically significant evidence of immunosuppression. The strongest evidence has been generated for PFOA and PFOS with limited data for other PFASs. One example for other PFASs is from a case-control study in Taiwan [128] that reported that among children with asthma, nine out of the ten PFASs evaluated were positively associated with at least two of the three immunological biomarkers (immunoglobulin E (IgE), absolute eosinophil counts (AEC), and eosinophilic cationic protein (ECP)). However, this study did not account for the fact that multiple PFASs serum concentrations are positively correlated and therefore did not distinguish whether all PFASs or a subset of PFASs were associated with immune suppression.

Results with organ/system-level outcomes such as asthma, infection, and allergies are more inconsistent. Slightly more than half of the studies on asthma and infection show statistically significant results. Similar to the molecular-level outcomes, stronger evidence has been established for PFOS and PFOA than other more minor PFASs. Buser et al. [129] found serum levels of PFASs were associated with higher odds of self-reported food allergies among teenagers in NHANES 2007–2010. This is the only study out of the six studies reviewed with a statistically significant finding, but the cross-sectional design of this study necessitates further investigation using longitudinal studies. Existing studies have limitations such as outcome measurement error. For example, some studies measure asthma using a self-reported questionnaire but did not validate these data with medical records. Some studies used hospitalization due to infection as an outcome but hospitalization may not be necessary for most infections. In addition, since infection and allergy be caused by food and airborne allergens, it is challenging to identify the contribution of PFAS exposures in a low signal-to-noise setting.

Metabolic effects

We reviewed 69 epidemiological studies published between 1996 and 2018 based on human populations in Australia, Canada, China, several European countries, Japan, South Korea, Taiwan, UK, and the US. We identified 26 out of 69 studies as longitudinal and 59 out of 69 studies were based on environmental exposures. Diverse demographic groups have been studied for this health endpoint, including infants, mother–child pairs, children, teenagers, adults, workers, and special subpopulations such as diabetic patients and obese individuals in randomized clinical trials. Measured serum PFAS concentrations were the most widely used exposure assessment method (65 out of 69 studies). Two occupational studies used job-exposure matrix and work history to estimate lifetime cumulative exposures. Gilliland [130] was the earliest study and used total serum fluorine to quantify the exposure. Only one study [131] examined the different isomers of PFOA and PFOS (linear vs. branched) using data from NHANES 2013–2014.

There is relatively consistent evidence of modest positive associations with lipid profiles such as total cholesterol and triglycerides, although the magnitude of the cholesterol effect is inconsistent across different exposure levels. There is some but much less consistent evidence of a modest positive correlation with metabolic diseases such as diabetes, overweight, obesity, and heart diseases (Table 3). The majority of studies are cross-sectional, which have limited causal interpretation [132]. A few studies provided stronger evidence than observational studies, such as Diabetes Prevention Program Trial [133] and a diet-induced weight-loss trial [134].

The majority of the studies examined found associations between elevated serum PFASs and detrimental lipid profiles, such as elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C), or reduced high-density lipoprotein cholesterol (HDL-C). PFOS and PFOA exhibit the most consistent finding across studies. The effect size varies across studies, which can be a result of different exposure levels. Increases in serum PFOA and PFOS from the lowest to the highest quintiles among children in C8 health project was associated with 4.6 and 8.5 mg/dL total cholesterol (reference level for children is <170 mg/dL) [135]. Among NHANES 2003–2004 participants, increases in serum PFOA and PFOS from the lowest to the highest quartiles were associated with 9.8 and 13.4 mg/dL total cholesterol (reference level for adults is <200 mg/dL) [136]. Maisonet et al. [137] reported a non-linear relationship between prenatal PFOA concentrations and total cholesterol at ages 7 and 15 of the child.

Eighteen studies have examined the associations between PFAS exposures and glucose metabolism, insulin resistance, and diabetes. Overall the results across different

Table 3 Summary of the epidemiologic literature on PFAS exposures and immunotoxicity

Outcome	# of total studies	# of significant studies	# of significant studies by each PFAS
Vaccine antibody	5	4	Mixture: 1; PFOA: 2; PFNA: 1; PFHxS: 1; PFOS: 2
Immune markers	7	5	PFHpA: 1; PFOA: 5; PFNA: 2; PFDA: 1; PFTeDA: 1; PFDoA: 1; PFBS: 1; PFHxS: 2; PFOS: 4
Asthma and biomarker of asthma	9	5	PFHpA: 1; PFOA: 5; PFNA: 3; PFDA: 3; PFDoDA: 1; PFBS: 1; PFHxS: 2; PFOS: 4
Infection and other autoimmune diseases	13	8	PFOA: 6; PFOS: 4; PFDA: 1; PFDoDA: 1; PFNA: 2; PFUnDA: 1; PFHxS: 1; PFOSA: 1
Allergy	6	1	PFOA: 1; PFHxS: 1; PFOS: 1

Details of the studies examined are provided in the Supporting Information Table S2

studies are inconclusive. Lin et al. [138] were the first to report a positive association between serum PFAS concentrations and glucose homeostasis among adults and adolescents in NHANES. They reported a considerable effective size—doubling serum PFNA concentrations was associated with hyperglycemia odds ratio (OR) of 3.16 (95% CI 1.39–7.16). Later studies tend to report smaller effect sizes. Exposure during pregnancy may affect the mother and child during gestation and later in life. In a small pregnancy cohort in the US, each standard deviation of increase in PFOA was associated with a 1.87-fold increase of gestational diabetes risk (95% CI 1.14–3.02) [139]. In a larger Spanish cohort, a null result was reported for PFOA, but PFOS, PFHxS, and gestational diabetes had positive associations: OR per log10-unit increase = 1.99 (95% CI: 1.06, 3.78) and OR = 1.65 (95% CI: 0.99, 2.76), respectively [140].

Results for hypertension and other vascular diseases including stroke are also inconsistent. Two of the earliest studies examined the relationship between PFAS exposure and hypertension among NHANES and found different results for children and adults. Adjusted OR = 2.62 for hypertension comparing 80th vs. 20th percentiles serum PFOA among NHANES adults in the US [141], while among children a null finding was reported [142]. In some later cohort studies, null results and even protective effects associated with PFAS exposure and hypertension were reported [143, 144]. A cross-sectional study on carotid artery intima-media thickness in adolescents reported increased risks with an increase in plasma PFOS [145]. However, a more recent study on artery stiffness found protective effects of PFOA and PFNA among children and adolescents enrolled in the World Trade Center Health Registry [146].

Other metabolic endpoints include thyroid disease (which could also be considered an endpoint for endocrine disruption), cardiovascular diseases, uric acid metabolism, and body weight. Except for uric acid metabolism, most results are inconclusive. An increase in hyperuricemia risks and PFOA exposure was observed in all four studies (two from NHANES and two from C8 Health Project).

In summary, the strongest evidence for a relationship between PFAS exposure and metabolic outcome is in the area of dyslipidemia. Animal studies have found decreases in serum cholesterol levels associated with increased PFAS exposures, which contradicts epidemiological findings. The difference may lie in different levels of expression for nuclear receptors involved in the toxicological pathway, such as peroxisome proliferator-activated receptor (PPAR)-alpha. It may also be related to differences in exposure levels. Dietary factors can influence metabolic outcomes [147], introducing bias into observed relationships if not controlled for properly. Explanations for null findings

include healthy worker effects and non-linear relationships, such as decreasing slopes as exposure increases (log-linear relationships) [148].

Neurodevelopmental effects

In vitro studies suggest PFOS can trigger the “opening” of tight junction in brain endothelial cells and increase the permeability of the blood brain barrier [149]. There has therefore been some interest in investigating the neurotoxic effects associated with PFAS exposures. In laboratory animals, it has been reported that PFOS, PFOA, and PFHxS exposures during the peak time of rapid brain growth in mice resulted in an inability to habituate in the unfamiliar environment [150]. Liew et al. [151] reviewed 21 epidemiological studies in 2018 and concluded that evidence is mixed regarding neurodevelopmental effects of PFAS exposures. Health outcomes examined included developmental milestones in infancy, attention-deficit/hyperactivity disorder (ADHD) and behaviors in childhood, and neuropsychological functions such as IQ and other scales or scores. Neurodevelopmental trajectories are highly complicated and there is great heterogeneity in the instruments and methods to evaluate neurodevelopmental endpoints. Additional research is needed to establish a link between neurodevelopmental outcomes and PFAS exposures.

Future directions

Challenges associated with quantifying the full-diversity of individual PFASs present in environmental samples and a paucity of toxicity data highlight the need for data and tools to better understand new and emerging fluorinated compounds. EOF provides an estimate of all combustible organofluorine compounds present and provides a proxy measure for unquantified PFASs [86]. Yeung and Mabury [152] reported that quantifiable PFASs accounted for 52–100% of EOF in human plasma samples collected between 1982 and 2009 in two German cities. The amount and proportion of unidentified organofluorine in human plasma increased after 2000 in one city. This study hypothesized that humans are exposed to many new and unidentified organofluorine compounds, which is consistent with the environmental exposure literature [3, 74, 153, 154].

The toxicity of new and emerging PFASs for ecosystems and humans is poorly understood. This is problematic because in communities with high concentrations of alternative PFASs, the magnitude of potential health impacts associated with exposures has not been quantified and such information is generally considered necessary to engage in risk mitigation actions. Chemical manufacturers have claimed that replacement PFASs are not associated with

adverse health effects and that shorter-chain homologues with shorter half-lives in the human body are not likely to bioaccumulate [155, 156]. However, ongoing work suggests shorter chain compounds have a higher potential to interact with biomolecules due to less steric hindrance than the longer chain homologues [157, 158]. For example, fluorinated carbon chains in perfluoroalkyl ether carboxylic acids (PFECAs), an important new class of PFASs, are broken into shorter units by the insertion of oxygen molecules that are thought to make them more reactive [159]. One known PFOA alternative is the ammonium salt of perfluoro-2-propoxypropanoic acid, a PFECA that has been produced since 2010 with the trade name “GenX” [160]. A recent hazard assessment based on the internal dose of GenX suggests it has higher toxicity than PFOA after accounting for toxicokinetic differences [18]. The extreme environmental persistence, bioaccumulation, and potential toxicity of the entire class of PFASs has led some researchers to question the use of any highly fluorinated chemicals and call for a class approach in managing them [161].

In summary, additional research is needed to better understand the exposure pathways and health outcomes associated with emerging PFASs and to understand the timescales of exposures to legacy PFASs associated with drinking water and seafood contamination. Risk mitigation measures require new technology for reducing PFAS concentrations at contaminated sites and in drinking water supplies. Delayed action on legacy PFASs has resulted in widespread human exposures and risks and lessons should be learned from this example and not repeated for the newer PFASs entering the market [89]. Although additional data are needed to understand the full extent of impacts of PFAS exposures on human health, particularly at sensitive life stages, we assert that this should not be used as a justification for delaying risk mitigation actions. The phase-out in PFOS and its precursors between 2000 and 2002 was extremely effective at rapidly reducing exposures of humans and wildlife globally to these compounds and provides an example of the potential benefits from the coordinated global action.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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