Review Article

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Per and polyfluoroalkyl substances scientific literature review: water exposure, impact on human health, and implications for regulatory reform

<https://doi.org/10.1515/reveh-2020-0049>

Received April 18, 2020; accepted August 19, 2020; published online September 30, 2020

Abstract: Among other emerging contaminants in water, per and polyfluoroalkyl substances (PFASs) have garnered international attention from the scientific community on a global scale. Some countries, such as the United States, have found that PFASs are present in humans on a wide scale. Although two PFASs have been widely studied—Perfluorooctanoic acid and Perfluorooctanesulfonic acid—many more PFASs are being created by industry and are either not known, not studied, or both. The objective of this literature review on PFASs is to give an overview of the information available about PFASs related to human exposure. The information from this literature review on the exposure of humans to PFASs through drinking water and the lack of many conventional drinking water treatment systems' ability to remove PFASs (particularly short-chain PFASs) suggests that current regulatory limits are insufficient to adequately protect humans. This is especially true for particularly vulnerable populations such as infants, young children, and developing children (pubescent). The gaps in the current knowledge and in current regulatory approaches could have long-term effects on human health.

Keywords: drinking water; per and polyfluoroalkyl substances; PFAS; PFAS and drinking water; PFAS exposure in children.

Introduction

Perfluoroalkyl substances are a group of highly stable carbon-fluorine compounds. The high stability comes from the C–F bond, which is one of the strongest in organic chemistry. PFASs offer technical properties superior to hydrocarbons such as thermal stability, surface activity, dielectric properties, chemical resistance, and physiological inertness [1]. These compounds have been used since the 1940s. They serve as surfactants, making products stain-proof, greaseproof, water repellant, and fire repellant [2]. There are nearly 5,000 types of PFAS. However, many PFASs are not well-known or studied, so their impact on public health is unknown [3]. PFASs have broad applications among textiles, paper, hard metal plating, paints and others [1].

Some PFASs that have been studied include perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), perfluorononanoic acid (PFNA), perfluorobutanesulfonic acid (PFBS), perfluorohexanesulfonic acid (PFHxS), and perfluoroheptanoic acid (PFHpA) [4]. Of these, the two most widely studied and well-known are PFOA and PFOS. Both are no longer produced within the USA [5]. In fact, PFOS had been listed under the Stockholm Convention on Persistent Organic Chemicals and PFOA was being considered for listing by 2017. As a result, companies, like 3 M, developed their own unique PFASs replacements for which they claim intellectual property right protections. They do not disclose the replacements as new PFASs, thus increasing the difficulty of tracking PFASs [3].

Both PFOA and PFOS are considered long-chain PFASs. The term “long-chain PFASs” refers to

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perfluorosulfonic acids with six or more carbon atoms or perfluorocarboxylic acids with eight or more carbon atoms [5]. Long-chain PFASs include PFOS, PFOA, PFNA, and PFHxS. Short-chain PFASs include PFBS and PFHpA. According to a widely cited study by Hu et al. in the USA, long-chain PFASs occur more frequently in groundwater and short-chain compounds in surface water. There is an inverse relationship between PFASs' mobility and chain length [4].

Some PFASs are released into the environment both during production and the life cycle of the products. Perfluoroalkyl acids (PFAAs) are considered the final degradation products of many PFASs, which can degrade under relevant conditions. In addition to direct PFAAs emissions, precursor substances emit indirectly and contribute to global PFASs emissions. PFAAs are a small substance group within PFASs but are highly persistent [1]. Some examples of PFAAs include PFCAs, PFSAAs, PFECAs, and PFESAs. Studies have found that PFAAs travel long distances through water currents because of their water solubility and high persistence [3]. Certain PFASs are ubiquitous in the population and found through biomonitoring. Food and water are primary routes of exposure [2].

Methods

Evidence acquisition

The objective of this review was to survey the approaches that identify the scope of the threat that PFASs present to humans through water contamination from a regulatory reform perspective. Sources for this review were found using the search terms “PFAS”, “PFASs”, “PFAS routes of exposure”, “PFAS water exposure”, “PFAS and drinking water”, and “PFASs and water” in several databases. These included the National Center for Biotechnology, ScienceDirect, PubMed, Elsevier, and Google Scholar. Themes and terminology used in scientific literature emerged from the search [6]. The review focused on research articles from 2017 to 2020 available online from 2015 to July 15, 2020. A complimentary search using the term “PFASs human health effects” was also conducted.

The focus of follow-up searches was on PFAS exposure and water, PFAS exposure and impacts on human health, and PFAS exposure in contaminated food. PFAS exposure was consistently linked to women's health issues, and outcomes were often compounded. Therefore, health studies on the impact of women's health were included. All searches were limited to articles for which full text was

available in English and, for scientific articles, available in peer-reviewed journals.

A third search included general and specific terms for PFAS exposure from water other than drinking water or consumption. The search included multiple peer-reviewed journals: EBSCO, ProQuest, ScienceDirect, MEDLINE, PubMed, and others.

Lastly, a search for recent literature was conducted in Google Scholar and PubMed, focusing on geographic areas or populations that had produced few results from the previous searches. These searches included the terms “perfluoroalkyl substances OR PFOA OR PFOS AND” (for example) “Africa” OR specific country name for each country in the region for each of the following regions and populations: Central America, South America, Africa, the Middle East, and minority groups in the United States.

Selection of articles and studies and criteria of inclusion

Studies analyzing a wide range of matrices, including blood, urine, breast milk, and seminal plasma across different countries, were included to give a global picture of the health effects of PFAS exposure. Articles that covered the most recent developments in monitoring and standards served as focal points for the selection criteria, namely PFAS distribution in drinking water, regulatory frameworks, and legal implications. Countries of interest as the result of data that emerged included the United States, China, and countries in the European Union. Search results related to food exposure were restricted to examples directly linked to water contamination. Op-eds were excluded in the search to reduce bias and improve the reliability and trustworthiness of the data [7]. Several additional criteria were used to exclude articles. These include small sample sizes, sole authors, studies funded solely by companies currently facing multiple lawsuits as manufacturers (or former manufacturers) of PFASs, PFASs removal technologies, duplicates, PFASs measurement technologies, posters, presentations, no direct link to humans, and animal studies. Screening was performed by reviewing abstracts and the full text of the articles. The quality of the study was determined using conflict of interest statements, sample sizes, calculations for confounding variables, and statements provided in the studies by the researchers.

Potential biases may include publication bias and confirmation bias. Most of the research makes recommendations for further evaluation; many caution against wide use of PFAS to protect human health or recommend

increased/stricter regulations, health advisories, or health guidelines.

Results

Table 1 shows the PFAS literature reviewed for Asia and is sorted by location. The information suggests that most authors found adverse association between PFAS and health outcomes many of which related to mothers and children. The table also shows that there is a risk of PFAS exposure from consuming food affected by PFAS contamination.

Table 2 shows the PFAS literature reviewed for Europe and is sorted by location. The information also suggests adverse association for mother and child health related to PFAS. However, further explores differences between adults, mortality rates and gender. The table also provides some evidence that there is a disparity in the effectiveness of wastewater treatment plants to remove PFAS.

Table 3 shows the PFAS literature reviewed for North America and is sorted by location. The information further demonstrates association for mother and child health related to PFAS exposure and includes analysis from the National Health and Nutrition Examination Survey. Northern American literature including more information on race than other regions in this review. The table below also shows water treatment effectiveness varies and an increase in PFAS water contamination over time.

Table 4 shows additional studies not group with the previous regions. The data also shows adverse relationships to health outcomes. The information includes two examples of PFAS risk assessment for consuming food and water in the region.

Drinking water

Water is one of the direct pathways to contamination of per-and polyfluorinated substances. The closer a PFAS source is to a water supply, the greater the chance of pollution. PFASs in drinking water raise questions about potential health effects. The literature suggests that PFASs are present globally and are marked by differences in geography and production. Infrastructure is insufficient to limit its spread.

Domingo and Nadal conducted a literature review for the period from 2009 to 2019 focused on human exposure to PFASs through drinking water, including tap water and bottled water [55]. Overall, the authors concluded that the studies from around the world of PFAS exposure showed

that PFASs in drinking water did not pose an imminent threat to human health or was of concern for regular consumers of tap water as measured by various (and widely diverging) health advisories, guidelines, and regulations.

Yet PFASs' persistence in groundwater may impact the quality of drinking water for generations. Studies indicated that bottled water consumption is linked to lower PFAS levels in humans in areas with known or suspected PFAS-contaminated public drinking water systems [25, 26, 35, 55].

USA

According to Hu et al. low exposure to PFASs through drinking water can still lead to elevated exposures in humans. Elevated PFAS concentrations have been reported near industrial sites that produce PFASs or use them in numerous US regions. For example, PFOA concentrations were measured at 190 times the US EPA recommended lifetime health advisory (70 ng/L) in drinking water near a fluorochemical facility in Washington, West Virginia, that used PFOA during fluoropolymer production. Groundwater and surface water are reported to have 3–4 orders of magnitude above the US EPA health advisory level for drinking water for PFAS levels near many military fire training airports and civilian airports. Wastewater treatment plants are another source of PFASs because standard treatment does not remove PFASs from effluent, thus changing the concentrations of effluent relative to influent [41].

Hu et al. performed a spatial and statistical analysis on publicly available information about six PFASs in 36,149 drinking samples between January 2013 and December 2015. According to that study, 16.5 million Americans in 33 different states, three territories (American Samoa, Guam, and the Northern Mariana Islands), and the Salt River Pima-Maricopa Indian Community had PFASs present at or above the Maximum Recommended Levels by EPA in 194 of 4,864 public water sources. Drinking water for 13 states accounted for 75% of the frequency detection occurrences. PFASs were detected in drinking water from groundwater twice as much as that sourced from surface water. The study found a positive association in detecting all PFOS, PFOAs, PFHxS, and PFHpA, with statistical significance for PFHxS and PFOS in areas around military sites. They detected a small but significant increase in PFOA and PFOS in areas surrounding wastewater treatment plants. There was no association between proximity to the airport and elevated PFASs in drinking water near civilian airports

Table 1: Asia PFAS studies.

<i>Location</i>	<i>Study design/ Model</i>	<i>Sample</i>	<i>Result</i>	<i>Conclusions</i>	<i>References</i>
China (Guangzhou)	Birth cohort	372 mother-child dyad	Maternal serum 6:2 Cl-PFESA and 8:2 Cl-PFESA concentrations (conc.) associated with lower birth weight, maternal serum 6:2 Cl-PFESA conc. associated with higher risk of preterm birth	PFOS alternatives may be reproductive toxicants in humans	Chu et al. 2020 [8].
China (Tianjin)	Cross-sectional	252 (19 – 87yrs)	PFAES and TFA widely detected (>90%); median conc. (ng/mL): PFAES 8.64, TFA 8.46, PFOA 14.83, PFOS 14.24. Significant association (assoc.) between PFOA, PFNA, fasting glucose levels and HbA1c	6:2 Cl-PFAES and TFA showed more significant contributions to PFASs in serum and supported assoc. between PFAS exposure and fasting glucose and HbA1c	Duan et al. 2020 [9]
China (Shanghai)	Prospective cohort	3220 women in early pregnancy	No assoc. between maternal plasma conc. of PFASs in early pregnancy and gestational hypertension, preeclampsia, or hypertensive disorders in singleton livebirths	PFASs did not have a significant or consistent assoc. pattern with gestational hypertension or preeclampsia	Huo et al. 2020 [10]
China (Anji)	Human biomonitoring	85	Mean serum conc. ng/mL: PFOS: 5.9 ng/mL, PFOA: 3.3 ng/mL, 6:2Cl-PFAES: male 6.5, female 5.6; significant increase in 6:2Cl-PFAES conc. with age in males.	Study provides baseline of Cl-PFAESs in the general Chinese population and suggests direct exposure was a significant source of PFCAs and PFASs in human serum.	Jin et al. 2020 [11]
China (Wuhan)	Cross-sectional	374 neonates	PFOS, PFOA, and replacements positively associated with progesterone, cortisol, and 11-deoxycortisol: 6:2 Cl-PFESA with $\Delta 13.3\%$ in cortisol in girls; PFBS, PFOS, and PFHxS in cord sera with progesterone	PFASs other than PFOS and PFOA may impact newborns' glucocorticoids and progestogens.	Liu et al. 2020 [12]
China	Water transportation pathway	56 freshwater and marine species	PFOA overall contribution: >90%, max. conc. 2161 ng/g ww. Trophic magnification factor freshwater species v. marine species: 1.10 vs. 1.28	PFAA levels were in edible tissues of 56 aquatic species in a habitat affected by a fluorochemical industry park, PFOA conc. differ depending on fish.	Wang et al. 2020 [13]
China (Shenyang)	Cross-sectional	1202 (22–96yrs)	Median PFAS bloods levels visual impairment vs. normal (ng/mL): Σ PFOS: 27.59 vs. 21.75, Σ PFOA: 5.79 vs. 6.28; vitreous disorder risk increase with long-chain PFASs exposure: PFTrDA (odds ratio (OR): 1.86, 95% Confidence Interval (CI):1.51, 2.9), PFDA (OR: 1.79, 95% CI:1.36, 2.36) had most significant assoc.	The study suggests an assoc. between higher serum PFASs levels and increased risk of visual impairment and vitreous disorder in Chinese adults.	Zeeshan et al. 2020 [15]
China	Cross-sectional	1612	Stronger assoc.: PFOA and serum uric acid for branched (br.) PFOA and different from other PFASs according to adult kidney function (strongest GF-3b/4 ($\beta=1.26$, 95% CI: 0.34, 2.18)).	Serum uric acid levels higher for each log-unit increase in br-PFOA, br-PFOS, and linear PFOS (n-PFOS) conc. assoc. between uric acid and PFAS inverted “U” shaped pattern across kidney function stages.	Zeng et al. 2019 [16]

Table 1: (continued)

Location	Study design/ Model	Sample	Result	Conclusions	References
Japan (Hokkaido)	Prospective birth cohort	1985 mother-infant pairs	Inverse assoc. with prenatal conc. per log unit R^2 coefficient: $\beta = -96.2$ g (95%CI, -165.3 to -27.1) PFNA and $\beta = -72.2$ g (95% CI, -138.1 to -6.3) PFDA with birthweight, $\beta = -0.48$ cm, 95% CI; -0.86 to -0.11) PFNA with birth length	Prenatal, maternal exposure to longer-chain PFAS inversely associated with newborn birth size, especially females.	Kashino et al. 2020 [17]
Taiwan	Case-control	120 breast cancer patients, 119 controls	Assoc. between PFOS and breast cancer risk in young Taiwanese women (≤ 50): Adjusted OR 2.34 (95% CI=1.02, 5.38) per natural log unit increase for PFOS; women ≤ 50 risk of higher es- trogen receptor positive tumors OR: PFHxS 1.82(95% CI=1.09, 53.03), PFOS 3.25(95% CI=1.29, 8.23)	PFAS was associated with breast cancer risk of estrogen receptor-positive tumors in Taiwanese women, particu- larly younger women (≤ 50)	Tsai et al. 2020 [18]

certified to use aqueous firefighting foam (AFFF). The study noted that much data is missing for determining PFAS contamination in US drinking water. This is due to misclassification of airport AFFF eligibility versus actual use and poor information about PFAS release from smaller industrial facilities that often label this data as confidential business information [41].

Although a 2019 study found that exposure to consumer products with PFAS resulted in different body burdens of PFAS between African American women and non-Hispanic white only women, residing in an area with PFAS-contaminated drinking water was associated with higher levels of PFAS body burden, even though that group ($n=6$) was small, showing that PFAS contaminated drinking water poses a major public health threat [40]. A study of El Paso, Colorado, a community with known PFAS-contaminated water from AFFF from a nearby military site, supports contaminated public drinking water systems as the dominant pathway for exposure to PFAS in humans [35].

Sweden

Many studies were conducted to examine the effects of PFAS contamination in Ronneby, Sweden. Since the mid-1980s, one third of households received drinking water contaminated with PFAS, likely from AFFF from a nearby military airfield [32]. These studies found that PFHxS has a

longer half-life compared to PFOA and PFOS and that drinking PFAS contaminated water resulted in higher serum concentrations and positive associations between PFAS exposure and serum lipids measuring cholesterol. There are potential associations between PFAS toxicity and downregulation of specific microRNAs, but they may have a high threshold of exposure. A study of residents of Ronneby also found evidence that linked raised risk of Crohn's disease for certain exposure periods [30–33]. Banzhaf et al. outlined 11 challenges to Sweden in addressing PFAS water contamination, which may impact drinking water for more than 3.6 million individuals. They identified a communication shortage among Swedish regulating authorities and researchers to establish clear guidelines for monitoring PFAS contamination [56].

Italy

Turning to Italy, a three-year monitoring campaign from 2010 to 2013 in northern Italy by Castiglioni, et al. indicated that there was widespread groundwater contamination by PFAA, but that drinking water treatments for Milan removed these contaminants and drinking water to consumers was far below proposed thresholds for PFAS [24]. In contrast, the highest levels of PFOA were detected in the River Po. The study identified wastewater treatment plants as a source of PFAS pollution, particularly when the plant received industrial waste [24].

Table 2: Europe PFAS studies.

<i>Location</i>	<i>Study Design/ Model</i>	<i>Sample Size</i>	<i>Results</i>	<i>Conclusions</i>	<i>References</i>
Denmark	Longitudinal prospective cohort	Childhood (n=590), during adolescence (n=444) (9–15 years), and into young adulthood (n=369) (15–21 years).	Correlation (Corr.) strongest in childhood and weakest in adulthood (corr. coefficients $r=0.31$ to $r=0.77$ ($p<0.01$) for exposure, from $r=0.59$ to $r=0.85$ ($p<0.01$) for adiposity); relatively large decrease in β -cell function in adolescence with higher levels of PFOA at 9 yrs.	Moderate to strong corr. between exposure to PFOS and PFOA during childhood with indicators of adiposity in adolescence and young adulthood. The study supports the notion childhood is particularly sensitive to endocrine disruption	Domazet et al. 2016 [19]
Denmark	Longitudinal population-based cohort	Two samples (n=722 and 445) of boys and girls from 11 years until full maturation	Start of puberty (e.g. pubic hair, menarche, etc.) girls (months): PFOS: -3.73 ; 95% confidence interval (CI): -6.59 , -0.87 ; PFHpS: -4.92 , 95% CI: -11.68 , 1.85 ; PFDA: -3.60 , 95% CI: -9.03 , 1.83 ; and boys: PFNA: 4.45 , 95% CI: -1.30 , 10.21 ; PFDA: 4.59 , 95% CI: -0.93 , 10.11	Study suggests sex-specific associations of prenatal exposure to PFASs and altered pubertal development.	Ernst et al. 2019 [20]
Faroe Islands	Benchmark dose	431 children from Faroese birth cohort	Serum-PFC conc. at age 5 and serum antibody conc. against tetanus and diphtheria toxoids at age 7 measured. Benchmark dose level for antibodies to vaccines was ~ 1.3 ng/mL serum for PFOS, 0.3 ng/mL for PFOA at a benchmark response of 5%	If no other sources contributed to PFOA exposure, water conc. were 1 ng/L or 0.001 $\mu\text{g/L}$, which suggests current limits for drinking water contamination are too lax and should be reassessed	Grandjean, P., and Budtz-Jørgensen, E., 2013 [21].
Faroe Islands	Longitudinal prospective	490 Faroese birth cohort: 275 at 18 m, 349 at 5yrs	Vulnerability to PFAS exposure from breastfeeding greatest in first 6 months (statistically significant decrease in tetanus antibody conc. by 19–29% at 5 years (y) for each doubling of PFAS exposure in early infancy). Prenatal exposures and serum levels in early infancy had inverse assoc. with antibody conc.	The findings support the notion that the developing adaptive immune system is particularly vulnerable to immunotoxicity during infancy, where vulnerability appears to be the greatest during the first 6 months after birth	Grandjean et al. 2017 [22]
Finland	Longitudinal human biomonitoring	54 children at 1, 6, and 10.5yrs	Significant decrease in median serum conc. with age. (1y, 6y) (ng/mL): PFOA (6.6, 2.7)>PFOS (5.5, 2.1)>PFNA (0.80, 0.54)>PFHxS (0.47, 0.42), by 10.5y PFOA and PFOS declined to 1.5 ng/mL; PFASs body burdens stayed same or increased with age, except for PFOA in female children; positive corr. between breastfeeding duration serum conc. of PFHxS, PFOS, PFOA, and PFNA at 1y	Body burdens better reflect differences in early-life to adolescence exposure as body burdens account for dilution compared to serum conc.	Koponen et al. 2020 [23]

Table 2: (continued)

<i>Location</i>	<i>Study Design/ Model</i>	<i>Sample Size</i>	<i>Results</i>	<i>Conclusions</i>	<i>References</i>
Italy	Water monitoring campaign	(n=84) samples from 6 wastewater treatment plants (WWTPs) in 2010, 2011, and 2013; (n=30) surface water (river); (n=32) raw groundwater from superficial aquifer in Milan 2010; (n=27) raw and treated groundwater from deeper (80–200 m) aquifer in Milan 2012–2013	Mean loads of WWTPs range: 3 to 6 µg/day per capita for PFOA, 1 to 8 µg/day per capita for PFOS; PFOA most abundant compound in WWTPs A and B mean (ng/L): 260, 790; Surface water: highest conc. PFAA: Bozzente (518 ng/L), Lura (889 ng/L), River Olona before crosses Milan: PFOA (59 ng/L), PFOS (30 ng/L); Groundwater: untreated range <LOQ–40 ng/L. Drinking water conc. medians in Lambro basin from North of Milan (industrialized), Milan, South of Milan (agricultural) (ng/L): PFCA short-chain 17, 7, <LOQ; PFOA 14, 7, <LOQ; PFCA long-chain: 5, <LOQ, <LOQ; ΣPFAA: 37, 13, <LOQ	The study confirmed PFAS are ubiquitous and found WWTPs receiving industrial wastes discharged up to 50x loads of WWTPs receiving municipal waste. It found PFAAs are generally not removed by WWTPs, affecting surface water and groundwater. Milan's drinking water treatments removed PFAA effectively. Drinking water conc. were below accepted limits. Thus, there is no risk for consumers from short term exposure.	Castiglioni, et al. 2015 [24]
Italy (Veneto Region)	Human biomonitoring	507 residents (257 in municipalities impacted by contamination); for genotyping: n=217 for exposed group (E) and n=241 for not exposed (NE) group	PFOA serum levels of PFAS-contaminated water E vs. NE median (ng/g): PFOA 13.77 vs. 1.64; PFOA median conc. in E: males 26.07 ng/g >female 7.88 ng/g, in NE male 2.04 >female 1.27; tap drinking water consumption inversely correlated with serum conc. in E and NE; in region most impacted only 41% declared drinking tap water vs. 72% in NE area.	The researchers found significantly higher PFAS conc. for 9 of the 12 substances analyzed for exposed subjects compared to nonexposed subjects. The study confirmed that water contamination resulted in higher PFAS exposure of the residents of PFAS-contaminated water areas in the Veneto region over time.	Ingelido et al. 2018 [25]
Italy (Veneto Region)	Human biomonitoring	629 subjects: 257 exposed; 250 in areas of presumed background exposure, 122 farmers in contaminated rural areas, sample between July 2015–Jan 2017	Farmers living in Veneto region (PFAS contamination from industrial plant): The median PFOA conc. 40 ng/g. Main factors influencing PFAS serum levels of farmers were residence area, the related extent of drinking water contamination, gender, and years of residence in municipalities, well water consumption, and consumption of self-grown food.	Highest PFAS serum conc. found in farmers. PFAS serum conc. in farmers residing in the Veneto region of Italy are among the world's highest levels.	Ingelido et al. 2020 [26]
Italy (Veneto region)	Ecological mortality	Data sets	Rate Ratios (RR) (male, female): both sexes: statistically significant higher RR for all causes mortality (1.19, 1.21), diabetes (1.21, 1.48), cerebrovascular diseases (1.34, 1.29), myocardial infarction (1.22, 1.24), and Alzheimer's	Higher mortality levels of deaths for some causes of death, potentially assoc. with PFAS exposure, were found in contaminated municipalities compared with uncontaminated ones with similar socioeconomic	Mastrantonio et al. 2017 [27].

Table 2: (continued)

Location	Study Design/ Model	Sample Size	Results	Conclusions	References
			disease (1.33, 1.35); females RR: significantly higher than 1.0 kidney (1.32), breast cancer (1.11), Parkinson's disease (1.35); males, increased risk, which was not statistically significant, was detected for testicular and pancreatic cancer as well as Parkinson's disease.	status and smoking habits. Individual-level analytic studies to delineate causal assoc. are needed.	
Italy (Veneto Region)	Cross-sectional	18,345 participants born between 1978 and 2002, 14–39 years of age at recruitment	Highest PFAS serum conc. (ng/mL): PFOA [median: 44.4, IQR: 19.3–84.9], PFHxS [median: 3.9, IQR: 1.9–7.4], PFOS [median: 3.9, IQR: 2.6–5.8]; Serum conc. of PFOA, PFOS, and PFHxS were lower in females than in males; PFOA conc. decreased until 35–39 years, and raised again to match the youngest 14–19 age group levels. PFOS and PFHxS bioaccumulation with age. PFOS had a negative assoc. with obesity, and positive assoc. with PFHxS. Gender, residence area, and duration of residency were the main predictors of serum levels.	Serum PFAS levels were higher in populations living in Veneto, where the groundwater was contaminated with PFAS from a PFAS manufacturing plant than people with background PFAS exposure.	Pitter et al. 2020 [28]
Norway (Oslo)	Cross-sectional and longitudinal	378 participants with PFAS measurements at 10 years (cross-sectional) and 16 years (longitudinal) of the Environment and Child Asthma Study (Oslo)	Atopic dermatitis: (inverse assoc. in girls 10 to 16 with PFNA risk estimates of a similar magnitude (RR) range [95% CI] 0.51 [0.35;0.73] per IQR of 0.28 ng/mL and PFUnDA 0.45[0.29;0.69] per IQR of 0.12 ng/mL after Bonferroni adjustment); lower respiratory tract infection (positive assoc. with PFHpA, PFOA, PFHpS, PFOS RR range: 1.1–1.3)	The results support the immunosuppressive effect of PFASs on atopic dermatitis and lower respiratory tract infection. Gender seems relevant to some assoc. There was no clear pattern exposure-health assoc. for exposure period, except for asthma.	Kvalem et al. 2020 [29]
Sweden (Ronneby)	Human biomonitoring	n=106, collected 7 rounds of blood samples over 3 years, of participants between age 4–84 years, 53% female.	Average rates of decrease in serum were PFHxS, 13% per year; PFOS, 20% per year; and PFOA, 26% per year. The mean estimated half-life was 5.3 years (95%CI 4.6 to 6.0) for PFHxS, 3.4 years (95%CI 3.1 to 3.7) for PFOS, and 2.7 years (95%CI 2.5 to 2.9) for PFOA.	The estimated half-life for PFHxS was longer. For PFHxS and PFOS, more rapid elimination was seen in women versus men.	Li et al. 2018 [30]
Sweden (Ronneby)	Human biomonitoring	n=1945, aged 20–60 years, where 1160 participants were recently exposed,	PFOS (median 157 ng/mL), PFHxS (median 136 ng/mL) and PFOA (median 8.6 ng/mL) serum levels observed,	High serum levels due to exposure to various PFAS in drinking water were detected. The study provides	Li et al. 2020 [31]

Table 2: (continued)

Location	Study Design/ Model	Sample Size	Results	Conclusions	References
Sweden (Ronneby, Karlshamn)	Human biomonitoring	living in the region between 2005 and 2013. 293 non-smoking women (aged 20–45 years) with known AFFF (PFOS and PFHxS) PFAS contam- inated water with (n=250) of control group	between 5 and 100 times higher than in the control group. Consistent assoc.: miR-101-3p, miR-144-3p and miR-19a-3p all downregulated with increasing PFAS exposure; threshold exposure for miRNA effects may be high (113– 315 ng/mL PFOS; 93–366 ng/ mL PFHxS; 2–12 ng/mL PFOA).	evidence of causal associ- ation between PFAS expo- sure and serum lipids. PFAs toxicity was associated with modulation of miRNAs in humans. This modula- tion is apparent in the downregulation of specific miRNAs.	Xu et al. 2020 [32]
Sweden (Ronneby)	Registry and biomarker	Registry: residents of Ronneby at least 1 year between 1980 and 2013 (n = 63074; 33218 men and 29856 women). Biomarker: 189 par- ticipants from Ron- neby and Karlshamn (control).	Registry study: Early period exposure only (1985–1994) showed raised hazard ratios (HRs) for Crohn's disease (HR=1.58, p=0.048), other non-specified irritable bowel disease (IBD) (HR=1.38, p=0.037), but no raised HRs for diagnosed IBD for subjects with 1995–2004, 2005–2013 exposure compared to never exposure; Biomarker study: Karlshamn showed higher fecal calprotectin levels (me- dian=99.6 mg/kg vs. 66.8 mg/kg in Ronneby, p=0.04). A trend of decreased calprotectin with increased serum PFAS indicated higher PFAS assoc. with lower degree of gut inflammation (p=0.002).	The study found no consis- tent evidence to support PFAS exposure as a risk factor for irritable bowel disease.	Xu et al. 2020 [33]

Mastrantonio et al. conducted an ecological mortality study in the Veneto Region of Italy to assess the differences among general populations residing in areas with PFAS contaminated groundwater versus unaffected areas [27]. Areal selection criteria were based on monitoring reports and campaign results for PFOS, PFOA, and other PFAS conducted between 2013 and 2015 by environmental, public health, and government agencies in the region. Overall, 24 contaminated and 56 uncontaminated municipalities were represented in the study. Specifically, the research team delineated the following four factors that could influence mortality rates: smoking habits, socio-economic status, sex, and age. Using epidemiological data from the National Agency for New Technologies, Energy and Environment (ENEA), three calculations were applied in the study areas for each cause of death recorded between

1980–2002 and 2003–2013: standardized mortality rates, sex-specific number, and rate ratios (RR) [27].

The researchers found that elevated mortality rates for some causes of death, potentially associated with PFAS exposure, occurred in contaminated municipalities in contrast with uncontaminated ones with similar socio-economic status and smoking habits. In contaminated municipalities, statistically significant rate ratios for both males and females were found for the following conditions: general mortality (1.19 in males; 1.21 in females), diabetes (1.21 in males; 1.48 in females), cerebrovascular diseases (1.34 in males; 1.29 in females), Alzheimer's disease (1.33 in males; 1.35 in females), and myocardial infarction (1.22 in males; 1.24 in females). Although RR values were greater than 1 for bladder cancer and leukemia for both sexes, they were not deemed statistically significant. For females, RR values were

Table 3: North America.

Location	Study Design/ Analysis	Sample Size	Results	Conclusions	References
Canada	Longitudinal cohort	1739 pregnant Canadian women from Maternal-Infant Research on Environmental Chemicals (MIREC) study	Median PFHxS conc. 50% higher among preeclampsia vs. normal blood pressure; assoc.: each doubling of PFHxS conc. with higher odds ratio (OR=1.32, 95% CI: 1.03, 1.70) of developing preeclampsia; no assoc.: PFOA or PFOS with either gestational hypertension or preeclampsia.	Fetal sex might modify assoc. Higher levels of PFHxS were assoc. with preeclampsia, stronger among women carrying female fetuses.	Borghese et al. 2020 [34]
USA (Colorado)	Human biomonitoring	213 non-smoking, non-pregnant adults (19–93) from 3 water districts resident for at least 2 years during known PFAS contamination from aqueous film-forming foams (AFFF)	90th percentile PFHxS PFAS conc. of participants 49.7 ng/mL; median conc. of PFAS study participants vs. 2015–2016 National Health and Nutrition Examination Survey (NHANES) (ng/mL): PFHxS: 14.8 vs. 1.2; PFOS 9.7 vs. 4.8; PFOA 3.0 vs. 1.57; PFHxS, PFOS, PFOA, and PFNA in 99.5% of samples, PFHpS in 82.6%; PFOS Geometric Mean (GM) (ng/mL): females 8.4<males 11.7; PFAS conc. GM (ng/mL): drinking mostly or only tap water (18.9) >half tap/half bottled water (12.4)>only or mostly bottled water (10.8).	Participants' dominant PFAS exposure route was probably the consumption of PFAS-contaminated water. Factors predicting PFAS conc. in serum were home water district, frequency of bottled water use, age, sex, and smoking history. Other factors: race/ethnicity, firefighter, and military service (e.g., non-Hispanic white participants have higher PFAS levels). All conc. showed a significant positive corr. with age.	Barton et al. 2020 [35]
USA	Water monitoring	50 samples from 25 drinking water treatment plants representing 24 states in the USA	Sum of 17 PFASs in the water range: <1 ng/L to 1102 ng/L; median total PFAS conc.: source water=21.4 ng/L; treated drinking water 19.5 n/gL.	PFAS were detected in all samples. Only 5 locations showed a statistically significant difference in total PFAS before treatment (source) and after treatment. Only water at 1 drinking water treatment plant exceeded the US EPA drinking water health advisory (70 ng/L PFOA, PFOS, combined)	Boone et al. 2019 [36]
USA	Human biomonitoring multigenerational cohort	178 middle-aged women enrolled in Child Health and Development Studies with blood samples and interviews	Life style and PFAS assoc.: flossing with Oral-B Glide (24.9% (95% CI: 0.2–55.7) higher levels of PFHxS); having stain-resistant carpet or furniture (PFNA (18.7%, 95% CI: 0.5–40.2); and PFDeA (39.6%, 95%CI: 5.9–84.2) for non-Hispanic whites only), living in city served by a PFAS-contaminated water supply (PFOA 100.3% (95% CI: 18.2–239.5), PFNA 83.6% (95% CI: 16.6–189.2), PFHxS 103.5% (95% CI: 10.3–275.2).	African American women were associated with 52.6% (95% CI: 34.4–65.8 ng/mL) lower levels of PFOA than non-Hispanic white women. The frequency of eating food prepared coated containers as associated with higher levels of 4 PFASs in African Americans.	Boronow et al. 2019 [37]

Table 3: (continued)

Location	Study Design/ Analysis	Sample Size	Results	Conclusions	References
USA (Cincinnati)	Prospective birth cohort	204 children 8 years; 316 children between 2 and 8; 468 pregnant women initially from HOME study	Assoc. between women in top two PFOA terciles than in the 1st tercile and adiposity in children at 8 years by tercile: waist circumference (cm) among children in 2nd (4.3; 95% CI: 1.7, 6.9), and 3rd (2.2; 95% CI: -0.5, 4.9) compared to 1st; HOME study median PFOA conc. vs. NHANES 2003–2004 and 2005–2006 cycles (ng/mL): 5.3 vs. 2.3; risk of being overweight if born to woman in 2nd and 3rd terciles of PFOA conc.: 84%.	Higher prenatal serum PFOA conc. was associated with greater adiposity at 8 years and a more rapid increase in body mass index (BMI) between 2 and 8 years compared to first tercile. PFOS, PFNA, and PFHxS were not associated with adiposity.	Braun et al. 2016 [38]
USA (Alaska)	Cross-sectional	85 participants from St. Lawrence Island, Alaska (Yupik)	Study participants vs. NHANES median conc. (ng/mL): PFNA [men: 2.74, women: 2.13 vs. men: 1.4, women: 1.0], PFUnDA [median men: 0.74, women 0.72 vs. both: 0.14]; overall PFAS in study participants (median, max values (ng/mL) PFOS: 4.5, 16.0; PFNA: 2.2, 12.1; PFOA: 1, 2.9).	Elevated levels of PFAS among participants compared to the U.S. general population are likely due to exposure to traditional foods (e.g., fish). Sentinel fish species contained both PFASs and PBDEs, which suggests atmospheric deposition, bio-accumulation, and local environmental contamination.	Byrne et al. 2017 [39]
USA	Longitudinal human biomonitoring	75 White, Black, and Chinese women (age 45–56 in 1999–2000) in Study of Women's Health Across the Nation (SWAN) cohort, sampled 1999–2000, 2002–2003, 2005–2006, 2009–2011	1999–2011 trends: longitudinal reduction median conc.: n-PFOA (3.30 to 2.60 ng/mL, $p=0.001$), n-PFOS (17.00 to 7.5 ng/mL, $p<0.0001$), sm-PFOS (6.20 ng/mL to 2.50 ng/mL, $p<0.0001$), PFHxS (1.50 to 1.20 ng/mL; $p=0.05$); PFNA increasing: 0.50 to 1.30 ng/mL; Trends by race/ethnicity by p for interaction: n-PFOA (0.001), n-PFOS (0.0007), temporal trends of sm-PFOS and PFHxS (0.03 and 0.008 respectively). Parous to nulliparous decrease in conc.: n-PFOA: -40.5% (95% CI: -58.5%, -14.6%), n-PFOS: -47.7% (95% CI: -65.6%, -20.7%); sm-PFOS: -45.5% (95% CI: -64.0%, -17.4%).	The results suggest a longitudinal reduction of legacy PFAS and increases of new PFASs from 1999 to 2011 in midlife women. Temporal trends in PFAS conc. in women are not uniform across race/ethnicity and parity groups. Chinese women had consistently higher PFNA conc. than other groups ($p = 0.03$ at baseline for race/ethnicity).	Ding, et al. 2020 [40]
USA	Spatial analysis	2013–2015 national drinking water PFAS conc. from the US EPA's third Unregulated Contaminant	Assoc. of % increase of PFAS with each additional military site within a watershed's eight-digit hydrologic unit: 20% PFHxS, 10% PFHpA, 10% PFOA, 35% PFOS; with each additional major	Predictors of PFAS detection frequencies and conc. in public water supplies include the no. of industrial sites that manufacture or use PFAS	Hu, et al. 2016 [41]

Table 3: (continued)

Location	Study Design/ Analysis	Sample Size	Results	Conclusions	References
		Monitoring Rule (UCMR3) program	industrial site: 24% PFHxS, 10% PFHpA, 81% PFOA, 46% PFOS	compounds, no. of military fire training areas, and no. of wastewater treatment plants. Drinking water supplies for 6 million US residents exceed the US EPA's lifetime health advisory of 70 ng/L for PFOS and PFOA.	
USA	Estimate relative source contribution (RSC) to PFAS exposure	225 women living in 22 states (Nurses' Health Study) for home tap water PFAS; 110 women for plasma samples	Modeled median contributions of tap water to plasma conc.: PFOA 12% (95% probability interval 11–14%), PFNA 13% (8.7–21%), nPFOS 2.2% (2.0–2.5%), brPFOS 3.0% (2.5–3.2%), PFHxS 34% (29–39%).	Tap water collected from 5 locations in 2013–2016 compared to samples from 1989 to 1990 showed increase in PFAS. The 1989 to 1990 results compare well with the default 20% RSC used in other risk assessments for legacy PFAS by several agencies to measure drinking water to human PFAS exposures.	Hu et al. 2019 [42]
USA (Atlanta)	Cross-sectional	74 children with physician-diagnosed nonalcoholic fatty liver disease (NAFLD) between 7 and 19 years old, mostly boys (71%), Hispanic (51%), and obese (85%)	Median conc. (IQRs) of plasma (ng/mL): PFOA 3.42 (1.65), PFOS 3.59 (4.46), PFHxS 1.53 (3.17); odds ratio (OR) per interquartile range (IQR) plasma of conc. of PFAS for NASH assoc. with each IQR increase of plasma conc. OR (95% CI): PFOS OR: 3.32 (1.40–7.87), PFHxS OR: 4.18 (1.64–10.7), PFAS composite variable OR: 4.89 (1.86–12.8); adjusted OR of having lobular inflammation compared to children w/o lobular inflammation per IQR increase: PFHxS: 2.87 (95% CI: 1.12–7.31), PFAS composite variable: 3.44 (95% CI: 1.11–10.7); OR of mild portal inflammation per IQR increase: PFHxS 2.87 (95% CI: 1.27–5.67), PFAS composite variable 2.71 (95% CI: 1.18–6.25)	The risk of nonalcoholic steatohepatitis (compared to children with steatosis only) was significantly increased with each IQR increase of PFOS and PFHxS. Each IQR increase of PFHxS was assoc. with increased odds for liver fibrosis, lobular inflammation, and higher nonalcoholic fatty liver disease activity score. Higher PFAS exposure was assoc. with more severe disease in children with nonalcoholic fatty liver disease.	Jin et al. 2020 [43]
USA (NHANES)	Cross-sectional	6967 adults (≥ 20 years old) from 2003 to 2012 NHANES	Compared with the lowest tertile, OR (95% CI) of hypertension for the highest tertile: PFOA 1.32 (1.13, 1.54), PFOS 1.14 (0.97, 1.34), PFHxS 1.16 (0.99, 1.36), and PFNA 1.18 (1.01, 1.37)	These cross-sectional data showed a J-shape assoc. between hypertension and PFOA and PFNA	Liao, et al. 2020 [44]
USA (Boston)	Longitudinal prebirth cohort	726 mothers and 465 neonates from Project Viva (a Boston,	Positive assoc. with n-PFOS with T_4 levels ($\Delta 25$ th to 75th percentile: 0.21 $\mu\text{g/dL}$; 95% credible interval: -0.03 , 0.47); assoc. with	Study provides evidence that combined effects of prenatal exposure to multiple PFAS may affect	Preston, et al. 2020 [45]

Table 3: (continued)

Location	Study Design/ Analysis	Sample Size	Results	Conclusions	References
		Massachusetts area longitudinal pre-birth cohort)	higher conc. of PFAS mixture: significantly lower maternal Free T ₄ Index, infants: lower T ₄ levels, primarily in males, with PFHxS and MeFOSAA contributing most to weighted quantile sum (WQS) and PFHxS to Bayesian kernel machine regression (BKMR)	maternal and neonatal thyroid function, but outcomes may differ across individual PFAS	
USA (Cincinnati)	Human biomonitoring	336 who completed follow-up surveys about breastfeeding practices and had complete co-variate data	Compared to women in the 1st quartile: women in the 4th quartile of PFOA serum conc. had 1.77x the risk of ending any breastfeeding by 3 months; 1.41x the risk of ending any breastfeeding by 6 months; women in the 4th quartile of PFOS serum conc. had 1.32x the risk of ending any breastfeeding by 3 months.	Maternal serum PFOA conc. were inversely related to breastfeeding duration in the cohort, even after controlling for a previous history of breastfeeding	Romano et al. 2017 [46]
USA (Boston)	Human biomonitoring	1645 women during early pregnancy (median 9.7 weeks gestation) in the Boston-area Project Viva cohort, recruited during 1999–2002	Assoc. lower glomerular filtration rates (GFR) with 3–4% higher PFAS conc., higher albumin with 4–6% higher PFAS conc.; PFASs detected in 99–100% of samples except for PFDeA and PFOSA	Higher early pregnancy PFAS conc. was assoc. with younger age (except PFNA), less educational attainment, nulliparity, no history of breastfeeding, and higher pre-pregnancy BMI in adjusted models. Assoc. with GFR and albumin, strongly related to PFAS.	Sagiv et al. 2015 [47]
USA (New York)	Longitudinal cohort study	302 pregnant women in the Columbia University WTC birth cohort between Dec. 13, 2001 and June 26, 2002; complete case sensitivity analyses: 1y (n=156), 2y (n=157), 3y (n=127), 4y (n=124), 6y (n=110)	GM range conc. of PFAS (cord blood plus maternal-to-cord transformed) (ng/mL): PFOS: 6.03 (1.05, 33.7), PFOA: 2.31(0.18, 8.14), PFNA: 0.43 (<LOQ, 10.3), PFHxS: 0.67 (<LOQ, 15.8); adjusted analysis at 2 years trend of stronger positive assoc. between PFOS and Mental Development Index (MDI) for females compared to males (p interaction=0.04); at 3 years assoc. between PFAS principal component (PC2) and lower psychometric development index (PDI) scores in both adjusted and unadjusted models	These results indicate that several PFAS were associated with increases in cognitive outcomes in females and overall (males and females combined), with some positive assoc. among females but not males. The results suggest a sex- and compound-specific relationship between childhood neurodevelopment and prenatal exposures to PFAS.	Spratlen et al. 2020 [48]
USA (NHANES)	Cross-sectional	n=1191 (12–19 yrs) for measles, mumps, rubella antibody conc. in NHANES 1999–2000 and 2003–2004; n=640 (12–19 yrs) for allergic	Adjusted survey-weighted model: doubling of PFOS conc. among seropositive children assoc. with decrease in antibody conc.: rubella: 13.3% (95% CI: –19.9, –6.2); mumps: 5.9% (95% CI: –9.9, –1.6); higher PFOS less likely to be sensitized	No adverse assoc. was found between PFAS exposure and allergic conditions, including asthma. Increased exposure to several PFAS was associated with lower levels of antibody conc. to	Stein et al. 2016 [49]

Table 3: (continued)

Location	Study Design/ Analysis	Sample Size	Results	Conclusions	References
		conditions and allergic sensitization in NHANES 2005–2006	to any allergen: OR: 0.74 (95%CI: 0.58, 0.95).	mumps and rubella, particularly among sero-positive individuals, which may indicate a less robust response to vaccination or greater waning of vaccine-derived immunity over time.	
USA	Human biomonitoring	n=639, 3–11 year old participants in NHANES 2013–2014 (nationally representative subsample)	GM (95% CI) conc. (in ng/mL): Σ PFOS 3.88 (3.53–4.27), Σ PFOA 1.92 (1.75–2.12); most frequently detected PFAS: n-PFOS 2.51 (2.30–2.74), n-PFOA 1.81 (1.64–2.01), Sm-PFOS 1.23 (1.09–1.40), PFHxS 0.843 (0.756–0.939), and PFNA 0.794 (0.681–0.926).	PFOS, PFOA, PFHxS, and PFNA were detected in all children at conc. levels similar to NHANES 2013–2014 adolescents and adults, even though these children were born after the phase of PFOS in the US in 2002. PFOA conc. were highest among the C8 study participants (chemical plant and known PFAS contaminated drinking water system). Study suggests Hispanics had lower conc. of PFOA and PFOS.	Ye, et al. 2018 [50]

significantly greater than 1 for Parkinson's disease (1.35), kidney cancer (1.32), and breast cancer (1.11). For males, no statistically significant risk was found for pancreatic cancer, testicular cancer, and Parkinson's disease [27].

Moreover, no increased risks were found for several serious diseases, such as liver cancer, non-Hodgkin's lymphoma, and prostate cancer. However, the researchers did observe a significantly lower risk of liver cancer when males and females were considered together. Lastly, myocardial infarction risks were 13–45% higher in communities living near a PFOA chemical plant. The research team concluded that the results “warrant further individual level analytic studies to delineate causal associations” [27].

After alarming levels of PFASs were found in the Veneto Region's drinking water in 2013, Italy's National Health Institute (ISS) decreed the following industry performance limits in 2014: PFOS: ≤ 30 ng/L; PFOA: ≤ 500 ng/L; other PFAS: ≤ 500 ng/L [25]. Following this precaution, Ingelido and her team at ISS compared exposed and non-exposed groups from the general population residing in the Veneto region in an area near a plant that produced PFAS for decades and where drinking water contamination with PFAS was discovered. The human biomonitoring study was

conducted by measuring PFAS concentrations, particularly PFOA, in human sera by taking blood samples from residents in the region and comparing those to concentrations in neighboring populations at background PFAS exposure. In addition, the population was genotyped for the OATP1A2*3 allelic variant. The PFAS concentrations measured in human sera were correlated with drinking water consumption by aqueduct and private well. Other variables from a questionnaire on lifestyle habits were also considered. Ingelido et al. found that the difference in PFAS concentrations between exposed and not exposed groups was significantly higher for 9 of the 12 PFAS substances analyzed [25]. This finding confirmed water contamination had resulted in a high PFAS exposure of the residents over time. Ingelido et al. found that the main factors influencing PFAS serum levels was residence in the area and the related extent of drinking water contamination [25]. Other factors that played a role included sex (male PFAS levels higher than female PFAS levels), water consumption (higher consumption of tap water correlated with higher levels of serum PFAS concentrations), years of residence (in areas with contaminated water), and raising own livestock. The study found no relationship between the genetic trait for

Table 4: Various other studies.

<i>Location</i>	<i>Study Design/ Model</i>	<i>Sample Size</i>	<i>Results</i>	<i>Conclusions</i>	<i>References</i>
Brazil (BRISA)	Nested case-control	252 pregnant women (birth outcomes cases (n=63), matched controls (n=189))	Median whole blood conc. of PFAS (ng/mL) (range): PFOS 3.41 (1.06–106); PFOA: 0.20 (0.11–2.77)	The study was the first to assess whole blood conc. of PFASs and their effect on fetal growth in pregnant Brazilian women. They found a significant positive assoc. between PFOS and PFOA and fetal growth restriction.	Souza et al. 2020 [51]
Faroe Islands, Denmark	Longitudinal birth cohort	559 Faroese children	Significant assoc. with doubling serum PFAS conc. at age 5 MMR unvaccinated: PFOA or PFNA with 10-fold increased odds of asthma at age 5 and 13, PFDA with asthma at age 5; assoc. was reversed among MMR-vaccinated children; no assoc. with pre-natal PFAS exposure	Although PFAS exposure may affect immune system functions, this study suggests that MMR vaccination might be a potential effect-modifier.	Timmermann, et al. 2017 [52]
Ethiopia (Lake Tana)	Water monitoring	7 sampling sites around Lake Tana	∑PFAS conc. range: 0.073 to 5.6 ng/L (on average, 2.9 ng/L) in surface water, 0.22 to 0.55 ng/g dry weight (dw) (on average, 0.30 ng/g dw) in surface sediment, and non-detected to 5.8 ng/g wet weight (ww) (on average, 1.2 ng/g ww) in all fish species	The levels of PFOS in fish will not likely cause any harmful effects for the observed Ethiopian fish-eating population.	Ahrens et al. 2016 [53]
Various countries: Burkina Faso, Canada, Chile, Ivory Coast, France, Japan, Mexico, Norway, USA	Water monitoring	97 drinking water samples (n=38 bottled; 59 tap) in 2015–2016	PFAS in bottled water: PFOA range 3 ng/L Ivory Coast to <LOQ Canada, max ∑ ₂₉ PFAS 6.3 ng/L; Tap water mean conc.: Canada Great Lakes/St. Lawrence vs. Rest of Canada (ng/L): PFOS 3.4 vs. 0.4, PFOA 1.8 vs. 0.7, PFSA and PFCAs range tap water: <LOD to 3.9 in China, Japan, USA, Ivory Coast, Burkina Faso; Highest ∑ ₂₉ PFAS conc. tap water (ng/L): Burkina Faso 44	A risk assessment approach based on regulatory limits suggested that conc. of PFOA and PFOS analyzed for this study did not pose a health risk for drinking water consumers.	Kabore et al. 2018 [54]

renal transport (OATP1A2*3) and PFAS levels. Age did not seem to strongly impact levels of PFASs [25].

In a follow-up biomonitoring study, Ingelido et al. compared a subgroup of 122 farmers living in rural areas in the Veneto region, where public drinking water contamination was discovered in 2013–2017. The farmers produced and consumed their own livestock and vegetables. They frequently used well water. Ingelido et al. compared these farmers exposed to PFAS drinking water contamination and people not exposed to drinking water contamination in

the Veneto region [26]. Ingelido et al. compared PFAS levels in human sera; divided the area into subareas depending on proximity to PFAS groundwater plumes; segmented the population based on gender, age, and whether the farmers grew and raised their own food; performed a genetic analysis of an allele, and considered information from a questionnaire. Ingelido et al. found that the highest levels of PFAS were in exposed farmers in the rural contaminated areas. They concluded that the main factors influencing PFAS levels in farmers were “residence area and the related

extent of drinking water contamination, gender, years of residence in the municipalities, well water consumption and consumption of own produced food” [26].

Ingelido et al. found higher concentrations of PFAS in males than females for PFOA, PFHxS (5 times as much) and PFOS (3 times as much) when comparing median levels [26]. When comparing exposed farmers for PFOA, that subgroup had three times as much PFOA in human sera compared to exposed groups in the region and 25 times as much to the non-exposed group. Their research seemed to support that individuals consuming their own livestock were linked to higher PFAS levels in human sera. A limit of the study was a self-reported data questionnaire for amounts of food eaten. Nonetheless, they also concluded that the primary source of PFAS exposure to people in the Veneto region was consuming contaminated public drinking water. As an example of the main factors that influenced PFAS levels in humans, the researchers mentioned that the highest concentration of PFOA was found in a 44 year old man who lived in a contaminated area (ULSS 5) who drank contaminated tap water and grew his own fruits, vegetables, and animals raised with contaminated water [26].

China

In China, Yan et al. found a strong link for PFASs between groundwater near landfills and tap water supplies [14]. Moreover, PFASs were found to be almost ubiquitous in drinking water across China, with levels ranging from 4.49 to 179.93 ng/L. Other sources contributed to these values, including proximity to fluorochemical manufacture sites and water sources in or near metropolitan areas [14].

Duan et al. investigated the general distribution of PFASs, including ultrashort and short-chain PFASs, in Tianjin, China, finding that PFOS alternatives were widely distributed (> 90% of samples). Long-chain and ultrashort PFCAs (Σ PFCAsC2–C3), accounted for 70 and 28.4% of PFCAs respectively in the human body burden as measured in human sera. They reported a significant positive association between serum PFAS concentrations and HbA1c, a glycemic biomarker, in people 55 years or older [9]. Several studies found adverse impacts on prenatal, neonatal, and natal health outcomes and PFAS exposure, including replacement PFASs [8, 12, 17]. Huo et al. did not find a significant and consistent pattern of association with PFAS exposure and gestational hypertension, preeclampsia, or hypertensive disorders of pregnancy [10]. Associations between PFAS body burden and visual impairment diseases in China and increased risk of breast cancer, particularly among younger Taiwanese women were also found [15, 18].

Faroe Islands, Norway, Finland, Denmark

The studies covered in this review conducted in Norway and the Faroe Islands lent support to evidence that PFAS may have immunosuppressive effects [21, 22, 29]. Studies conducted in Denmark found associations between PFAS exposure during childhood two outcomes: adiposity in adolescence and young adulthood, and effects on puberty onset [19, 20]. A study from Finland noted that body burdens are a better indicator of PFAS than serum concentration in children as it accounts for dilution, noting an increasing temporal trend in PFHxS and PFNA during early childhood [23].

Various countries, Africa, Central America, South America

Some studies tested bottled and tap water samples from around the world for PFASs, which helped to allow comparisons. Overall, bottled water bought at markets around the world had lower levels of PFASs compared to tap water [54]. PFAS concentrations in tap water in Burkina Faso and the Ivory Coast were also found to be comparable to PFAS concentrations in Canada [54, 57]. A critical review of environmental levels and human body burdens noted that the two studies of drinking water in Africa encompass three countries and indicate a broader problem in Africa of potential PFAS contamination in tap water from nearby industries and wastewater treatment plants [57]. By contrast, Ahrens et al. concluded that the levels of PFOS in fish from Tana Lake, Ethiopia did not present a risk to the fish-eating population [53].

There are few studies of PFAS contamination from Central and South America. However, a recent study assessing whole blood in Brazilian pregnant women found a significant positive association between PFOS and PFOA and fetal growth restriction [51]. A study from Denmark and Faroe Islands found evidence suggesting links between PFAS levels and increased odds of asthma in children at ages 5 and 13 [52].

Water exposure other than drinking water

Recreational exposure to PFAS

The Environmental Work Group (EWG) and the Social Science Environmental Health Institute of Northeastern

University estimate that 19 million Americans are affected by contaminated drinking water [58]. However, concerns have arisen about additional pathways, including recreational and dietary exposure. Concerns over exposure to emerging contaminants have been well documented and publicized from recent accounts of ground and municipal drinking water contamination [58]. However, the evidence does not support a severe risk of dermal exposure to PFASs from swimming or other recreational water-related activities, beyond the risk posed from accidental ingestion of contaminated water or foam. This contrasts with the dangers associated with dermal and inhalation exposure seen in occupations such as carpet installation, firefighting, and other sources. As a result, the presence of PFASs in both the natural and industrialized food chain adds a significant risk to the overall exposure of PFASs to affected residents, including exposure from mother to child through breast milk [59].

Dietary & food source exposure to PFAS

Fishing may be one pathway of PFAS exposure. Different rates of elimination between humans and fish will require new methods of assessing evaluations of weight-of-evidence to comprehend bioaccumulation mechanisms across different hierarchical levels in ecological pyramids for PFASs. To add to this, the accumulation of PFAS in the environment will lead to increased external exposures [3].

Studies show that low-income households consumed more self-caught fish than those with higher income and education [60]. The results of a US survey indicated that recreational or self-caught fish consumption rates vary regionally and are not well understood, making it difficult to support national-scale assessments. Low-income respondents were more likely to harvest fish as a food staple and reported the highest consumption rates. In contrast, the higher income and education respondents reported higher incidences of self-caught fish but overall lower consumption rates. There were also regional differences. Respondents from the East-South Central and New England regions reported the lowest consumption rates from self-caught fish (12 to 16 g/day). By contrast, Mountain, Pacific, and Mid-Atlantic reported the highest consumption rates from 44 to 59 g/day. Respondent-specific consumption rates and national-level data on fish tissue concentrations of PCBs, MeHg, and PFOS suggest that 10–58% of respondents reporting self-caught fish consumption are exposed to concentrations of PFOS at levels that exceed threshold levels for health effects, estimated to represent 2.3 to 19 million people [60].

Fish consumption may also differ across cultural cuisines with differing levels of exposure to PFASs. PFASs are found in freshwater arctic wildlife, which are traditional food sources for indigenous peoples of the region [39]. In addition, a recent longitudinal study of PFAS body burden in US midlife women investigating differences on the basis of race/ethnicity, parity (parous/nulliparous), and menstrual status noted that Chinese women had higher levels of PFNA as a baseline and temporally [40]. This may relate to diet (fish consumption).

Health effects on humans

Short-chain PFASs

According to Brendel et al. studies have linked long-chain PFASs to either toxic for reproduction or persistent, toxic, and bio accumulative properties or both [61]. Long-chain PFASs are subject to regulation under REACH (EC No. 1907/2006). By contrast, short-chain PFASs do not fall within the regulatory ambit of REACH. As a result, short-chain PFASs are widely used as an alternative to long-chain PFASs. This is in part because short-chain PFASs are not regulated as persistent organic pollutants (POP) under measures such as the Stockholm Convention or the European Chemicals Regulation (REACH EC No. 1907/2006) [61].

Short-chain PFASs are persistent to the same extent as long-chain PFAAs and widely distributed in the environment. There is not a lot of information about short-chain PFASs as they are not regulated. Compared to long-chain PFAAs, short-chain PFAAs have a greater potential for long-range mobility. Brendel et al. concluded that drinking water resources were extremely sensitive to short-chain PFAAs contamination. Because of low adsorption potential, short-chain PFAAs do not bind with other chemicals, so they remain dissolved in water, including drinking water resources [61]. Short-chain PFAAs in contaminated drinking water resources lead to exposure in humans that is poorly reversible. This lack of removal leads to continuous exposure through the drinking water, which is independent of short-chain PFAAs' elimination half-lives (Brendel et al. 2018). Because of the increased use of short-chain PFASs, regulating them is imperative under REACH in the European Union [61].

Research on these traditional PFAS alternatives is limited, even though there are some indications that they produce similar adverse health effects as their predecessors and are even more fluid within the environment. Some studies suggest even greater dangers of toxicity [62, 63]. Temkin et al. examined PFASs, including short

PFASs, from a toxicological standpoint using the Key Carcinogens framework. They also noted the lack of studies on PFOS and PFOA alternatives, such as short-chain PFASs [64].

Long-chain PFASs

Post, Gleason, and Cooper conducted a study in 2017 detailing the toxicological effects of exposure to long-chain PFAAs. Breastfed babies are at a higher risk than older individuals, even from low contamination levels to which the lactating mother is exposed. This is because long-chain PFAAs are passed many times over through the mother's breastmilk to the infant [65]. Thus, infants are at a greater risk of developing adverse developmental health effects in their earlier, more sensitive stages of life.

Adults are not without health effects from long-chain PFASs exposure, however. Zeeshan et al. investigated the relationship between PFAS in human blood and eye diseases, including visual impairment in the Chinese population, concluding that risk of the vitreous disorder increases with long-chain PFAS exposure [15].

General populations

Australian National University's National Centre for Epidemiology and Population Health, Research School of Population Health, reviewed 221 pieces of published literature to determine if PFAS exposure influenced health outcomes. They conducted their review in 2017, and at that time, their investigation assessed PFASs association of health outcomes across 12 categories. These included skeletal, immunological, body weight, cardiovascular health, cancer, diabetes, neurological, thyroid, metabolic, reproductive, maternal health, infant health, neonatal health, and respiratory health. The team used a multi-domain risk of bias tool to evaluate their sources. Their evaluation found adequate proof that PFAS exposure increased blood cholesterol by a low but significant amount. They found additional but limited proof of PFAS links to kidney disease, kidney cancer, testicular cancer, high uric acid concentration in the blood, and immunity for rubella and diphtheria following vaccination [64].

In 2020, because PFAS has been identified as a probable human carcinogen, a novel, state-of-science review by Temkin et al. applied key characteristics analysis into risk assessments. This approach is being increasingly used in the USA and international government agencies, to data for several PFAS (26 chemicals) for each characteristic to

evaluate the strength of evidence as a carcinogen [64]. Temkin et al. applied the Key Characteristics of Carcinogens framework. They identified differences in the strength of evidence between long-chain and short-chain PFAS. For example, Temkin et al. found strong evidence of oxidative stress and suppressed immune response for PFOA and several long-chain PFASs, but only suggestive evidence for one short-chain PFAS for those health effects. Well-studied PFAS such as PFOA and PFOS were found to have up to five key characteristics of carcinogens. Temkin et al. noted that although over 600 different PFAS are known to be inactive use over the last decade, for most of those compounds, no toxicological information is available [64].

A study by Duan et al. found novel PFASs PFAES and TFA widely detected in high concentrations in an adult population in Tianjin, China [9]. Jin et al. found that an isomer of PFAES concentrations increases with age in a Chinese population in Anji, China [11]. Among Chinese adults, Zeeshan et al. observed that blood levels of PFASs were significantly higher in a group with eye disease when compared to a group without such disease. A recent study found evidence suggesting an association between PFAS and uric acid varied according to adult kidney function and isomer [15].

Prenatal, maternal, infant

Maternal, prenatal, and infant exposure to PFAS will be addressed together as they are inextricably interrelated pregnancy, delivery, and lactation are known excretion routes for women, and serum concentrations dropped with increasing deliveries [28].

Although PFOA and PFAS were not found to be associated with hypertensive disorders during pregnancy, PFHxS was positively associated with preeclampsia in a study with 1,739 participants from the Maternal-Infant Research on Chemicals (MIREC), a longitudinal cohort of pregnant Canadian women [34]. The Borghese et al. 2020 study may have found the strongest effect of any PFAS observed to date; they observed that the risks of developing preeclampsia were 3-fold higher among pregnant women in the highest (relative to lowest) tertile of PFHxS. This finding may have been a result of using a definition of preeclampsia as defined by guidelines by the Society of Obstetricians and Gynecologists of Canada instead of the American College of Obstetricians and Gynecologists.

Because studies have shown that alterations in thyroid function in the mother during pregnancy are associated with several adverse fetal outcomes such as preterm delivery, insufficient fetal growth, and neurodevelopment

deficits, Preston et al. investigated the recent epidemiological studies' suggestion that PFASs may alter maternal and neonatal thyroid function [45]. Specifically, Preston et al. sought to assess the effect on maternal and neonatal thyroid function from exposure to PFASs individually and in mixtures in a prospective cohort in Boston by using two statistical methods: weight quantile sum regression (WQS) and Bayesian kernel machine regression (BKMR). Using both statistical methods, Preston et al. found that the PFAS mixture was inversely associated with maternal FT4I and neonatal T4 levels, primarily in male infants. The researchers noted the BKMR results identified other associations and that BKMR and WQS regression analysis were relatively consistent. The use of BKMR permitted analysis of potentially non-linear exposure-response functions and interactions among PFAS. This is one of the first epidemiologic studies, if not the first, to examine PFAS mixture effects on maternal and neonatal thyroid function [45].

Although the emerging literature on prenatal PFAS exposure and neurodevelopment is still in its nascence and so inconsistent, a study from 2020 show associations between prenatal exposure to PFAS and neurodevelopment [48]. Studies examining prenatal PFAS exposure and IQ and other childhood cognitive outcomes have had inconsistent results, some adverse on IQ while others were positive. These developmental effects and delays have been found to last years into childhood. Spratlen et al. found evidence suggesting sex-specific associations between prenatal exposure to PFASs and childhood neurodevelopment; specifically, higher prenatal PFAS exposure may be associated with higher scores for some cognition for females but not for males. Spratlen, et al., noted that these findings should be interpreted with caution due to limited data and statistical tests and citing different results from other studies [48].

PFOS and PFOA can cross the placental barrier between mother and child and alter the size, birth weight, Intrauterine Growth (IUGR), and gestational age [51]. Preterm birth, or Intrauterine Growth Restriction (IUGR), has been associated with increased risk for several diseases later in life, including cardiovascular disease, obesity, and endocrine disorders. A study in Brazil examined the potential links between PFASs concentrations in the whole blood samples of 252 pregnant mothers and preeclampsia, low birth weight, preterm birth, and IUGR [51]. The study in Brazil found no significant association between increasing PFOS and PFOA and preterm birth, preeclampsia, and low birth weight. The bivariate analysis, however, showed a positive association between concentrations of PFOA and PFOS and IUGR. Souza et al. 2020 also found a significant association between socioeconomic status and

PFOS/PFOA levels; more affluent women had higher concentrations of PFASs. Whole blood concentrations of PFOS and PFOA were also significantly associated with fetal growth restriction in pregnant Brazilian women [51].

The maternal serum concentration of an alternative to PFOS used in China (Cl-PFESA) was associated with lower birth weight and higher risk for preterm birth [8]. A stronger association between PFAS and gestational age among female infants was found, the reason for the sex-difference was unknown. Kashino et al. also found that prenatal concentrations of PFAS were linked with adverse birth outcomes, including birth weight [17].

In short, there is support in the literature for the notion that humans excrete PFASs through breastfeeding [46]. A 1-month-old formula-fed baby consumes 137 mL of drinking water per kg in a day, while, by contrast, an 11-year child consumes 13 mL per kg per day [68]. As a result, infants show elevated serum PFAA levels because they are exposed to more contaminants [65].

PFAS exposure and children

According to a 2017 literature review of 64 studies that address links between PFAS exposure and child health outcomes done by Rappazzo et al. six outcomes emerged, namely immunity/infection/asthma, neurodevelopmental/attention, thyroid, cardio-metabolic, renal, and puberty onset [2].

Regarding asthma, a 2020 study by Kvaalem et al. had two designs: cross-sectional and longitudinal and investigated PFAS exposure and asthma. They noted that no firm conclusions could be drawn about PFAS exposure and asthma and asthma-related health outcomes, because, although cross-sectional studies (including theirs) do link PFASs and asthma health outcomes, longitudinal studies of PFASs' relationship to asthma (including theirs) do not find a link (or a clear gender pattern) [29]. Nonetheless, Kvaalem et al. did find a pattern of a positive association between allergic sensitization and PFASs in all participants, regardless of study design (cross-sectional or longitudinal). Despite that finding, they concluded that no conclusion could be drawn between PFASs and rhinitis or allergic sensitization as there are inconsistent findings and too few studies. The longitudinal study found an overall trend between increased PFAS levels in human serum and lower respiratory tract infection between the ages 10 and 16 for all participants, which varied based on gender. Kvaalem et al. found that the increased risk of lower respiratory tract infection in the longitudinal study at different exposure periods suggested a PFAS exposure may induce

immunosuppression both after prenatal and childhood exposure [29].

Several studies add to the growing evidence that children, especially when young, are particularly vulnerable to PFAS exposure, particularly for immune responses [21, 22]. A recent NHANES study collected information about PFAS concentration in children's serum, finding that PFAS concentrations were generally higher in children whose samples were collected in the mid to late 2000s, after regulated PFASs such as PFOS and PFOA were in decline. Interestingly, the researchers found that Mexican Americans had lower PFOS and PFOA concentrations than non-Hispanic persons [50].

PFAS exposure and adolescents

A study found that exposure to PFOS during childhood was associated with increased adiposity in adolescence and young adulthood [19]. Ernst et al. observed that PFAS concentration in maternal plasma was associated with lower age at puberty marked onset for certain PFASs but later puberty onset for other PFASs [20].

Women

As ovarian function can indicate overall health in midlife women, a comprehensive literature review was conducted to assess available information about PFAS exposure and ovarian function [68]. The findings from the studies suggest that PFAS exposure can adversely affect ovarian function, including essential functions such as folliculogenesis and steroidogenesis, to which girls compared to adults may be more vulnerable. Despite the growing body of literature, the review concluded that the inconsistencies of previous findings from studies and lack of longitudinal evidence prevented making causal inferences at this time [68].

Ding et al. performed a longitudinal study that temporally observed PFAS trends in human serum concentrations comparing race/ethnicity, parity (parous/nulliparous), and menstruation in a national cohort across the USA among White, African American, and Chinese women [40]. The comparisons by race/ethnicity were novel and showed differences in body burden and rate of an increase or decrease in PFASs over time. Also, to our knowledge, this was the first longitudinal study of midlife women to compare PFAS concentrations between parous and nulliparous women; it found that parity was a significant determinant of serum PFAS concentrations. Parous

women had lower PFAS concentrations. The study also strengthened the evidence that menstruation status influences serum PFAS concentration; menstruating women had lower PFAS concentrations. In sum, the results depict a decline in legacy PFAS (PFOA, PFOS) and their branched isomers and precursors among women living in the USA during 1999 and 2011. This is consistent with reduced environmental burden [40].

In a case-control study, Tsai et al. examined the relationship between PFAS exposure and risk of breast cancer, stratified by age group (>50 , ≤ 50) [18]. Tsai et al. noted that the few studies between breast cancer and PFAS were in the USA and Europe, and stated that more research was needed in "ethnic populations" [16]. The results showed that younger women had a higher risk of breast cancer based on PFOS exposure compared to older women (>50), which differed from other studies. They also found a higher risk of women 50 and younger of ER-positive tumors compared to women over 50 due to PFHxS and PFOS exposure. In contrast, young women had a lower risk of ER-negative tumors compared to older women based on PFNA and PFDA exposure. They noted that because the recruitment of participants was cross-sectional, causal inferences could not be made [18].

Discussion

Regulatory frameworks, information gaps, risk assessment

Because many standards are voluntary, there is still a need for enforceable regulations on PFAS limits in drinking water. Although some governments and regions are moving towards regulating PFAS with enforceable limits, a constellation of different health advisories, guidelines, and provincial regulations have emerged Table 5.

The US regulatory framework serves as a microcosm of the myriad of considerations in assessing risk and implementing guidelines and regulations. In assessing the disparity regarding health advisories, health-protective guidelines, and standards to limit exposure to PFASs via drinking water, three underlying influences are noted: scientific uncertainty; varying degrees of risk assessment decisions; and an array of economic, social and political factors [5]. In numbers, the range of levels considered safe by different jurisdictions spans from 12 ng/L to 600 ng/L [5]. The final limit on PFAS in drinking water reflects a series of compromises in creating regulation among many stakeholders who consider many factors.

Table 5: Recommended PFAS levels in Drinking Water by Jurisdiction.

<i>Jurisdiction/ Entity</i>	<i>Concentration, ng/L</i>	<i>PFAS Sum</i>	<i>Enforceable?</i>	<i>References</i>
EU	PFAS 20 listed: 100; PFAS Total: 500	20 PFAS listed	(pending) legally binding	Livsmedelsverket Swedish Food Agency [69]
Italy	500, 30, 500	PFOA, PFOS, Other PFAS	guidance only	Mastrantonio et al. 2018 [27]
Sweden	90	PFOA, PFOS, PFHxS, PFHxA, PFHpA, PFBS, 6:2 FTS, PFBA, PFPeA, PFNA, PFDA	guidance only	Livsmedelsverket Swedish Food Agency [69]
Canada	200, 600	PFOA, PFOS	guidance only	Government of Canada 2019 [70]
US EPA	70	PFOA, PFOS, combined	guidance only	US EPA [74]
New Hampshire	12, 15, 18, 11	PFOA, PFOS, PFHxS, PFNA	regulations (court injunction)	Martin, J. 2020 [71]

Cousins et al. proposed several approaches from a sound, scientific perspective to set regulatory standards. They discussed how to handle current knowledge gaps, cost considerations, current implementation of the different approaches used today, and the danger to human health and the environment from PFASs regulations. Different jurisdictions must decide which approach is suitable [72]. However, Cousins et al. point out, a broader approach that considers scientific uncertainty and knowledge gaps will require less expertise to apply. They will likely incur less expensive to implement while protecting human health and the environment under current circumstances. Based on the research for this review, we believe that an insistence on a chemical-by-chemical approach to regulating PFASs appears to have a sunset in regulatory approaches for two reasons: 1) public awareness about PFASs' pervasiveness and (at least some) adverse health effects; 2) the fact that PFASs' creation (estimated 4700+) has outpaced regulation and scientific research (2 consistently PFOA/PFOS) for decades. The USA's recent direct legislation of PFAS requiring notification for releases in the USA and the EU's recent actions regarding PFASs and REACH in 2020 serve as support for our belief. Furthermore, it seems that broader regulation of PFASs is a question of how as opposed to whether and when.

While having one global standard for PFAS contamination in drinking water may forever be impossible under current structures, at the very least, clear national standards should be set in every country, if not regional organizations. Otherwise, like judicial forum shopping in which a forum participant seeks the jurisdiction with the rules most favorable to the participant, industry stakeholders may continue to engage in regulatory forum shopping to set up PFAS manufacturing facilities, thus

thwarting community efforts to manage PFAS contamination risks to human health. Authors reporting a recent community-led health survey of residents in Merrimack, New Hampshire, a place where a local chemical plant led to PFAS-contaminated public drinking water and private wells, the authors seem to have outlined such a regulatory-forum shopping approach by an industry stakeholder [73]. Although national and local jurisdictions have borders, water sources often cross those borders. As a result, clear standards covering larger geographic areas are necessary. This approach would benefit communities as well as industry stakeholders, who would then have clear rules to follow instead of risking litigation and its resulting uncertain legal and financial liabilities. To take one historical example, the C8 panel, and the funding for its numerous longitudinal studies resulted from the settlement of a lawsuit. A strong public awareness campaign about PFAS to targeted groups, such as people who are likely to eat harvested fish, is also needed in the public health approach.

From a scientific perspective, studies that have considered drinking water limits also provide a range of possibilities. To protect against potential immunosuppressive effects in children as evidenced by antibody responses to vaccines, one benchmark dose study recommended 1 ng/L limit for PFOA [21]. Another study noted the European Food Safety Authority Daily Intake limit and applied the World Health Organization conversion rules to state a limit of 3000 ng/L for PFOA and 300 ng/L PFOS [24]. In 2019, a report by scientists assessing limits for Michigan's public water drinking systems urged that scientific evidence supports a need for a maximum contaminant level in drinking water of 0 for all PFASs [63].

Inconsistent and insufficient monitoring

While the lack of standards presents a problem for global comparison and consensus, it also presents a gap of evidence with more regional and community-based implications. The variability in standards and observed values is particularly problematic when issuing guidance and advisories for PFAS-related health issues across multiple geographies. Moreover, testing protocols within each territory may not reflect the complete scope of PFAS contamination of community water sources. For example, Michigan has well-documented efforts to identify PFAS contamination in over 100 public water systems; yet their testing protocol excludes small private wells that are not designed for public use [63]. Thus, the extent of PFAS exposure to Michigan residents is still unknown.

Recent biomonitoring studies by the Centers for Disease Control (CDC) and the United States National Health and Nutrition Survey (NHANES) found it paramount to include biomonitoring for multiple PFASs beyond PFOS and PFOA to include PFDoA, PFNA, MeFOSAA, PFUA, PFDeA, PFHpA, PFBS, FOSA, EtFOSAA, and PFHxS [63].

Although CI-PFESA is a widely used PFOS alternative in China, there is no human data available to assess the reproductive toxicity of this PFAS [8]. As Temkin, et al. noted, for the majority of 600 PFAS in wide use for the past decade, there is no toxicological data [64].

Rapazzo et al. note two considerations for future studies of PFASs and childhood health outcomes: longitudinal studies and variations in outcome measurement [2]. These authors of the Australian report observed a significant potential risk (potential) of bias based on factors such as study design and researcher motivation [66].

Observations

The design of the studies, the reporting measurements, statistical models, and other factors makes comparing results complex. Many of the studies relied on interviews of participants to gather information about lifestyle habits to identify covariates; some studies noted that participants might have recollection bias while others noted the possibility of underreporting in examining differences between self-reports of lifestyle behaviors. Moreover, self-reporting may be faulty. Thus, many studies that identified covariates through interviews without confirmation with other records may have a bias.

As Ding, et al. noted, the studies also vary in how they report human body burdens of PFAS (e.g., ng/mL in serum versus odds ratio versus risk ratio versus ng/kg bw/day)

which makes it difficult to compare the results across the studies [68].

Several studies also noted observations about the sample and the ability to generalize the results. Recent studies noted a lack of ethnic/racial diversity in study cohorts that may limit the generalizability of the findings to general populations that are not as homogeneous as the study cohort [45]. Tsai et al. noted that PFAS burden differs across ethnic groups in which PFAS are found in higher concentrations, it may be helpful to ensure a diverse cohort in addition to a more robust study of different PFAS for future studies of PFAS exposure and links to maternal, prenatal, and neonatal health outcomes [18]. Future studies conducted in the USA should include persons of Hispanic/Latinx ethnicities and Asian Americans [37, 40].

Although all studies used accepted statistical methods and approaches, the use of multiple statistical tests may have resulted in false positives, as several studies noted. Moreover, the wide array of statistical models both for analyses and adjustments make comparing results across studies difficult because, as one study showed Preston et al. 2020, results of associations changed depending on which statistical approach was used [45]. Although this review focused on the time period between 2015 and 2020, older studies were also reviewed, some of which were included. It was observed that older studies did not summarize in as much detail as studies from the past five years the statistical method calculation process.

The potential for reverse causality and the necessary need for caution in interpreting results recurred in many biomonitoring studies, particularly when interviews without access to medical records were performed at the time blood samples were taken. Moreover, study design itself may also affect which and whether associations are found (e.g., asthma and cross-sectional studies) [29].

Conclusions

Although scientists have made a lot of progress over the past decade in examining and identifying potential pathways of exposure to PFASs in humans and research suggests some links between health effects and exposure to PFASs through water exposure, many gaps in the information remain. In addition, some of the emerging research suggests that new PFASs such as short-chain PFASs could replace long-chain PFASs as a potential and pervasive threat to human health. Many PFASs are already in the environment and without an existing way to remove them from the environment. Perhaps more significantly,

recent research points to the fact that current health restrictions, advisory or mandatory, may not protect vulnerable populations such as babies and children, with possible long-term effects on lifelong health. This research suggests that more comprehensive views of regulatory restrictions on PFASs levels and human exposure, particularly in drinking water but also including production, to protect human health are necessary in the short term while a better understanding of PFASs is being determined.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Conflict of interest: None declared.

Informed consent: Not applicable.

Ethical approval: Not applicable.

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