

## CRITICAL REVIEW

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## Potential human health effects of per- and polyfluoroalkyl substances (PFAS) prevalent in aquatic environment: a review

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The widespread incorporation of per- and polyfluoroalkyl substances (PFAS) in various daily-use items has garnered considerable attention regarding environmental and health hazards in the last decade. Among different categories of PFAS, a paradigm shift has occurred towards short-chain PFAS alternatives like GenX, ADONA, and F53B, driven by environmental considerations and regulatory changes. Exposure to PFAS can happen through consuming contaminated food and drink, inhaling contaminated dust, or skin contact with PFAS-containing objects. Furthermore, occupational exposure might result from manufacturing and firefighting operations employing fluorinated compounds. In humans and monkeys, perfluoroctanoic acid (PFOA) and perfluoroctanesulfonic acid (PFOS) exhibit an increased affinity for plasma proteins. However, the exact extent of this affinity is still a matter of research. The buildup of PFOS in the liver might cause injury or dysfunction by interfering with its regular operation. Compared to other human tissues, the liver has been shown to accumulate higher amounts of PFOS. Although there is an absence of epidemiological studies on PFOS, a possible connection between the health disorder and elevated cholesterol levels has been established by many researchers. Considering the transition as a future environmental burden, this review aims to bring together ongoing research compilations on short-chain PFAS, delving into their persistence, prevalence, and bioaccumulative toxicity in aquatic environments and focusing on critical areas of research gaps. An extensive literature analysis assessed the relative abundance of short-chain compounds compared to their long-chain counterparts within aquatic ecosystems. US EPA has setup new guidelines specifically for drinking water for PFOA and PFOS compounds which is 4 ppt. Furthermore, this review highlights emerging regulatory measures being implemented worldwide to safeguard public health. These measures encompass a range of strategies, from the European Union's emphasis on banning certain manufacturing and production practices under the REACH regulations to establishing exposure limits and disposal protocols in the United States.

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### Environmental significance

The widespread incorporation of per- and polyfluoroalkyl substances (PFAS) in various daily-use items has garnered considerable attention regarding environmental and health hazards in the last decade. Among different categories of PFAS, a paradigm shift has occurred towards short-chain PFAS alternatives like GenX, ADONA, and F53B, driven by environmental considerations and regulatory changes. Exposure to PFAS can happen through consuming contaminated food and drink, inhaling contaminated dust, or skin contact with PFAS-containing objects. The significant of the current review is distinct from previous works, focusing specifically on consolidating recent literature concerning short-chain PFAS and providing insights into the regulatory measures implemented and adopted globally to address the persistent environmental presence and human health risks posed by PFAS.

## 1. Introduction

Per- and polyfluoroalkyl substances (PFAS) have seen extensive global use in various consumer products since the mid-20th century. These compounds are commonly integrated into everyday items to fulfill multiple purposes, such as preventing food adhesion to packaging or cookware, imparting stain resistance to textiles and carpets, and enhancing the efficacy of firefighting foam (SI Fig. S1). Perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are known for their remarkable resistance to degradation, which contributes to their persistent presence in the environment over time.<sup>1</sup>

PFAS molecules are interconnected carbon and fluorine atoms, forming strong carbon-fluoride bonds. Due to this bond's resilience, these chemicals do not readily degrade in nature. PFOS and PFOA have garnered significant attention as persistent organic pollutants (POPs) because of their unnoticed existence in the environmental ecosystem, including human serum and tissues.<sup>2</sup> They are classified as long-chain PFAS, distinguished by their eight-carbon backbone with sulfonate and carboxylate functional groups. Their ability to repeal water (hydrophobicity) and oil (oleophobic), combined with a variety of other chemical attributes, renders them valuable in a myriad of consumer goods.<sup>3,4</sup>

The adoption of shorter-chain PFAS over long-chain molecules in the early 2000s marked a shift towards using compounds with carbon backbones containing fewer than seven carbons in industrial and environmental applications.<sup>5</sup> Noteworthy among these shorter-chain substitutes are GenX (hexafluoropropylene oxide dimer acid (HFPO-DA)), ADONA (4,8-dioxa-3H-perfluororononanoate), and F53B (chlorinated polyfluoroalkyl ether sulfonate), which have gained widespread usage.<sup>6</sup> GenX is employed in various industrial processes.<sup>7</sup> ADONA is applied as a replacement for PFOA in synthesizing fluoropolymers,<sup>1,8</sup> whereas F53B serves as a replacement for PFOS and functions as a mist suppressant in electroplating processes.<sup>9,10</sup> Despite extensive research on the toxicity and health impacts of PFAS, gaps remain in understanding the unique challenges posed by short-chain variants.<sup>11–13</sup>

While existing literature, including comprehensive reviews and empirical studies, has explored the effects of PFAS primarily in rodents, wildlife, fish, and through human autopsy cases, there is a critical need for deeper analysis into the impacts on other animal species and studies on human health.<sup>14–16</sup> Furthermore, the effectiveness of global regulatory responses to PFAS, key emerging contaminants, exhibits significant variability across different jurisdictions. This

inconsistency complicates efforts to mitigate the environmental and health impacts of PFAS and hampers the ability to conduct comprehensive, comparative analyses of policy efficacy.

Divergent regulatory landscapes, ranging from stringent prohibitions in some countries to more lenient guidelines in others, pose a challenge for multinational enforcement and global environmental protection strategies. Furthermore, the lack of uniform standards impedes the development of international agreements that could facilitate more effective management of PFAS pollution. The primary objective of the current review is distinct from previous works, focusing specifically on consolidating recent literature concerning short-chain PFAS and providing insights into the regulatory measures implemented and adopted globally, which is the novelty aspect of the current review. The specific objectives of this review are: (i) providing a comprehensive survey to compare the persistence and prevalence of short-chain molecules with their long-chain counterparts in aquatic environments, (ii) identifying knowledge gaps by conducting an in-depth literature review on the bioaccumulation of ADONA and GenX in various aquatic organisms and assessing potential eco-toxicological implications, and (iii) evaluating the human health risks connected with exposure to short-chain PFAS. Lastly, this review seeks to evaluate how these disparate regulatory frameworks influence PFAS management and control, aiming to identify best practices and recommend approaches for regulatory harmonization that could enhance global efforts to address the persistent environmental presence and human health risks posed by PFAS.

## 2. Methodology

The literature survey details on the potential health effects of PFAS on human health are presented in SI Fig. S2(a–c), which schematically shows the workflow for the bibliometric analysis that led to the narrowed set of references used in this review. This analysis also indicates how the various selection criteria were grouped (SI Fig. S2b) and gives a keyword co-occurrence map (SI Fig. S2c) related to the searched topics. A literature search was conducted in Science Direct, Google Scholar, PubMed, and Web of Science Core Collections with the following searching terms: TS=(“per- and polyfluoroalkyl substances (PFAS)” OR “human health” OR “aquatic environment”) AND TS=(“source” OR “GenX” OR “men” OR “women” OR “short-chain PFAS” OR “drinking water” OR “cancer”) AND TS=(“contamination” OR “contaminant” OR “pollutant” OR “toxic”). A total of 1731 results were retrieved and visualized using the VOSviewer software (version 1.6.19).



### 3. Categories of PFAS

PFAS can be divided into two primary categories: polymer and non-polymer types (Fig. 1). Polymer PFAS can be divided into fluoropolymers, side-chain fluorinated polymers, and per-fluoropolyether (PFPEs). Fluoropolymers are characterized by carbon-only backbones with directly bonded fluorine atoms such as polytetrafluoroethylene (PTFE), polyvinylidene fluoride (PVDF), fluorinated ethylene propylene (FEP), and per-fluoroalkoxy alkanes (PFA).<sup>17–19</sup> Another category, side-chain fluorinated polymers, features non-fluorinated carbon backbones with polyfluoroalkyl side-chains of varying compositions. PFPEs, the third group, are fluorinated polymers with carbon and oxygen backbones, directly connected to fluorine atoms. Non-polymer PFAS include perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkane sulfonic acids (PFSAs), with legacy compounds like PFOA and PFOS, and short-chain alternatives such as PFHxA, PFBS, GenX, and ADONA. Perfluorononanoic acid (PFNA), another long-chain PFCA, is also a non-polymer PFAS, though it has been historically used as a processing aid in fluoropolymer production. In addition, polymer PFAS, such as fluoropolymers (e.g., PTFE and PVDF), are generally less bioavailable but may degrade into non-polymer PFAS under certain conditions. Hence, this review primarily focuses on non-polymer PFAS, especially short-chain variants, due to their widespread occurrence in aquatic environments, increased mobility, and emerging regulatory concern. These compounds differ significantly in environmental occurrence, behavior, and

toxicity, which are the core topics addressed in the following sections.

#### 3.1. Occurrence of short-chain PFAS in aquatic environment

Short-chain PFAS like ADONA, HFPO-DA, and chlorinated poly-fluorinated ether sulfonate (6:2 Cl-PFAES) have been under environmental surveillance alongside other associated compounds.<sup>20</sup> 6:2 Cl-PFAES has been notably found in industrial effluent from chrome plating facility in Hangzhou Bay, China, exhibiting extremely high levels ranging from 150 to 155  $\mu\text{g L}^{-1}$ .<sup>21</sup> A similar study reported high concentrations in effluent, with levels ranging from 980 to 985  $\mu\text{g L}^{-1}$ . Additionally, systematic detection in municipal sewage sludge samples across China revealed a median value of 1.94  $\text{ng L}^{-1}$ .<sup>22</sup> Its environmental distribution was confirmed by its detection in remote Polar Regions, suggesting its ability to undergo long-range transport.<sup>23</sup>

HFPO-DA (Gen-X) has been identified in surface waters in Germany and the Netherlands, particularly downriver from fluorochemical production units, reaching concentrations of  $\sim 800 \text{ ng L}^{-1}$ .<sup>24,25</sup> It was found during a comprehensive survey of surface waters across China, European countries, Korea, and the USA, showing 0.18 to 144  $\text{ng L}^{-1}$  concentration levels.<sup>26–29</sup> ADONA, identified in the Rhine River (Europe) water samples with a 75% detection frequency, generally exhibited low concentrations ranging from less than 0.01 to 1.5  $\text{ng L}^{-1}$ .<sup>30,31</sup> These compounds' environmental presence is concerning, primarily due to their high mobility in soil and water systems.<sup>27</sup>

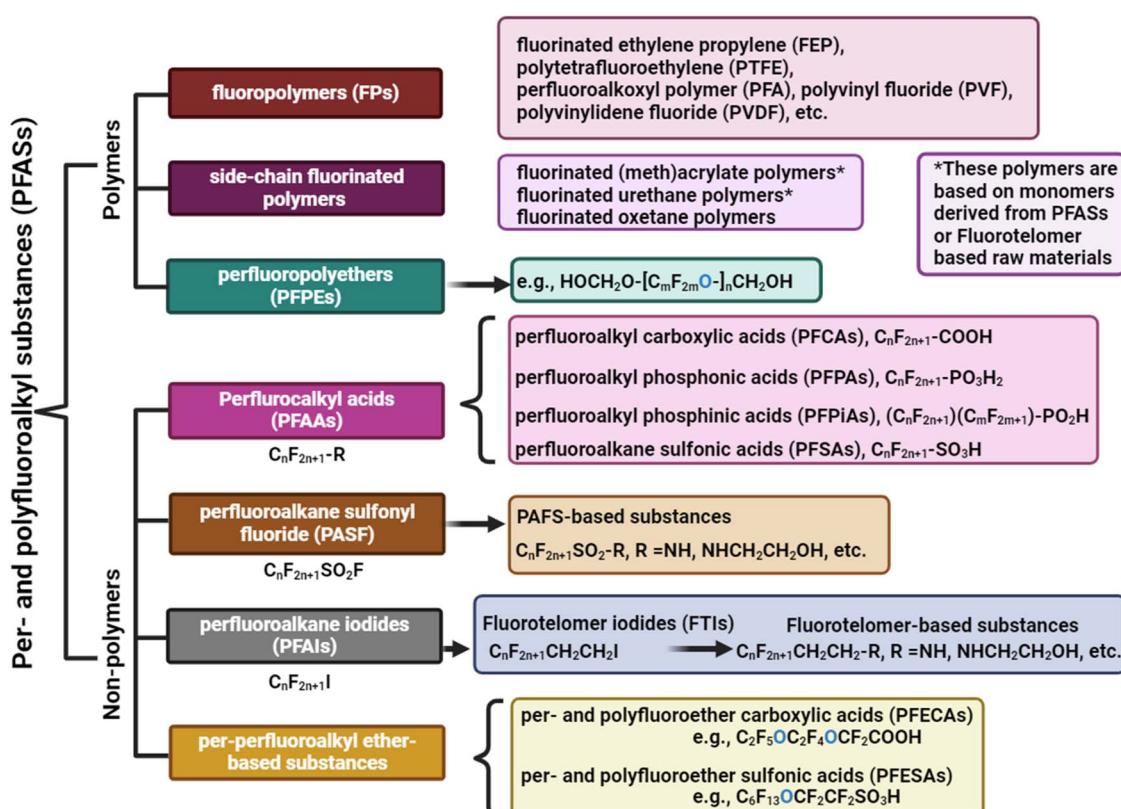


Fig. 1 Schematic representation of different categories of PFAS, mainly polymer and non-polymer types.



Table 1 Global occurrence of short-chain PFAS in drinking water sources, including tap water, bottled water, and groundwater<sup>a</sup>

Country	City	No: of short chain PFAS	Drinking water		Ground water (ng L <sup>-1</sup> )	References
			Bottled water (ng L <sup>-1</sup> )	Drinking water sources (ng L <sup>-1</sup> ) (households, municipalities)		
Singapore	Multiple locations (East, NortheastWest and Central Singapore)	5	● PFPeA ● PFHxA ● PFHpa ● PFBS ● PFHxS	● 0.08–0.88 ● 0.06–0.94 ● 0.07–0.17 ● 0.06–0.83 ● 0.08–0.14	● 0.11–3.51 ● 0.21–4.63 ● 0.07–1.79 ● 0.07–1.99 ● 0.06–0.97	— 124
China	Hubei province	5	● PFBS ● PFHxS ● PFPeA ● PFBA ● PFHxA	— ● BDL – 31.0 ● BDL – 160.1 ● BDL – 0.6 ● BDL – 2.4 ● BDL – 3.4	● BDL – 31.0 ● BDL – 160.1 ● BDL – 0.6 ● BDL – 2.4 ● 0.1–3351.4	● 6.4–9238.5 ● BDL – 5999.2 ● BDL – 1259.8 ● 13.0–8639.5 125
South Korea	Multiple location	4	● PFPeA ● PFHxA ● PFHxS	● 12.7 ● 12.9 ● 5.92	— — ● 5.68	— 126
Combine	Mainly Canada (n = 95), USA (n = 22), France (n = 9)	3	● PFBS ● PFBA ● PFPeA ● PFHxA ● Gen-X	— ● 0.084–87.61 ● 0.043–84.41	● 0.113–104.6 ● 0.084–87.61 ● 0.043–84.41	— 127
Belgium	Flanders	4	● PFBA ● PFBS ● PFPrS ● TFMMS	— — — ● BDL – 15	● BDL – 12 ● BDL – 7.3 ● BDL – 0.6 ● BDL – 5.6	● 21 128
Norway	Various municipality water suppliers	7	● PFBA ● PFPA ● PFPrS ● PFBS ● PFPS ● 6:2 FTS ● PFHxA	— ● 0.11 ● 0.052 ● 0.077 ● 0.0041 — ● 0.083	● 0.019 ● 0.11 ● 0.052 ● 0.077 ● 0.0041 — ● 0.083	● 9.4 — 129
Italy	Vicenza	3	● PFBA ● PFPeA ● PFHxA ● TFA ● PFPrA	— ● 38 ● 38	— ● 61 ● 38	130
Netherlands	Different treatment plants	13	● TFA ● PFPrA ● PFBA ● PFPeA ● PFHxA ● PFBS ● PFPeS ● 4:2 FTS ● 4:2 FTA ● PF40PeA ● 6:2 diPAP ● ADONA	— ● 0.12–28.39 ● 0.3–1.17 ● 0.03–0.3 ● 0.03–0.35 ● 0.02–0.12 ● 0.03–0.09	● 88.44–482.95 ● 0.12–11.13 ● 0.03–3.69 ● 0.03–0.54 ● 0.19–0.54 ● 0.02–0.1 ● 0.03–0.17	● 87.7–520.9 ● 0.12–11.13 ● 0.03–3.69 ● 0.03–0.54 ● 0.19–0.54 ● 0.02–0.1 ● 0.03–0.17 — — — — — — — 131

Table 1 (Contd.)

Country	City	No. of short chain PFAS	Name of short chain PFAS	Drinking water		Ground water (ng L <sup>-1</sup> ) (municipalities)	References
				Bottled water (ng L <sup>-1</sup> )	Drinking water sources (ng L <sup>-1</sup> ) (households, municipalities)		
Czech Republic	Various Household around Czech Republic	4	● PFHxA ● PFBS ● PPPeS ● PFHxS	—	● 0.048–97.7 ● 0.093–3.10 ● 0.049–0.699 ● 0.026–0.772	—	132
US	Baltimore metropolitan area	7	● PFPeA ● PFHxA ● PFBS ● PPPeA ● PFPeS ● PFHxA ● PFHxS	● 0.45–6.52 ● 0.51–1.40 ● 0.19–1.44 ● 2.84–3.27 ● 0.21–0.23 ● 0.41–1.98 ● 0.31–0.64	—	—	133
Turkey	Multiple locations	4	● PFBA ● PPPeA ● PFHxA ● PFBS	● 0.26–0.46 ● 0.08–0.14 ● 0.08–0.21 ● 0.19–0.21	● 0.27–1.93 ● 0.08–1.23 ● 0.08–2.90 ● 0.11–0.85	—	134
India	Different points of Ganges	—	● PFHxA ● PFBS ● PFBA	—	—	● 0.8–4.9	135
Brazil	Porto Alegre metropolitan area & other locations	4	● PFHxA ● PFBS ● PFHxS ● PFHxA ● PFHxS ● PFHxA ● PFHxA ● PFHxA ● PFHxA ● PFHxA ● PFHxA	● 3.1–3.6 — — — ● 5.7–6.8 — ● 4.8–11.8 — ● 5.7–17 ● 1.3–6.7 — ● 6.7 ● 4.5–25	● 0.48–16 ● BDL – 15.9 — — ● 5.2–36 ● 2.8–24 ● 14–58 — ● 5.7–17 ● 4.1–42 ● 2–15 ● 5.8–6.8 — ● 13–33	● 0.5–3.5 — — — — — — — ● BDL – 9.2 ● 0.5–3.5	136
Spain	Barcelona metropolitan area& other locations	4	● PFBS ● PFHxA ● PFHxS ● PFHxA ● PFHxA ● PFHxA ● PFHxA ● PFHxA	— ● 4.8–11.8 — — — — — —	— ● 14–58 — — — — — —	— — — — — — — —	136
France	Toulouse, Montpellier, Nimes, Avignon, Valence, Grenoble, Lyon and Perpignan	4	● PFBS ● PFHxA ● PFHxA ● PFHxA ● PFHxA	— — — — —	● 4.1–42 ● 2–15 ● 5.8–6.8 — —	— — — — —	136

<sup>a</sup> BDI: below detection limit.

Furthermore, certain research findings indicate that their ultimate degradation byproducts exhibit persistence.<sup>32</sup>

Additionally, the data from 15 countries covering the occurrence of short-chain PFAS in various drinking water matrices (tap, bottled, and groundwater) was collected and tabulated. Table 1 includes 13 short-chain PFAS, with PFBA, PFPeA, PFHxA, PFBS, and PFHxS being the most frequently reported across global studies. The Netherlands reported the highest diversity with 13 short-chain PFAS detected in treated waters, including ultra-short-chain compounds like trifluoroacetic acid (TFA) and 6:2 diPAP, with concentration ranges reaching up to  $520.9 \text{ ng L}^{-1}$  for TFA. China demonstrated the highest concentrations overall, with PFBA and PFHxA exceeding  $9000 \text{ ng L}^{-1}$  and  $8000 \text{ ng L}^{-1}$  respectively in drinking water sources near a former fluorochemical facility. Singapore, South Korea, and Norway reported moderate levels (typically  $<10 \text{ ng L}^{-1}$ ), suggesting a relatively lower burden or effective regulatory mitigation. The US and Canada revealed a widespread but moderate-level presence of multiple SC-PFAS in bottled and municipal waters.

Countries such as India, Brazil, and Spain showed notable occurrence of PFBS and PFHxA in both groundwater and household drinking water sources, indicating ongoing exposure risks in developing and middle-income regions (SI Fig. S3).

### 3.2. Exposure to PFAS and their negative health impacts

PFAS exposure can occur through polluted food and water ingestion, contaminated dust, air inhalation, and dermal

contact with PFAS materials (Fig. 2). The United States Food and Drug Administration's (US FDA's) seafood survey in 2022 concluded that water and seafood were the most generic supplies (74%) of PFAS exposure for the public.<sup>33</sup> Additionally, certain occupations, such as firefighting and manufacturing, involving PFAS-containing products can cause occupational exposure.<sup>19</sup>

However, data regarding the adverse impacts of PFAS on other animal species and humans remains limited (Fig. 2). Studies have advocated that the long half-lives of PFAS in humans may be due to their strong binding to plasma proteins.<sup>34,35</sup> Both PFOA and PFOS demonstrate a heightened attraction to plasma proteins in monkeys and humans, although the precise degree of binding remains incompletely characterized. PFOS tends to accumulate more prominently in the liver and serum, carrying significant implications.<sup>36</sup> Accumulation of PFOS in the liver can disrupt its normal functioning and potentially lead to liver damage or dysfunction.<sup>37</sup> Higher levels of PFOS accumulation in hepatic tissues maybe attributed to enterohepatic recirculation, wherein PFOS is excreted in bile and subsequently reabsorbed from the gut.<sup>38</sup> In the bloodstream, PFOS in the serum can circulate throughout the body, potentially affecting various organs and systems. During the 1990s, studies conducted in the United States revealed that serum samples from pooled blood banks had average PFOS concentrations ranging from  $28 \text{ ng g}^{-1}$  to  $44 \text{ ng g}^{-1}$ .<sup>39</sup> Similarly, research conducted in Europe reported mean serum PFOS concentrations of  $17 \text{ ng g}^{-1}$  in Belgium,  $53 \text{ ng g}^{-1}$  in the Netherlands, and  $37 \text{ ng g}^{-1}$  in Germany, all based on pooled

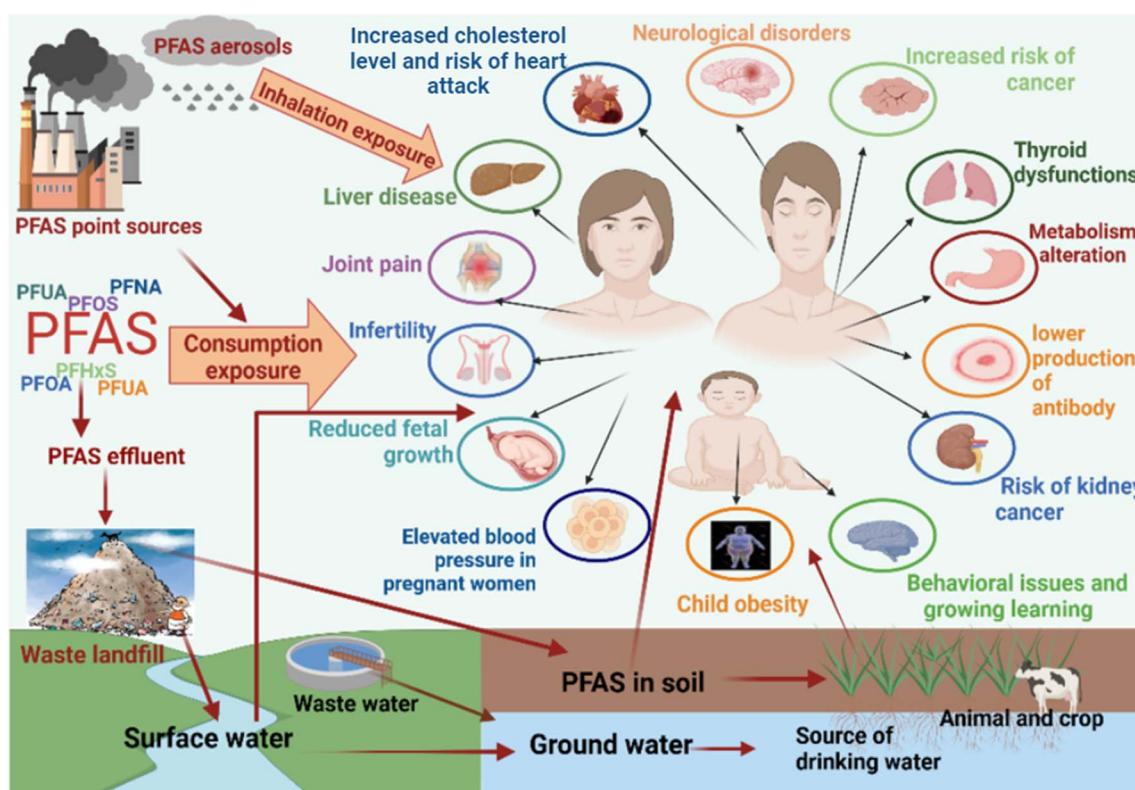


Fig. 2 Exposure pathways and health effects of PFAS on human life.



blood bank samples.<sup>40–42</sup> Among 23 human donors with paired samples, it was found that the mean PFOS concentrations were 20.8 ng g<sup>−1</sup> in the liver and 1.32 µg mL<sup>−1</sup> in the serum.<sup>39</sup>

Several reviews have examined the prevalence of PFOA and its involvement in a large population's health hazards, such as immunomodulation.<sup>43,44</sup> The earlier studies consistently observed moderate increases in cholesterol and uric acid levels with PFOA. However, results regarding long-term disorders with an inflammatory component, such as diabetes and stroke, were inconclusive. The same authors also reported reproductive and developmental disorders in humans.<sup>43</sup> The study concluded that low birth weight resulting from PFOA exposure was typical and did not carry significant clinical implications. Granum *et al.* (2013)<sup>45</sup> also reported alterations in serum immunoglobulin levels, and male PFOA workers showed an association with elevated monocyte counts in residents exposed to PFOA-contaminated water, as Brieger *et al.* (2011)<sup>46</sup> reported. While epidemiological data on PFOS is limited, existing information suggests a potential link to health disorders associated with increased cholesterol levels.

**3.2.1. Health effects of short-chain PFAS.** Short-chain PFAS also affect human health, although their concentrations in humans are usually below those linked to toxicity in laboratory animals (Table 2). For instance, breast milk's highest reported human PFAS concentration was 360 ng L<sup>−1</sup>, significantly lower than levels linked to adverse effects in laboratory experiments.<sup>8</sup> A study spanning three years and involving 752 females in China discovered a link between prenatal exposure to short-chain PFAS like perfluorobutane sulfonate (PFBS) and perfluoroheptanoic acid (PFHpA), where alterations in fetal gonadotropins were reported.<sup>47</sup> An updated review, incorporating the effects of endocrine disruption due to exposure to both short- and long-chain PFAS, found that these effects varied depending on gender and the stage of development.

PFOA exposure has been associated with thyroid diseases, and epidemiological research suggests a possible association with human cancers.<sup>48</sup> Young men experienced a decline in semen quality after coming in contact with PFOS, PFHxS, and PFOA.<sup>49</sup> Furthermore, these three chemicals have been related to early onset menopause in females, increased impulsivity, and delayed puberty in children.<sup>50,51</sup> The presence of PFHxA and PFBA in human autopsy tissues has revealed distinct patterns, with PFHxA predominantly detected in the brain and liver, while PFBA is frequently noticed and found at higher concentrations in the kidney and lung.<sup>52</sup>

**3.2.2. Effects of short-chain PFAS in reproductive system of animal models.** Toxicity assessments on aquatic organisms have revealed elevated Cl-PFESAs (trade name F-53B) and potassium salt of PFOS in zebrafish, ranging from 15.5 to 17 mg L<sup>−1</sup>, respectively.<sup>53</sup> The contact with F53B led to a rise in birth abnormalities, delayed egg emergence, and reduced chances of survival among embryos.<sup>54</sup>

Sub-chronic hepatotoxicity of Cl-PFAES in mice was observed, with fatty liver and indications of cell apoptosis and proliferation in groups exposed to doses exceeding 0.2 mg per kg per day.<sup>55</sup> Mice exposed to GenX showed a higher occurrence of placental abnormalities. In contrast, affected rats showed

higher expression of peroxisome proliferator-activated receptor (PPAR)-regulated genes in both livers, resembling the impacts of PFOA noted previously. GenX exhibited developmental toxicity in rats, leading to higher rates of neonatal deaths and lower birth weights in those exposed from gestational day 8 to postnatal day 2, with doses ranging from 1 to 125 mg per kg per day.<sup>56,57</sup>

### 3.3. Toxicity studies of perfluoroalkylated compounds (PFCs)

Although toxicity studies have historically focused on long-chain PFAS (e.g., PFOS and PFOA), increasing use of short-chain PFAS as replacements raises concerns regarding their potential health impacts. This section reviews available toxicity data, highlighting differences and similarities in the effects of short-chain and long-chain PFAS. Where applicable, we relate observed effects to molecular characteristics such as chain length, functional groups, and physicochemical behavior such as bioaccumulation and mobility.

**3.3.1. Cytotoxicity study.** Cytotoxicity refers to the capability of a xenobiotic substance to cause damage or cell death in living cells, often measured in biological and medical contexts.<sup>58</sup> It can manifest through various mechanisms, such as cell membrane damage, interference with cellular metabolism, or disruption of cellular DNA (Table 2). The severity of cytotoxicity depends on factors like dose, exposure duration, and cell/tissue sensitivity. Numerous studies have investigated the impact of PFCs on reactive oxygen species (ROS) formation in cultured cerebellar granule cells.<sup>58</sup> A detailed analysis of the toxicity mechanisms is out of the scope of the present study.

Studies conducted using rat neuron cultures have elucidated that the impact of PFCs is contingent upon their molecular arrangement, characterized by a carbon chain ranging from 4 to 16 atoms, enclosed by fluorine atoms. These compounds often contain a charged functional group, such as carboxylate, sulfonate salt, or acid, at one end.<sup>59</sup> Consequently, they have been observed to markedly elevate ROS formation within cells, potentially by activating pathways such as PPAR $\alpha$  or nuclear factor erythroid 2-related factor 2 (Nrf2). Although these effects may not directly precipitate cell death, they induce oxidative stress, damage DNA, and cause various physiological alterations. While long-chain PFAS like PFOA and PFOS have been well-documented for their cytotoxic effects,<sup>60</sup> few studies suggest that short-chain PFAS such as PFBS and PFHxA also induce oxidative stress, although at typically higher concentrations and with lower bioaccumulative potential.<sup>61,62</sup> This suggests reduced, but not negligible, toxicity for shorter-chain analogs.

The concentrations of PFAS associated with adverse health impacts in humans range from 2 to 20 ng mL<sup>−1</sup>, as reported by the NASEM in 2022.<sup>63</sup> However, individuals with occupational exposure to PFAS may have higher serum levels, with typical levels around 300 ng mL<sup>−1</sup> for PFOS and approximately 2000 ng mL<sup>−1</sup> for PFOA.<sup>64</sup>

**3.3.2. Genotoxic effects.** Genotoxicity refers to the process wherein cell injury leads to direct changes and modifications in

Table 2 Study analysis of toxicological impacts of PFAS on human life

PFASs	Population samples	Exposure route measurements	Countries	Impacts on human life	References
PF OA	Adults (54% women) (61% men)	Plasma	U.S state	• PFAS promoted liver disease and hepatocellular apoptosis through dysregulation of caspase – 3 enzyme	137
PF OS			West (Virginia)	• Exposure to PFHxS and PFOA increased the activation of C3a peptide in men and reduced it in women	
PF HxS				• PFAS has been shown to be associated with biological pathways such as proline, aspartate butanoate, and asparagine	138
PF NA	Children (8 years)	Venous blood	U.S state (Ohio)		
PF OA					
PF OS					
PF NA					
PF HxS					
PF OA	Children (8–14 years)	Plasma	America (Los Angeles)	• Significant dysregulation of several amino acids and lipids included tyrosine, proline, arginine and linoleic acid <i>de novo</i> lipogenesis observed with exposure of PFAS in children	139
PF OS				• Elevated concentration of PFAS caused liver fibrosis and lobular inflammation	
PF HxS					
PF OA	Children (7–19 years)	Plasma	United States (Atlanta)		
PF OS					
PF HxS					
PF OS	Pregnant women	Cord blood	China	• Hepatocellular ballooning was found in 40% of children	141
PF OA				• Exposure to PFAS has been shown to affect fetal growth such as body weight, head circumference, and body length at birth	
PF NA				• Impacts on estragon homeostasis also showed	
PF HxS				• Exposure to PDUmDA studied to have higher incidence of Atopic eczema or atopic dermatitis in girls children	142
PF OA	Children (0, 3 and 7 years)	Plasma	Norway	• Throat infection, pseudo-group bronchitis were observed in children at ages of 0-, 3- and 6-years kids	
PF OS				• The majority of girls child found to be infected	
PF UnDA					
PF OS	Children (7–8 years)	Plasma	United States (Boston)	• BMD affected by exposure to PFOS and PFOA substances	143
PF OA					
PF OS, PFOA	Pregnant women	Blood sample	Northern Norway	• The deregulation of thyroid homeostasis has been studied	144
PF NA, PF HxS					
PF UnDA					
PF DA					
PF HxS, PF OS	Children (5, 7 and 13 years)	Blood sample	Faroe Islands	• Fatal health have been affected by higher exposure to PFAS	
PF OA, PF NA					
PF DA					
PF HxS					
PF BA	—			• Children without given MMR vaccination at the age of 5 years, had the risk of allergic diseases and asthma	145
PF HxA					
PF BS				• Contact with PFOS and PFOA has been shown to induce estragon receptor activities and enhanced Astron secretion in H295R cells	
PF NA				• PFOA increased secretion of progesterone at higher concentrations (100 $\mu$ M) however, $<10$ $\mu$ M concentration did not showed any harmful impacts	146
PF HxS				• Dysfunction of kidneys and thyroid observed in that study	
PF DeA					
PF OA					
PF OS					

Table 2 (Contd.)

PFAS	Population samples	Exposure route measurements	Countries	Impacts on human life	References
PFOA	—	Human hepatocytes cells	Germany	• Liver cells dysfunctionalities were found at high concentration (100 $\mu$ M) of PFOA exposure to hepatocytes cells	148
PFOA	Adults	Semen sample	China	• Spontaneous acrosome reaction did not affect with contact of PFOA at 0.25 to 2.5 $\mu$ g ml <sup>-1</sup> concentrations	149
PFDA, PFOS	Women	Plasma	China	• In Chinese women, PFAS exposure has been linked to higher incidence of infertility	150
PFOA, PFUA					
PFD <sub>0</sub> A					
PFNA					
PFBS	Men and women	Blood sample	Italy	• PFAS contaminated drinking water, caused cerebrovascular diseases, diabetes, Alzheimer's disease and myocardial infarction	151
PFTA				• Risk of breast cancer and kidney infection observed	
PFOS					
PFDA					
PFBS					
PFOA, PFOS	Adults (18–25 years)	Blood lipids	U.S state	• A longitudinal study found that PFAS increased the risks of diabetes	152
PFHxS/ETFOSSAA				• Hypertriglyceridemia and hypercholesterolemia risks were also associated to exposure of PFAS	
MeFOSAA					
PFOA	Children (2–5 years)	Blood sample	America	• Children had thyroid dysfunctions (elevated FT4 level and reduction in THS) to exposure of PFAS through breastfeeding at early life stage	153
PFOS					
PFHxS					
PFNA					
PFDN					
PFOA	Mother and child pair	DNA methylome	Europe	• That study found that PFAS exposure may be caused significant respiratory diseases in children	154
PFOS	Pregnant women (mother-child pairs)	Blood sample	America	• Study analyzed symptoms of cerebral palsy (neurological disorder) in infants to high exposure level of PFAS through their mothers	155
PFOA				• Exposure to PFNA has been showed negative association with bone health	
PFNA	Children (8–12 years)	Blood sample	U.S state (Ohio)	• Low density lipoprotein cholesterol and increased of systolic blood pressure was observed	
PFOA				• Lower weight was observed in females prenatal with the association of PFHxS and PFOS	156
PFOS	Pregnant women	Maternal fasting blood sample		• Exposure to MeFOSAA, in early life stage, affected adiposity	
PFHxS					
MeFOSAA					
PFOS	Pregnant women	Pregnant women	Denmark	• Exposure to PFOA, PDFA, PFHxS and PFHps were linked with infant girls while PFHps and PFHxS with infant boys, but no significant impact was observed	157
PDFA					
PFHxS					
PFHps	Women	Blood sample	Canada	• Exposure to PFOS and PFHxS reduced fecundability (ability to conceive a pregnancy)	158
PFHxS					

Table 2 (Contd.)

PFAS	Population samples	Exposure route measurements	Countries	Impacts on human life	References
PFOS	172 mother-child pairs	Maternal cord serum	Faroe Islands	<ul style="list-style-type: none"> <li>PFAS has been shown negative association with head circumference, body weight and height</li> <li>PFOA and PFOS were responsive to elevated THs concentration, but did not show any impact on birth weight</li> <li>Study analyzed positive association between PFAS and low density lipoprotein cholesterol, total cholesterol and triglycerides</li> <li>Higher concentration of PFOA and PFOS was observed in diabetic participants as compared to non-diabetic</li> </ul>	159
PFOA	Men and women (20–40 years)	Blood sample	Korea (Seoul)		160
PFHxA, PFBS					
PFOS					
PFUnDA					
PFDS, PFDODA					
PFTrDA	Children (boys and girls, 10–16 years)	Blood sample	Norway	<ul style="list-style-type: none"> <li>PFHPA caused asthma in girls at age of 10 years</li> </ul>	161
PFOA					
PFHPA					
PFDA					
PFUnDA					
PFHxS				<ul style="list-style-type: none"> <li>Atopic dermatitis observed in girls to exposure of PFUnDA, PFDA and PFOA in boys</li> <li>In a cross- sectional study from Norway, it was observed that girls had higher risk of allergies than boys</li> <li>In Canada, a cohort research discovered that PFAS had no significant relationship with gestational weight growth</li> </ul>	162
PFHps					
PFOs					
PFOs	Pregnant women	Maternal plasma	Canada		
PFOA					
PFHxS					
PFOs, PFOA	Pregnant women (early stage of pregnancy)	Blood sample	China (Shanghai)	<ul style="list-style-type: none"> <li>Exposure to PFAS did not show any positive association with PE (preeclampsia) and GH (gestational hypertension) at birth time</li> </ul>	163
PFHUnDA					
PFHxS, PFDA					
PFBS, PFHPA					
PFOs, PFDOA					
PFOs	Men and women (>20 years)	Blood sample	United States	<ul style="list-style-type: none"> <li>The risk of diabetes in men was studied due to exposure of PFOA</li> <li>However, PFAS has been shown association with total cholesterol observed in adult candidates</li> <li>Toxic impacts such as liver cirrhosis, liver cancer, diabetes and malignant neoplasm were observed in PFs factory's workers due to high exposure of PFOA</li> </ul>	164
PFHxS					
PFOA					
PFOA	Male workers (PFS factory)	Blood sample	Italy	<ul style="list-style-type: none"> <li>Longitudinal study found immunotoxicity due to exposure of PFAS in offspring</li> <li>PFHxS caused a high risk of infections in girls children</li> <li>Otitis media, respiratory syncytial virus and pneumonia diseases were observed due to exposure of PFAS in children at age of 4 years</li> </ul>	165
PFOs and PFHxS	Mother child pair	Blood sample and questionnaires	Japan (Hokkaido)		166
PFOA and PFOS	Male adults (10–21 years)	OUS (quantitative ultrasounds)	Italy	<ul style="list-style-type: none"> <li>Elevated PFAS exposure may raise the incidence of osteoporosis (bone weakening) in men between the ages of 18 and 20</li> </ul>	167



Table 2 (Contd.)

PFAS	Population samples	Exposure route measurements	Countries	Impacts on human life	References
PFOA PFDoDA, PFUnDA, PFOS, PEBS	Pregnant women and mother-newborns pairs	Cord blood	China (Wuhan)	• PFOA and PFOS were positively correlated with 11-deoxy cortisol, cortisol and progesterone in newborns	168
PFDA PFOA	Adults ( $\geq 20$ years) Obese and non-obese	Blood sample	United States	• PFAS had impact on dysregulation of lipid biomarkers, including LDA and TC in obese participants • However, PFNA, PFHxS, PFOA were found to be positively correlated with caline amiotransferase in obese participants • Exposure to PFAS may lead to elevated TSH in male and reduced it in females during adolescence • PFAS may be responsible to increased TT3, TT4 in females	169
PFDA PFHxS PFHxS	Men, women and children (12–80 years)	Venous blood	United States	• A longitudinal study revealed that PFDA, PFOA, PFOS, PFHxA were positively linked with liver enzymes like ALT and ALP	170
PFOA PFOS, PFOA	Men and women (70, 75 and 80 years)	Blood sample	Sweden		171
PFOA PFDA, PFmDA PFDoDA PFHxA					171

genetic material, encompassing DNA damage, gene mutations, chromosomal defects, and alterations in genetic content. Recent studies have employed genotoxicity assays on human cells to evaluate the impact of oxidative stress-induced genotoxicity.<sup>65</sup>

Experiments on HepG2 cells have shown that PFOA can induce genotoxic effects. Research by ref. 66 and 67 suggested that among various PFCs, only those with eight or nine carbon atoms in their structure were capable of producing ROS or causing DNA damage in HepG2 cells. However, the observed impact was mild, and a clear dose-response relationship was not established.<sup>68,69</sup> PFCs also cause oxidative damage associated with nuclear receptor proteins that regulate gene expression.<sup>70</sup>

**3.3.3. Carcinogenic effects.** Carcinogenic effects refer to the ability of certain substances to cause cancer or enhance the risk of developing cancer. Extensive examination of the toxicity of PFOS and PFOA in rodents has shown severe hazardous impacts, particularly with the potential for liver cancer. Studies on rodents with long-term PFOA exposure reported an increase in liver tumor cases.<sup>71</sup>

The carcinogenic potential of PFOA has been shown in human MCF-7 breast cancer cells due to its estrogen-like properties, indicating the endocrine-disrupting capabilities of PFCs.<sup>72</sup> Additionally, PFOA and perfluoro-*n*-decanoic acid (PFDA) have been linked to an increased risk of breast cancer in Chinese women. This association is attributed to the disruption of hormone balance caused by the combined xenoestrogenic and xenoandrogenic activities of serum POPs, thereby increasing susceptibility to breast cancer.<sup>73</sup>

A study investigated the prevalence of cancer among workers of a perfluorooctane sulfonyl fluoride (POSF) manufacturing facility, finding that employees with higher exposure had a higher incidence of deaths due to bladder cancer.<sup>74</sup> However, there is still debate regarding a clear link between PFOA exposure and human disease incidence.<sup>75</sup> Studies on rodents have shown that PFOS and PFOA act as peroxisomal proliferators. Notably, peroxisome proliferators' carcinogenic potential does not appear to impact humans.<sup>71</sup>

The potential mechanisms of exposure to PFAS and cancer development can be broadly categorized into four significant aspects. Firstly, PFAS compounds can influence hormone receptors and disrupt the delicate balance of the endocrine system, leading to alterations in hormone receptors and potential hormonal imbalances.<sup>76</sup> Secondly, PFAS have been found to activate a specific receptor known as PPAR $\alpha$ . This activation can induce oxidative stress within the body, a state with excess harmful ROS. Oxidative stress is known to be detrimental to cellular health and can contribute to the development of cancer.<sup>77</sup> The third mechanism involves PFAS-induced epigenetic alterations, encompassing changes in DNA methylation patterns. It also modifies gene expression-regulating proteins, mostly histones. PFAS exposure-induced epigenetic changes may contribute to tumorigenesis.<sup>78</sup> Lastly, PFAS are associated with reproductive toxicity, potentially increasing susceptibility to carcinogens and impacting breast cancer risk.

**3.3.4. Immuno-toxicity.** Exposure to foreign substances can harm the immune system, potentially heightening the risk of developing allergies later. While there might not always be a direct link to inherited allergies, exposure to immunotoxic chemicals can still influence immune function. The outcome of such exposure depends on various factors, including age, sex, and individual genetic makeup. A study by ref. 79 examined different age groups, ranging from mother-newborn pairs to adults aged 50–65. The study found that asthma, allergic rhinitis, and eczema were prevalent among participants, with approximately 30% of the total 1092 participants across the five studies reporting these conditions. The study highlighted the widespread impact of allergies on individuals exposed to immunotoxic substances. PFCs can target immune cells and interfere with the production of cytokines, which are signaling molecules involved in immune responses. This interference can affect pro-inflammatory and anti-inflammatory cytokines, leading to dysregulation of the immune system's balance and potentially contributing to allergic reactions.<sup>80</sup>

**3.3.5. Reproductive toxicity.** Teratological effects of PFOS (potassium and lithium salts) on rats, rabbits, and mice were also investigated earlier in laboratory studies.<sup>81,82</sup> These studies observed developmental disorders, including decreased fetal weight, cardiac defects (ventricular septal damage and right atrium enlargement), anasarca (edema), and delayed bone ossification (sternebrae and phalanges). The highest treatment levels of PFOS resulted in structural abnormalities, reduced weight gain, and decreased food intake in pregnant women. It is worth noting that these birth disorders cannot be solely attributed to maternal malnutrition.<sup>82</sup> Comparisons between mice and rats revealed increased abnormalities in mice, although the reduction in maternal weight gain was less pronounced. Additionally, changes in parental and embryonic thyroid hormone levels were reported, indicating the potential reproductive toxicity of PFOS.<sup>82</sup>

The mechanism behind PFOS-induced neonatal death is currently unknown. However, PFOS targets organ systems that develop during the later stages of pregnancy, which aligns with previous research and teratological outcomes.<sup>83</sup> Additionally, PFOS-mediated organ failure contradicts postnatal survival, suggesting that lung development and pulmonary function may be a significant point of impact.<sup>84</sup> Instances of neonatal mortality linked to PFOS exposure share similarities to the effects of nitrofen, an herbicide known for interfering with fetal lung growth, leading to compromised cardiopulmonary function and increased neonatal rat mortality.<sup>85</sup> The research studies indicate observable changes in lung structure and size in PFOS-exposed newborns, resulting in hindered development of the lungs during the perinatal period.

As presented in Fig. 3(a), PFAS exposure has been associated with multiple adverse effects on the male reproductive system. Research has shown that PFAS compounds can interfere with hormone regulation, leading to disruptions in testosterone levels and sperm quality. An imbalance in hormone levels can lead to problems like lower sperm count, reduced sperm movement, and changes in sperm shape. Additionally, PFAS

exposure has been related to testicular damage and dysfunction, including testicular atrophy and impaired spermatogenesis. These effects can ultimately lead to fertility problems and reproductive disorders in males. PFAS exposure can also impact the female reproductive system in several ways, as presented in Fig. 3(b). Similar to males, PFAS can disrupt hormone regulation in females, affecting estrogen and progesterone levels. This hormonal imbalance can lead to menstrual irregularities, reduced fertility, and difficulties in conceiving. Compared to long-chain PFAS, short-chain alternatives like show weaker binding to hormone receptors and reduced transplacental transfer; however, some studies still report endocrine disruption and fetal development concerns at elevated doses.<sup>86</sup> Furthermore, prenatal exposure to PFAS has been correlated with reduced birth weight and elevated preeclampsia risk. Studies have also suggested a potential connection between PFAS exposure and an increased incidence of gynecological conditions like endometriosis and ovarian cysts.<sup>87</sup>

**3.3.6. Lipid metabolism disturbances.** PFOS has been noted to interfere with lipid metabolism in rodents and humans, mainly due to its structural resemblance to fatty acids.<sup>88</sup> Research on mice revealed that PFOS treatment disrupts the homeostasis of lipid metabolism, resulting in reduced liver glycogen storage and elevated serum glucose levels. Furthermore, PFOS has been shown to affect lipid balance, particularly the secretion and normal function of low-density lipoproteins.<sup>88</sup> PFOS primarily targets the liver, essential for detoxification and lipid metabolism, making it a significant site for PFOS action. Additionally, the liver serves as a bioaccumulation site for various pollutants.<sup>89</sup> PFOS has been found to impact the activity of hepatic genes associated with fatty acid processes, hormone regulation, and cholesterol metabolism.<sup>90</sup> Studies also suggest a relationship between gene expression related to cholesterol metabolism and exposure to PFOA or PFOS, potentially contributing to conditions like hypercholesterolemia and other health disorders.<sup>91</sup> The human biomonitoring studies have revealed that exposure to long-chain PFAS such as L-PFOS, PFOA, and PFDA is significantly associated with alterations in lipid metabolism, as well as increased levels of apolipoproteins (ApoB, ApoA1), fatty acids, and phospholipids. In contrast, PFHxS, a short-chain PFAS, did not show significant associations with cholesterol sub fractions, highlighting differential biological effects between PFAS types. These findings underscore the need for further human-focused investigations on how specific PFAS subclasses interact with lipid regulatory pathways and contribute to cardiometabolic risk, particularly given the growing prevalence of short-chain PFAS in the environment.<sup>92</sup>

**3.3.7. Endocrine disruptive effects.** The chemical structure of PFOS suggests that its interactions with serum proteins, especially the sulfonic acid group or the hydrophobic alkyl chain, maybe the underlying mechanism. PFOS targets specific serum proteins involved in vital endocrine and immunological functions, crucial for maintaining a healthy hormonal balance.<sup>93</sup> Exposure to PFCs has been shown to produce estrogenic effects in cell cultures using the 'E-screen assay'.<sup>94</sup> However, it's important to note that not all PFCs provoke the



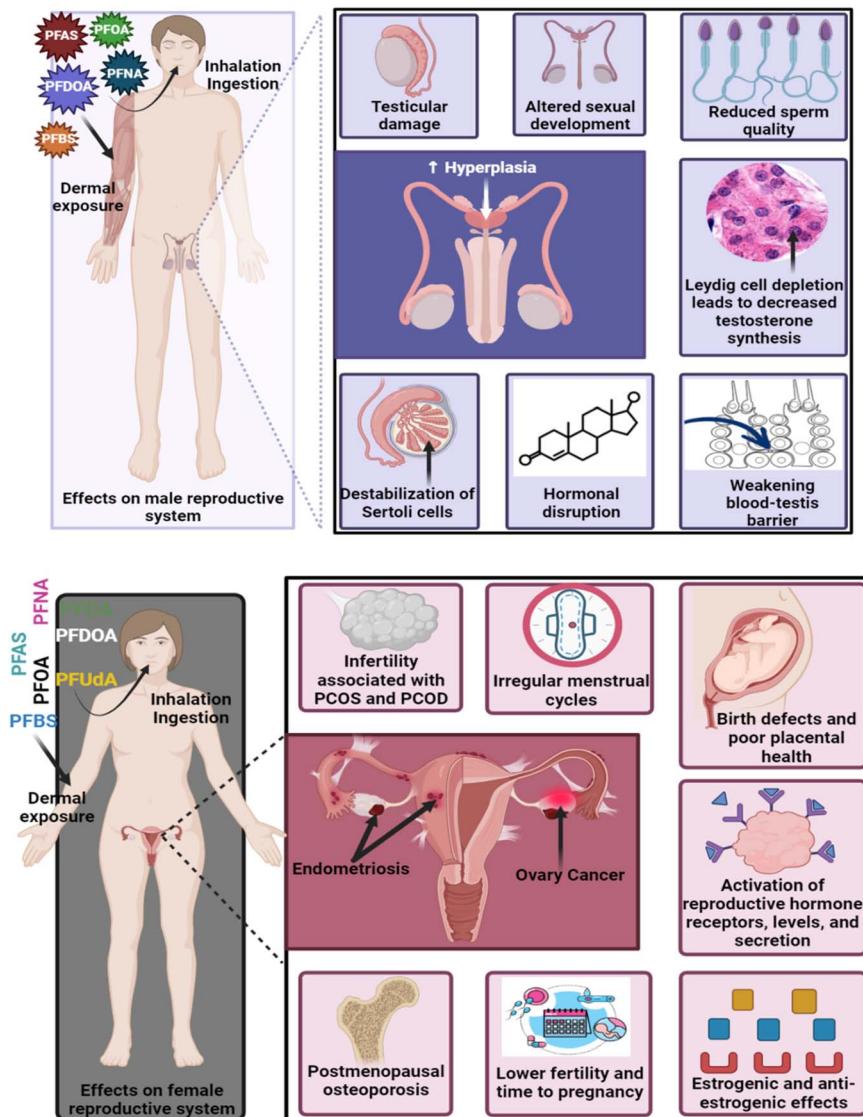


Fig. 3 Illustration of the health impacts of PFAS on male (a) and female (b) reproductive system.

same response. For instance, fluorotelomer alcohols like 6:2 FTOH and 8:2 FTOH have been found to stimulate breast cancer cell growth and enhance the estrogen receptor. In contrast, PFOS, PFOA, and PFNA don't exhibit similar effects.<sup>95</sup> Despite the variable effects of PFCs, they are recognized as potential disruptors of the endocrine system in adult rats, leading to altered hormonal function characterized by suppressed testosterone levels and elevated estradiol levels.<sup>96</sup>

Exposure to PFOA has been found to disrupt hormonal balance in rodents, resulting in Leydig cell hyperplasia and the formation of Leydig cell adenomas.<sup>97</sup> Studies on adult rats treated with greater than 5 mg perfluorododecanoic acid (PFDA) per kg body weight daily for two weeks have observed testicular damage, along with changes in gene expression, particularly the suppression of genes responsible for cholesterol transport and steroidogenesis, as well as a decrease in serum testosterone levels.<sup>98</sup> These alterations are concerning, as Leydig cell

hyperplasia is commonly observed in impotent men with lower testosterone levels compared to normal individuals.<sup>99</sup> Improper testicular function is associated with testicular dysgenesis syndrome (TDS).<sup>100</sup> It is believed that TDS is caused by exposure to endocrine disruptors during fetal development, which can affect testis formation and lead to impaired testicular function in adulthood, including reduced semen quality.

Research conducted on rats during crucial developmental periods has revealed testis dysgenesis marked by Leydig cell hyperplasia and Leydig cell aggregation in the testis center. This condition leads to decreased testosterone levels and reduced fertility in adulthood.<sup>101,102</sup> The impaired function of Leydig cells results in the reduced expression of genes responsible for steroidogenesis.<sup>103</sup>

**3.3.8. Interactions and dynamics in mammals and humans.** Earlier studies have underscored the presence of binding sites for PFOS in mammals, acting as a protective

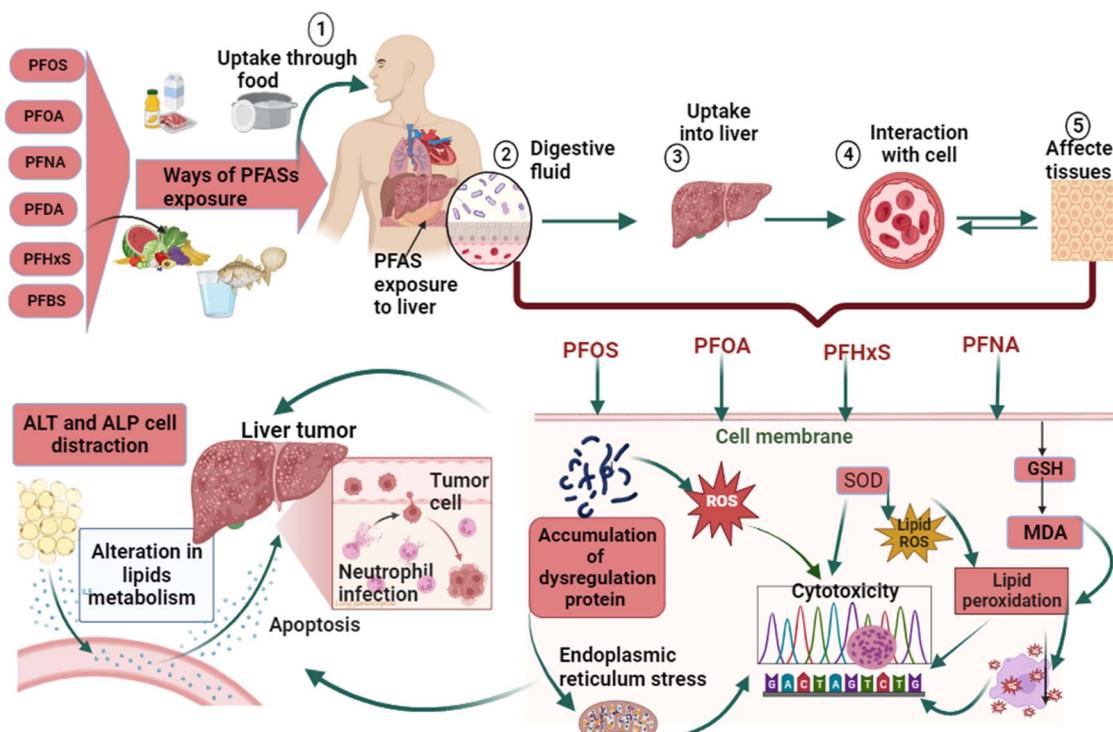


Fig. 4 Uptake, accumulation, and toxicity of PFAS exposure to human body.

mechanism against its harmful effects.<sup>104–106</sup> However, when the saturation level of these binding sites is surpassed, organisms exposed to high concentrations of free PFOS encounter toxic effects. Fig. 4 illustrates the potential uptake, accumulation, and toxicity of PFAS exposure in the human body. Mammalian studies have elucidated a clear concentration-effect relationship concerning the saturation of this binding pool. As long as the overall chemical burden within the organism remains within manageable limits, PFOS exposure is tolerated. It is evident that an escalation in the dosage results in a heightened mortality rate.<sup>107</sup>

Numerous investigations have delved into PFOS's capacity to bind with serum proteins, studying how it displaces steroid hormones from specific binding proteins in birds' and fish's serum. PFOS is constrained to displace estrogen or testosterone from carp serum steroid-binding proteins. However, it disrupts cortisone in avian sera at relatively low PFOS concentrations. Additionally, the disruption of corticosterone increases with the chain's length, with sulfonic acids being more effective than carboxylic acids.<sup>93</sup> The earlier research, which was focused on assessing the endocrine-disrupting potential of pollutants, mainly through non-receptor-mediated pathways, confirmed the interaction of contaminants with serum steroid-binding proteins as a potential mechanism. Previous research indicates that environmental pollutants like bisphenol A (BPA) and nonylphenol have limited efficacy in displacing human sex hormone-binding globulin (SHBG) ligands from SHBG to E2. Moreover, these contaminants have been found to increase the proportion of SHBG-unbound estradiol at 10 to 100 mM concentrations.<sup>108,109</sup>

Earlier investigations have indicated that humans exhibit an extended half-life for the serum removal of PFOS, PFHS, and PFOA.<sup>110</sup> Species-specific differences in pharmacokinetics may be attributed to saturable renal resorption mechanisms. The average duration of serum elimination was around 5.4 years and 4.8 years for PFOS, 8.5 years and 7.3 years for PFHS, and 3.8 years and 3.5 years for PFOA.<sup>110</sup> The extended half-life in humans for removing these substances might be due to differences in how they are excreted through bile and absorbed in the gut, possibly influenced by enterohepatic circulation.<sup>111</sup> Table 3 presents various human health effects of PFAS with detailed experimental insights.

## 4. Emerging regulation measures

Regulation measures for PFAS contamination typically involve a combination of prevention and remediation strategies. These include bans, restrictions, discharge limits, and drinking water standards at national and international levels. Fig. 5 represents the contamination pathways of short-chain PFASs, their impacts, and associated regulatory frameworks in drinking water systems.

### 4.1. European union regulations

Preventing the environmental release of PFAS necessitates implementing stringent measures and regulatory frameworks. Certain key PFAS producers have initiated a withdrawal from the market to reduce emissions. The 3M corporation undertook one such initiative, which was recognized as a pioneer of PFOA. They publicly declared on December 20, 2022, that they were



Table 3 Experimental insights into human health effects of PFAS

PFAS types (purity %)	Models used	PFAS doses (mg per kg per day)	PFAS exposure time (days)	Key conclusions	References
PFOS* ( $\geq 98\%$ )	Sprague–Dawley rats	PFOS – 0, 2, 20, 50 and 100	28	PFOS disrupts lipid balance and affects the endocrine system by reducing important hormones; however, it does not significantly impact the kidneys or cardiovascular system. PFOS primarily accumulates in the liver, with smaller amounts in the spleen and heart	172
PFOS (98%) PFOA* (96%)	Sprague–Dawley rats	PFOS – 5 and 20; PFOA – 5 and 20	28	Abnormal behaviour, substantial weight loss, and an enlarged liver were noted in the high-dose PFOS-exposed rats, with PFOS accumulation highest in the liver, followed by the heart, kidney, whole blood, lung, testicles, spleen, and brain, in that order	173
Potassium PFOS (87%)	C57BL/6 Mice	6, 12 and 24	23	Dietary PFOS led to a dose-dependent reduction in body weight, an increase in liver weight relative to the body, higher liver triglyceride levels, and elevated markers in the bloodstream, all pointing to liver toxicity and oxidative stress	174
PFOS ( $>98\%$ )	Sprague–Dawley rat	3	7	In PFOS-treated groups, liver weights were notably higher relative to body weights, with reduced serum thyroxine (TH) and no change in thyroid-stimulating hormone (TSH) levels. PFOS exposure caused lipid droplet formation, signifying TH disruption in both animals and humans, resulting in lower T4 and T3 levels in rats without TSH compensation	175
PFOS (98%) PFOA (96%)	C57BL/6 (H-2b) mice	PFOS and PFOA – 2, 10, 40	10	When comparing the impact of PFOS and PFOA on mice, both compounds, when administered at the same dose and duration (40 mg kg <sup>-1</sup> for 10 days), led to similar effects. These effects included liver enlargement (hepatomegaly), reduced body weight, decreased thymus and spleen weights, fewer cells in the thymus and spleen, which also affected different cell subpopulations related to the immune system, and structural changes in the thymus	176
PFOS (98%)	CD-1 mice	1, 5 and 10	21	Mitochondria dysfunction and the elevation of oxidative stress could promote the development of steatohepatitis	177
PFOS (98%)	C57BL/6J mice	2.5, 5, and 10	30	PFOS exposure induced hepatomegaly with dose-dependent increases in liver weight. Histopathology showed liver damage, edema, hepatocellular necrosis, and inflammation in PFOS-exposed mice	178
PFOA	Sprague–Dawley rats	1 and 10	14	The findings of this study revealed that a dose of 10 mg kg <sup>-1</sup> of PFOS in rats resulted in cardiac toxicity, characterized by heightened apoptosis and an upregulation of proinflammatory cytokines	179
PFOA ( $>98\%$ )	Kunming mice	1, 2.5 and 5	—	The current study found that maternal PFOA exposure had a minor influence on the testicular index of offspring mice. However, as the PFOA dosage increased the testes suffered varied degrees of damage	28
PFOA	Sprague–Dawley rats	0.5; 1.0; 3.0 and 6.0	28	PFOA exposure disrupts the male reproductive axis by affecting the hypothalamus, pituitary gland, and testis. This disruption involves changes in noradrenaline concentration, gonadotropin-releasing hormone (GnRH) gene expression, and hormone secretion	180
PFOS	Sprague–Dawley rats	5 and 10	21	Rats exposed to low dosages of PFOS during puberty may experience significant delays in the formation of Leydig cells, which is caused by the interruption of Leydig cell-specific gene expression. Furthermore, PFOS exposure is associated with lower seminal vesicle weights and reduced sperm counts	181

Table 3 (Contd.)

PFAS types (purity %)	Models used	PFAS doses (mg per kg per day)	PFAS exposure time (days)	Key conclusions	References
PFOS	C57 mice	0.5 and 10	35	The current study showed that PFOS can reduce sperm production in mice. This effect is linked to a decrease in germ cell proliferation and an increase in apoptosis within the testis. These observations indicate that PFOS-induced testicular toxicity is influenced by estrogen receptors (ERs). PFOS can damage sertoli cells and weaken the blood-testis barrier (BTB), which can allow PFOS to pass through the testes and cause abnormalities in male reproduction	182
PFOS	ICR mouse	0.25 and 50	28	The data indicated that PFOS led to a substantial reduction in sperm count and compromised the integrity of the blood-testis barrier (BTB)	183
PFOS ( $\geq 98\%$ )	ICR mice	0.5, 5 and 10	28	PFOS exhibits maternal and developmental toxicity in mice which causes early miscarriages, reduced survival after birth, delays in the growth and development of the whole body, and sex-specific changes in pubertal maturation, where male offspring show faster sexual maturation than female offspring	184
PF OA	Pregnant CD-1 mice	1, 3, 5, 10, 20, and 40	17	Male reproductive function may be adversely affected by PFOA exposure, as it interferes with testosterone levels and causes damage to the seminiferous tubules, resulting in decreased testosterone levels in the testes and an increase in spermatogonial apoptosis	185
PF OA (96%)	BALB/c mice	0.31, 1.25, 5 and 20	28	PFOS acts as an endocrine disruptor, lowering testosterone synthesis and altering fetal Leydig cells in rats, which affects the male reproductive system	186
PFOS	Pregnant Sprague-Dawley rats	5 and 20	19	PFOS exposure reduced serum testosterone levels in a dose-dependent manner, potentially affecting Leydig cell development in offspring, and additionally, it decreased adrenal hormone aldosterone	187
PFOS	Pregnant Sprague-Dawley rats	1 and 5	20	Mice exposed to PFOS had a greater concentration of apoptotic cells compared to the control group. This elevated apoptotic cell count was linked to the generation of reactive oxygen species (ROS) by PFOS, which led to the dissipation of mitochondrial membrane potential and triggered apoptosis in splenocytes and thymocytes. Additionally, PFOS exposure resulted in increased activities of glutathione reductase, catalase, and superoxide dismutase	188
PFOS ( $> 98\%$ )	C57BL/6 mice	1, 5, and 10	7	The prenatal exposure to PFOS can disrupt the balance of antioxidant systems, leading to oxidative stress, and trigger caspase-dependent death pathways in the lungs of rat offspring	189
PFOS ( $> 98\%$ )	Sprague-Dawley rats	0.1 and 2.0	21	Mice exposed to PFOS may experience cognitive deterioration, this could be due to the activation of a particular pro-apoptotic pathway generated by endoplasmic reticulum stress in the cerebral cortex neurons	190
PFOS	C57BL/6J mouse	0.2, and 2.0	6 months	The gestational exposure to PFOS can lead to lung issues in offspring like bronchopulmonary dysplasia (BPD), potentially contributing to the rise in developmental lung diseases	191
PFOS	Sprague-Dawley rats	1 and 5	18		192

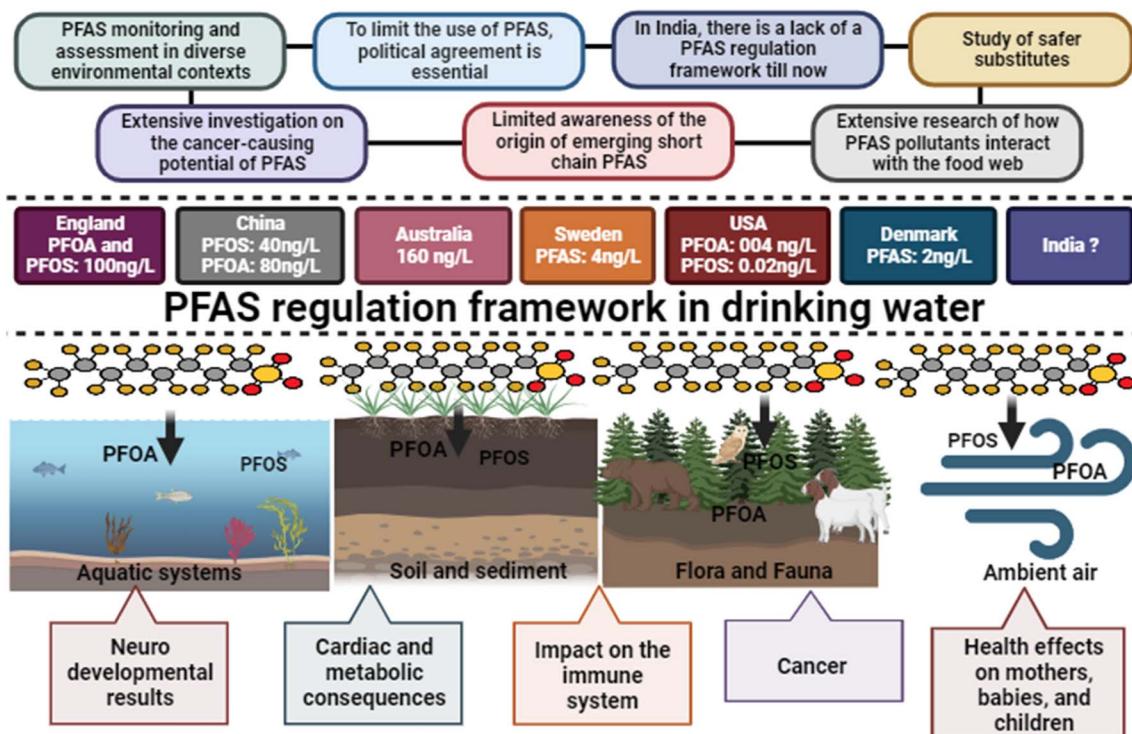


Fig. 5 Short-chain PFAS contamination, pathways, impacts and regulatory framework in drinking water.

committed to discontinuing the production of PFAS by the conclusion of 2025.<sup>112</sup>

The European Union (EU) has taken significant steps to address PFAS through various policy instruments. The EU Registration, Evaluation, Authorization, and Restriction of Chemicals (EU REACH) proposed restrictions on PFAS on February 7, 2023.<sup>113</sup> These restrictions were targeted at the manufacturing, usage, and trade of these ECs. After that, PFAS substances have been banned unless their concentration is below 25 ppb for C9-C14 PFCAs and their salts or 260 ppb for C9-C14 PFCA-related substances.

Under REACH, PFAS substances are increasingly being classified as Substances of Very High Concern (SVHC), and restrictions have been proposed on their manufacture, use, and trade. This list has seen the addition of some short-chain groups of PFAS, which consist of substances like 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propionic acid and their salts, acyl halides, PFBS, and PFHpA and their salts. In May 2020, Denmark prohibited the application of PFAS in food contact materials (FCMs). This law has been in effect and stipulates that paper and cardboard FCMs cannot be sold. Such targeted national bans have corresponded with measurable reductions in PFAS concentrations in sewage sludge, surface waters, and wildlife. However, it does allow for exceptions regarding PFAS use in FCMs if these products incorporate a functional barrier effectively preventing food contamination through PFAS.<sup>114</sup>

On February 20, 2025, the French Parliament passed pioneering legislation to phase out PFAS, targeting their widespread use and environmental persistence. The law bans PFAS

in cosmetics, textiles, ski wax, and footwear by 2026, extending to all textiles by 2030, with exemptions for protective gear. It mandates PFAS monitoring in drinking water and introduces the "polluter pays" principle to hold polluting companies financially accountable. This legislation, following Denmark's example, positions France as a leader in PFAS regulation and may influence broader EU policy, advancing a unified framework for managing these hazardous substances across member states.<sup>115</sup> Additionally, under the EU POPs Regulation, PFOS and PFOA compounds are strictly limited to trace amounts (0.001% by weight for PFOS and 0.0000025% by weight for PFOA), with exemptions allowed only for laboratory research or unintentional contamination.<sup>114</sup>

Within the EU, the principal legal framework overseeing water quality and access for human use is the Drinking Water Directive. This directive categorizes PFOS and related compounds as priority substances under water policy. A recent update in 2020 introduced new criteria, setting the 'PFAS Total' threshold at  $0.5 \mu\text{g L}^{-1}$  and a maximum of  $0.1 \mu\text{g L}^{-1}$  for the 'Sum of PFAS' in drinking water.<sup>116</sup>

#### 4.2. United states regulations

The United States Environmental Protection Agency (US EPA) has taken a proactive approach through a series of regulatory frameworks, including the PFAS Strategic Roadmap, the Clean Water Act (CWA), and the Safe Drinking Water Act (SDWA).

In October 2021, the US-EPA unveiled its PFAS Strategic Roadmap. The title for this was EPA's Commitments to Action 2021–2024, and it details a comprehensive strategy comprising

31 specific initiatives falling under the EPA's regulatory purview.<sup>117</sup> These initiatives are structured to be implemented over varying timeframes, encompassing discrete and ongoing projects. Key unresolved action points include:

On April 10, 2024, the U.S. EPA finalized drinking water standards for six PFAS under the National Primary Drinking Water Regulation (NPDWR). The rule sets legally enforceable Maximum Contaminant Levels (MCLs) at 4 ppt for PFOA and PFOS, and 10 ppt for PFNA, PFHxS, and HFPO-DA (GenX). It has also led to increased investment in PFAS treatment technologies and voluntary phase-outs. A Hazard Index approach is also adopted to address combined exposure from PFAS mixtures.<sup>118,119</sup>

In December 2022, the EPA issued guidance under the National Pollutant Discharge Elimination System (NPDES) framework permitting system for state-level agencies to limit PFAS discharges into water bodies from industrial sources. In August 2022, the EPA proposed designating PFOA and PFOS as hazardous substances under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), signaling significant consequences for environmental cleanup initiatives and legal responsibilities regarding liability.

In 2024, the U.S. EPA finalized PFAS reporting and record-keeping requirements under Toxic Substances Control Act (TSCA) Section 8(a)(7). Entities that have manufactured or imported PFAS or PFAS-containing products since January 1, 2011, must report detailed data on usage, volumes, disposal, exposures, and hazards. However, due to resource constraints, the EPA delayed implementation, with the reporting portal now scheduled to open in July 2025 and close in January 2026.<sup>115</sup>

#### 4.3. Other global regulations

**4.3.1. Australia.** The Intergovernmental Agreement on a National Framework for Addressing PFAS Contamination, a collaborative effort of the Australian federal, state, and territorial governments, was established in 2018. This agreement aimed to create an associational position statement that reflects the collective viewpoint of Australian governments, emphasizing the need for prudent restrictions on PFAS use to the greatest extent possible. Furthermore, it outlined objectives for preventing the application of PFAS within the Australian context.<sup>120</sup>

**4.3.2. New Zealand.** On December 21, 2022, the Environmental Protection Authority of New Zealand issued fresh regulations regarding Aqueous Film-Forming Foam (AFFF). These regulations, which occurred on January 1, 2023, explicitly prohibit using PFAS-containing firefighting foams. This prohibition applies specifically to AFFF formulations that incorporate compounds related to PFOA.<sup>121</sup>

**4.3.3. Asia.** China, Japan, and South Korea are taking decisive steps to regulate and oversee the utilization of PFAS, primarily focusing on compounds such as PFOS, PFOA, and perfluorohexane sulfonate (PFHxS). Across Asia-Pacific, regulatory actions on PFAS are intensifying. On June 30, 2025, Japan amended its food safety standards to include limits on PFOS and PFOA in mineral water, enhancing consumer protection. Taiwan's Ministry of Environment, on May 13, 2025, updated its toxic chemical substance regulations by adding PFOS and PFOA

salts to the controlled list. In Australia, the Water Services Association (WSAA) emphasized the need to address PFAS at the source, presenting key strategies to a Senate Select Committee on January 23, 2025 (ref. 122 and 123). In March 2023, China increased its dedication by including two long-chain PFAS in its updated List of New Pollutants for Priority Management. This inclusion is aimed at meticulous regulation and restriction of their production, usage, importation, and exportation. In October 2022, Japan and its neighboring country, South Korea, introduced fresh trade requirements specifically to PFOA, reinforcing their commitment to PFAS management.<sup>114</sup> Learning from this, even though the Bureau of Indian Standards (BIS) adopted the International Standards Organizations criterion for sampling and testing of PFOA and PFOS in 2020, more urgent action is required to address the uncontrolled use of toxic chemicals like phthalates and PFAS in consumer products used by adults and children, such as single-use plastics, processed food, packaging, and personal care and cosmetics. These products are the main sources of contact with serious negative effects on the environment and human health. The lack of data on the manufacturing, distribution, and usage of PFAS drive the urgent need for high-quality toxicological and epidemiologic studies in Indian scenario to quantify, evaluate, and assess the effects and mechanisms of these chemicals implicated in the development of early-onset chronic diseases, particularly health concerns related to women and children.

#### 4.4. Policy development directions and recommendations

While PFAS regulations are gaining momentum globally, further progress requires coordinated, forward-looking policies.

(i) The adoption of unified health-based guideline values for various PFAS beyond PFOA and PFOS is crucial to harmonize protection standards across regions. (ii) Precautionary regulation of PFAS as a chemical class, rather than individual compounds, can address the issue of regrettable substitution, as seen with GenX and ADONA. (iii) Integrating source control with polluter-pays mechanisms would strengthen environmental accountability, as exemplified by recent French legislation. (iv) Policies should incentivize development and certification of PFAS-free alternatives and safe disposal technologies. (v) Real-time PFAS occurrence and compliance monitoring systems must be embedded within policies to allow data-driven refinement of regulations. In addition, international coordination, possibly under platforms like the OECD or Stockholm Convention, could streamline efforts for sustainable PFAS management.

## 5. Conclusions

The review addresses the concerns surrounding PFAS and their alternatives, which are synthetic chemicals widely used in various consumer products. These substances exhibit persistence in the environment and accumulate in the bodies of animals and humans, posing potential health risks. Prolonged exposure to elevated levels of PFAS can result in adverse effects on organs, tissues, and cells, including developmental and

reproductive toxicity, immune system dysfunction, and an increased susceptibility to cancer. It is acknowledged that the accumulation of PFOS in the liver and serum disrupts normal liver function and may lead to liver damage. The ability of PFOS to interact with serum proteins has been the subject of numerous studies, which have examined how it removes steroid hormones from particular binding proteins in the serum of fish and birds. The ability of PFOS to remove testosterone or estrogen from carp serum steroid-binding proteins is limited. Even at relatively low PFOS concentrations, it does, however, interfere with cortisone in avian sera. Furthermore, the length of the chain increases the disruption of corticosterone, with sulfonic acids being more efficient than carboxylic acids. The interaction of pollutants with serum steroid-binding proteins was verified as a viable mechanism by earlier research, which evaluated the endocrine-disrupting potential of pollutants, mainly through nonreceptor-mediated pathways.

Although some of these health effects are well-documented, many studies have yet to establish the connection between PFAS accumulation and damage to various organs, underscoring the need for ongoing research to gain a more comprehensive understanding of potential risks. Through this extensive analysis, the review intends to contribute to a more profound knowledge of the health impacts of short-chain PFAS and provide insights for global regulatory strategies to address their risks effectively. Notably, even within EU member countries and across U.S. states, various agencies have independently enacted distinct policies before adopting more comprehensive union or federal directives.

## Author contributions

Srinithi Mayilswami, Nirav P. Raval, Rinki Tomar, Shailja Sharma – conceptualization, methodology, graphical design, writing—original draft, review and editing, and visualization. Sarva Mangala Praveena, Navish Kataria, Rangabhashiyam Selvasembian, Saravanan Ramiah Shanmugam – conceptualization, guidance, facilitation, writing—review, and editing. Ravinder Nath, Arindam Malakar, Sudeshna Dutta, Santanu Mukherjee – Supervision, data interpretation, and writing—review and editing.

## Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Abbreviations

ADONA	4,8-Dioxa-3 <i>H</i> -perfluorononanoate
AFFF	Aqueous filmforming foam
Cl-PFAES	Chlorinated polyfluorinated ether sulfonates
F53B	Chlorinated polyfluoroalkyl ether sulfonic acid
CERCLA	Comprehensive environmental response, compensation, and liability act

EPA	Environmental protection agency
EU	European union registration, evaluation, authorization, and restriction of chemicals
REACH	Fluorinated ethylene propylene
FEP	Hexafluoropropylene oxide
HFPO	Hexafluoropropylene oxide dimer acid
MCLs	Maximum contaminant levels
NPDES	National pollutant discharge elimination system
PFAS	Per- and polyfluoroalkyl substances
PFA	Perfluoroalkoxy alkanes
PFCs	Perfluoroalkylated compounds
PFBS	Perfluorobutane sulfonic acid
PFBS	Perfluorobutanesulfonate
PFDA	Perfluorododecanoic acid
PFHpA	Perfluoroheptanoic acid
PFHxS	Perfluorohexane sulfonate
PFDA	Perfluoro- <i>n</i> -decanoic acid
PFNA	Perfluorononanoic acid
PFOS	Perfluorooctane sulfonic acid
POSF	Perfluorooctanesulfonate
PFOA	Perfluorooctanoic acid
PFPE's	Perfluoropolyether
PFTrDA	Perfluorotridecanoic acid
PPAR $\alpha$	Peroxisome proliferator-activated receptor alpha
POPs	Persistent organic pollutants
PTFE	Polytetrafluoroethylene
PVDF	Polyvinylidene fluoride
ROS	Reactive oxygen species
SHBG	Sex hormone-binding globulin
SVHC	The substance of very high concern
TDS	Testicular dysgenesis syndrome

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Supplementary information is available. See DOI: <https://doi.org/10.1039/d4va00405a>.

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