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REVIEW ARTICLE

# Ubiquitously Occurring Perfluoroalkyl and Polyfluoroalkyl Substances: An Overview of Food and Environmental Contamination and Implications for Human Health

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## Abstract

Perfluoroalkyl and polyfluoroalkyl substances (PFAS), commonly known as 'forever chemicals' are synthetic, anthropogenic compounds widely used in food packaging, processing equipment and nonstick surfaces. Their strong carbon–fluorine bonds make them highly persistent in the environment and within living organisms, including humans. This review focuses on the chemical structures of PFAS, their similarity to fatty acids, environmental contamination pathways, their entry into the food chain and water systems, their biological behaviour and their adverse health effects. Presented observations suggest that the harmful effects of PFAS pollutants may be even more far-reaching, as they may jeopardise the function of the cardiorespiratory, neurological and reproductive systems in humans. PFAS analogues exhibit exceptionally long biological half-lives in humans with 2.7 to 5.1 years for perfluorooctanoic acid (PFOA), 3.4 to 5.7 years for perfluorooctane sulfonate (PFOS) and 2.8 to 8.5 years for perfluorohexane sulfonate (PFHxS), often persisting in blood and tissues for several years after exposure has ceased. This prolonged retention allows PFAS to accumulate over time, increasing the likelihood of chronic exposure and long-term health consequences even at low environmental concentrations. Evidence-based regulations by food and environmental regulatory agencies, along with projections of the impacts of regulatory intervention are needed to protect public health.

**Key words:** Fluorocarbons; PFAS; Forever chemicals; Food contamination; Bioaccumulation; Adverse effects; Environmental pollution.

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*"What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison."*
Paracelsus (1493-1541)

## Introduction

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) constitute a large and diverse class of synthetic fluorinated organic compounds that have attracted global attention due to their environmental persistence, widespread distribution and potential adverse effects on human health.[1] The term PFAS encompasses thousands of individual compounds characterised by carbon chains in which hydrogen atoms are partially or fully replaced by fluorine. The carbon–fluorine bond is considered one of the strongest covalent bonds in organic chemistry, imparting exceptional chem-

ical stability and resistance to thermal, chemical and biological degradation.[2] These chemical properties underpin both the industrial utility of PFAS compounds and their reputation as "forever chemicals."

## Historical perspectives

Anthropogenic PFAS compounds were first synthesised in the early 1940s, during a period of rapid industrial development and expansion in polymer chemistry during World War II. Their unique physicochemical and surfactant properties, particularly resistance to water, oil and heat, led to widespread use across numerous industrial sectors.[1] Applications include non-stick cookware coatings, grease-resistant food packaging, waterproof textiles, stain-resistant carpets, industrial lubricants and aqueous film-forming foams (AFFFs) used in firefighting operations.[3] The extensive use of PFAS in consumer products and industrial applications has resulted in sustained environmental releases over several decades, often without adequate safety assessment of long-term ecological exposure and of human health consequences.

For much of the 20th century, PFAS were considered biologically inert because of their apparent chemical stability. However, advances in analytical detection methods in the late 1990s and early 2000s revealed the presence of PFAS in environmental matrices and biological samples worldwide.[2] PFAS have since been detected in surface water, groundwater, soil, sediments, wildlife and human serum across diverse geographic regions, including remote and industrially undeveloped areas.[4] Their presence in the polar ecosystems, together with evidence of long-range atmospheric and oceanic transport, confirms that PFAS are contaminants of global concern rather than localised pollutants.

One defining feature of PFAS contamination is its persistence in environmental and biological systems. Unlike many organic pollutants that degrade through microbial activity, photolysis, or hydrolysis, PFAS resist these processes and can remain intact for decades.[1] This persistence facilitates their gradual accumulation in ecosystems and food webs. Aquatic systems are particularly vulnerable, as PFAS readily dissolve in water and are transported through rivers, lakes and groundwater, frequently contaminating drinking water supplies.[3] From these systems, PFAS enter the food chain through uptake by plants, invertebrates, fish and terrestrial animals, ultimately reaching humans primarily through dietary exposure.[4]

The relevance of PFAS to food safety has attracted growing scientific and regulatory interest. Food contamination can occur through multiple pathways, including the use of contaminated irrigation water, bioaccumulation in livestock and aquatic organisms and migration from PFAS-treated food-contact materials, such as packaging and processing equipment. Given the central role of food consumption in human exposure, understanding PFAS behaviour within food systems is critical for accurate toxicological risk assessment and the development of effective public health policies.

At the biological level, PFAS exhibit properties that distinguish them from many traditional persistent organic pollutants. Rather than preferentially accumulating in adipose tissue, PFAS bind strongly to proteins, particularly serum albumin and liver transport proteins, resulting in prolonged biological half-lives in humans. Structural similarities between PFAS and endogenous fatty acids enable these compounds to interact with lipid metabolism pathways, hormone transport mechanisms and nuclear receptors involved in gene regulation.[1, 2] These interactions raise concerns about chronic, low-dose exposure and its potential to disrupt physiological processes over time.

Epidemiological and experimental studies have increasingly linked PFAS exposure to a range of adverse health outcomes. Reported associations include immune suppression, altered thyroid hormone levels, liver dysfunction, metabolic disturbances, developmental effects, reduced fertility and an increased risk of certain cancers,[4, 5] Although the strength of evidence varies among individual PFAS compounds, the growing body of literature underscores the need for precautionary, science-driven approaches to PFAS management.

In response to mounting evidence of environmental persistence and health risks, regulatory agencies in several regions have begun imposing restrictions on specific PFAS compounds, partic-

ularly long-chain PFAS such as perfluorooctanoic acid (PFOA) and perfluoro-octanesulfonic acid.[3] Nevertheless, regulatory efforts face significant challenges, including the large number of PFAS, the continued use of replacement compounds with limited toxicological data and the technical difficulty of remediating contaminated environments. These challenges have prompted calls for class-based regulation and a comprehensive evaluation of PFAS as a chemical class rather than on a compound-by-compound basis.[5]

This review synthesises current knowledge on PFAS analogues, with a particular focus on their chemical structures, environmental distribution, biological interactions and relevance to food contamination and human health. By integrating mechanistic insights with exposure pathways, it highlights the implications of continued PFAS use and underscores the importance of evidence-based regulatory strategies to mitigate long-term environmental and public health risks.

## Proliferation and chemical structures compared with fatty acids

The extensive proliferation of PFAS in the environment is closely linked to their unique chemical structures and physicochemical properties. PFAS comprise a broad class of compounds defined by an alkyl carbon chain in which hydrogen atoms are partially or completely substituted by fluorine atoms. This fluorination fundamentally alters the molecule's behaviour, conferring exceptional stability and resistance to degradation. As a result, PFAS have been produced and used in large quantities for decades, leading to their widespread distribution across environmental, biological and food systems.[6]

## Chemical structure of PFAS

Most PFAS consist of three key structural components:

1. A linear or branched carbon backbone
2. A perfluorinated or partially fluorinated tail
3. A hydrophilic functional head group, typically a carboxylate ($-COO^-$) or sulfonate ($-SO_3^-$)

Long-chain PFAS, such as PFOA and perfluorooctanesulfonic acid (PFOS), contain seven or more fully fluorinated carbon atoms and are particularly persistent and bioaccumulative.[2] The replacement of hydrogen atoms with fluorine increases molecular size, electronegativity and bond strength, producing compounds that are chemically inert under most environmental and biological conditions.[7] PFAS are a large class of synthetic fluorinated organic chemicals characterised by a perfluoroalkyl carbon chain attached to a functional head group. The general structure formula is:

$$C_nF_{2n+1}-R$$

Were,

- $C_nF_{(2n+1)}$ = perfluoroalkyl hydrophobic tail
- $R$ = hydrophilic functional group[1, 4]

Example: PFOA structure is shown in Figure 1 and PFOS physicochemical properties in Table 1.

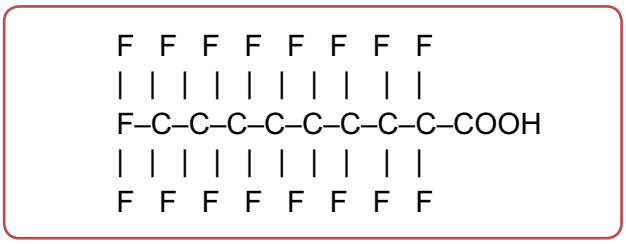


*Figure 1: Simplified chemical structure of perfluorooctanoic acid (PFOA), showing a fully fluorinated carbon chain and a carboxylic acid head group*

*Table 1: Summary of key physicochemical properties of perfluorooctane sulfonate (PFOS) compounds and their relevance to environmental behaviour*

| Chemicals property | Quality | Environmental implications | Ref |
|---|---|---|---|
| Carbon–fluorine covalent bond strength | Extremely strong | High resistance to degradation | [8] |
| Water solubility | Moderate to high (compound-dependent) | Long-range aquatic transport | [9] |

| | | | |
|---|---|---|---|
| **Volatility** | Low (terminal PFAS) | Persistence in water and soil | [9] |
| **Amphiphilicity** | Hydrophobic tail, hydrophilic head | Surfactant behaviour, mobility | [10] |
| **Protein affinity** | Strong | Bioaccumulation in organisms | [10] |
| **Environmental half-life** | Years to decades | Years to decades | [11] |

*PFAS: perfluoroalkyl and polyfluoroalkyl substances;*

## Comparison with natural fatty acids

PFAS share notable structural similarities with endogenous fatty acids, which are essential biological molecules involved in energy storage, membrane structure and cell signalling pathways. Fatty acids typically consist of a hydrocarbon chain with a terminal carboxylic acid group. This resemblance enables PFAS to act as structural mimics, thereby interacting with biological systems that normally process fatty acids.[4, 12] PFAS structurally resemble fatty acids because both contain a hydrophobic chain and polar head group, but their chemical properties differ significantly. Structural comparison diagram is shown in Figure 2 and major food categories at risk of PFAS analogues contamination in Table 2.

Despite these similarities, PFAS differ critically from fatty acids in their chemical behaviour. Fatty acids are biodegradable and readily metabolised through enzymatic pathways such as β-oxidation. In contrast, PFAS resist metabolic breakdown due to the strength of the carbon–fluorine bond, rendering them effectively non-biodegradable in both environmental and biological systems.[1, 12]

Natural fatty acid: $CH_3–(CH_2)^n–COOH$
PFAS (PFOA): $CF_3–(CF_2)^n–COOH$

*Figure 2: Comparison of a natural fatty acid and perfluorooctanoic acid (PFOA), illustrating hydrogen substitution by fluorine*
*PFAS: perfluoroalkyl and polyfluoroalkyl substances;*

*Table 2: Major food categories at risk of perfluoroalkyl and polyfluoroalkyl substances (PFAS) contamination*

| Food category | Primary PFAS exposure route | Risk factors | Ref |
|---|---|---|---|
| **Fish and seafood** | Contaminated water, bioaccumulation in aquatic food webs | Often, the highest PFAS levels globally are a strong contributor to total intake | [13] |
| **Meat** (beef, pork, poultry) | Contaminated feed and drinking water for livestock | Organ meats may show higher PFAS; wide regional variation | [13] |
| **Dairy products** | Contaminated feed, water and environmental exposure | PFAS detected in milk and related products | [14] |
| **Eggs** | Contaminated feed; soil/water exposure | Elevated concentrations have been observed in backyard and commercial eggs | [15] |

| | | | |
|---|---|---|---|
| **Vegetables and grains** | Irrigation with contaminated water, soil uptake | Generally lower levels, but a notable contribution where soils are contaminated | [16] |
| **Packaged foods** | Migration from PFAS-treated packaging | Higher PFAS levels seen in heat-processed and high-fat foods | [17, 18] |

## Implications of structural similarity

The structural similarity between PFAS and fatty acids has significant biological implications. PFAS can bind to fatty acid–binding proteins, serum albumin and nuclear receptors involved in lipid metabolism, including peroxisome proliferator-activated receptors (PPARs).[2] However, unlike natural fatty acids, PFAS do not undergo normal metabolic processing, resulting in prolonged tissue retention and disruption of physiological pathways.

This mimicry contributes to PFAS interference in:

- Lipid transport and storage
- Hormone signalling pathways
- Energy metabolism
- Gene regulation associated with cell growth and immunity.

## Role of chemical structure in proliferation

The chemical stability conferred by fluorination directly contributes to the environmental proliferation of PFAS. Their resistance to heat, acids, bases and microbial degradation allows PFAS to persist throughout industrial use, wastewater treatment and environmental transport. Furthermore, their amphiphilic nature, with both hydrophobic and hydrophilic regions, facilitates movement through aqueous environments whilst enabling binding to organic matter and biological tissues.[19]

PFAS have been detected worldwide in surface and groundwater, agricultural soils, food products, wildlife and human serum. Long-chain PFAS are particularly prone to bioaccumulation and biomagnification leads to increasing concentrations at higher trophic levels in food webs.[20] In summary, the widespread proliferation of PFAS is intrinsically linked to their chemical structure. Their fluorinated carbon chains confer extraordinary stability and persistence, while their structural similarity to fatty acids enables interactions with biological systems. These combined features explain both the industrial success of PFAS and the significant challenges they pose to environmental safety, food security and human health.[21]

## Physicochemical properties of PFAS

The PFAS exhibit a distinctive set of physicochemical properties that collectively explain their widespread industrial use, environmental persistence and biological relevance. These properties arise primarily from the high degree of fluorination along the carbon backbone, which profoundly alters molecular reactivity, polarity and stability. Understanding these properties is essential for interpreting the environmental behaviour, transport mechanisms and toxicological potential of PFAS.[22]

One defining characteristic of PFAS molecules is the strong carbon–fluorine (C–F) covalent bond, which is among the strongest single bonds in organic chemistry. The high bond strength of C-F is a result of high electronegativity of fluorine, strong bond length (~1.35 Å) and strong orbital overlap. This bond strength confers extreme resistance to thermal degradation, chemical oxidation, reduction and hydrolysis.[22, 23] Consequently, most PFAS molecules are highly stable under a range of severe conditions, whereas other organic contaminants degrade rapidly. This chemical stability is a primary reason PFAS persist in environmental compartments, including water, soil and sediments, as well as in foods.

PFAS also display unique amphiphilic behaviour, meaning they possess both hydrophobic and hydrophilic characteristics within the same molecule. The fluorinated carbon chain is strongly hydrophobic and oleophobic, while the terminal functional groups (eg carboxylate or sulfonate) are hydrophilic and often ionised under harsh environmental conditions. This combination confers surfactant properties on PFAS molecules, enabling them to accumulate at interfaces between air and water or oil and water.[24] These surfactant properties contribute to their effectiveness in industrial applications such as firefighting foams and grease-resistant coatings, while simultaneously facilitating environmental mobility.

Another important feature of PFAS is their higher water solubility, particularly for short-chain and ionic forms. Unlike many persistent organic pollutants that preferentially partition into sediments or lipids, many PFAS remain dissolved in aqueous systems, thereby enhancing their transport through rivers, groundwater and drinking water distribution networks.[25] This behaviour complicates containment and remediation efforts, as PFAS can migrate far from their original sources of release.

PFAS are also characterised by low volatility, particularly among ionic species, which limits removal by evaporation or air stripping. However, certain neutral and volatile PFAS precursors can undergo atmospheric transport and degrade into more stable terminal PFAS, contributing to secondary environmental contamination.[26] This transformation pathway further extends the environmental lifetime of PFAS as a chemical class.

From a biological perspective, PFAS exhibit chemical stability within living organisms, resisting enzymatic degradation and metabolic biotransformation. Their persistence in biological systems is closely linked to their affinity for proteins rather than lipids. This protein-binding behaviour distinguishes PFAS from many other hydrophobic contaminants and contributes to their long biological half-lives in humans and wildlife.[27] Consequently, repeated low-level exposure can lead to bioaccumulation in body organs, with higher concentrations over time.

PFAS also exhibit structural diversity within a common chemical framework, spanning a wide range of chain lengths, functional groups and degrees of fluorination. This diversity results in variability in environmental behaviour and toxicity among individual PFAS compounds. Nevertheless, their shared properties, including persistence, mobility and resistance to chemical degradation, justify greater scientific and regulatory considerations of PFAS as a chemical class rather than as isolated substances.[28]

Overall, the general physicochemical properties of PFAS molecules, including robust chemical stability, amphiphilic nature, high water solubility, low biodegradability and strong protein affinity, collectively contribute to their widespread environmental distribution and long-term persistence in biological systems. These same properties make PFAS technologically valuable tools and underlie the significant challenges associated with their environmental management and health risk mitigation.[5, 28]

## Major mechanisms of PFAS toxicity

### a. Binding with serum proteins

PFAS bind strongly to human serum albumin (HSA) through electrostatic and hydrophobic interactions. Mechanism: The hydrophobic fluorinated tail interacts with protein hydrophobic pockets and the anionic head group interacts with positively charged residues. This results in long biological half-lives.[4]

### b. Activation of nuclear receptors

PFAS activate peroxisome proliferator-activated receptor alpha (PPAR-α). Mechanism: PFAS enters hepatocytes and binds to the PPAR-α ligand-binding domain, activating transcription of lipid metabolism genes. Consequences:

i) Hepatomegaly
ii) Lipid metabolism disruption.[4, 5]

### c. Interaction with cell membranes

Due to surfactant properties, PFAS alter membrane fluidity and permeability.[4]

# Environmental contamination

Environmental contamination by PFAS is a direct consequence of their high industrial production, widespread use and extraordinary prolonged persistence in the environment. Over several decades, PFAS have been continuously released into the environment through industrial activities, con-

sumer product use, waste disposal and emergency firefighting applications. Once released, their resistance to biodegradation enables long-term persistence and global dispersion across multiple environmental compartments, including soil, groundwater, air, oceans, food and microbiota.[29]

## Sources of environmental release

Primary sources of PFAS contamination include manufacturing facilities, metal electroplating operations, textile manufacturing plants and sites where AFFFs are used extensively, such as military bases and airports.[30] Secondary sources include consumer products, such as food packaging, nonstick cookware and treated textiles, which release PFAS during use, washing and waste disposal. Wastewater treatment plants are a significant point source, as conventional treatment processes are largely ineffective at removing PFAS, allowing these substances to enter surface waters and sewage sludge.[31]

Landfills further contribute to environmental contamination through several leachates containing PFAS, which can infiltrate surrounding soil and groundwater. Agricultural application of PFAS-contaminated biosolids has also been identified as an important source of soil contamination and subsequent crop uptake.[32]

## PFAS-induced aquatic systems contamination

Aquatic environments are particularly vulnerable to PFAS contamination because many PFAS compounds are highly water-soluble and persistent. Once released, PFAS readily migrate through rivers, lakes, groundwater aquifers and coastal waters. Numerous studies have documented PFAS contamination of drinking water sources worldwide, often at concentrations exceeding health-based guideline values.[33]

In surface waters, PFAS can persist for extended periods and undergo long-range transport, resulting in contamination far from the original source. Groundwater contamination is of particular concern because remediation is technically challenging and costly and contaminated aquifers may remain unsafe for decades.[34]

## Soil and sediment contamination

PFAS contamination of soils occurs primarily through atmospheric deposition, irrigation with contaminated water, biosolid application and infiltration of landfill leachate. While some PFAS are highly mobile in soil, others adsorb to organic matter and mineral surfaces, resulting in long-term retention in terrestrial environments.[35] Sediments act as both sinks and secondary sources, releasing PFAS back into overlying water under changing environmental conditions. Soil contamination has direct implications for food safety, as PFAS can be taken up by crops and enter terrestrial food webs. Studies have demonstrated species-specific differences in PFAS uptake, influenced by soil properties, PFAS chain length and functional groups.[32]

## Atmospheric transport and global distribution

Although many PFAS compounds are non-volatile, certain PFAS precursors can volatilise and undergo atmospheric transport. These precursors may later degrade into stable terminal PFAS, thereby contributing to contamination in remote regions, including polar environments.[35] This mechanism explains the detection of PFAS in ecosystems with no direct industrial activity and underscores their global distribution.

## Ecological impacts and bioaccumulation

PFAS contamination has measurable effects on ecological systems. Aquatic organisms, particularly fish and invertebrates, readily accumulate PFAS from contaminated water and sediment. Unlike traditional lipophilic pollutants, PFAS bioaccumulate via protein binding, resulting in elevated concentrations in blood, liver and other organs.[36] Biomagnification has been observed in aquatic food webs, increasing exposure risks for predatory species, including humans. Chronic PFAS exposure in wildlife has been linked to growth retardation, reproductive impairment in males and females and immune system modulation, raising serious concerns about long-term safety, ecosystem resilience and adverse effects on human health.

As noted earlier, environmental contamination by PFAS is widespread, persistent and multifaceted, involving interconnected pathways across water, soil, air, plants and microbiota. Their unique chemical properties enable long-range persistence and long-term accumulation, making PFAS a global environmental issue that pos-

es significant challenges for remediation, food safety and ecological protection.[37] Summary of PFAS-related adverse health effects in humans is shown in Table 3.

*Table 3: Summary of perfluoroalkyl and polyfluoroalkyl substances (PFAS)-related adverse health effects in humans*

| Organ | PFAS-related adverse effects | Mechanism |
|---|---|---|
| Liver | Hepatic steatosis, elevated ALT/AST enzymes and cholesterol synthesis | PPAR-α activation, protein binding, lipid dysregulation |
| Thyroid gland | Thyroid hormone dysfunction, autoimmune thyroid effect | Competition for transport proteins and receptor binding interference |
| Metabolic and cardiovascular effects | High cholesterol, dyslipidaemia | Altered lipid metabolism, inflammation |
| Brain development | Low birth weight, cognitive and motor delays | Placental transfer, endocrine disruption, epigenetic changes |
| Immune dysfunction | Reduced antibody response, increased vulnerability to viral and bacterial infections | NF-κB activation, immune gene modulation |

*NF-κB: nuclear factor kappa-B; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PPAR: peroxisome proliferator-activated receptor;*

## Breakdown of PFAS

PFAS are resistant to natural degradation but can be broken down using advanced technologies.

Major degradation mechanisms:

A. Thermal destruction (incineration)
It requires high temperature to break C–F bonds, (temperatures > 1000 °C):

$$C_n F_{(2n+1)} COOH \rightarrow CO_2 + HF + CF_4$$

B. Electrochemical oxidation
i. PFAS adsorb onto the electrode surface.
ii. Electron transfer induces C–F bond cleavage.
iii. Sequential defluorination produces fluoride ions.

C. Plasma oxidation- Cold plasma generates radicals (OH, $e^-$) that attack PFAS.
i. Radical attack on the functional head group
ii. Chain shortening
iii. Fluoride release.

D. Photocatalytic degradation, UV light with catalysts (eg $TiO_2$) produces reactive radicals.[6, 32]

## Human exposure

Human adults and children are exposed to PFAS through environmental and consumer pathways. Ingestion of contaminated food and drinking water is a primary route of exposure. Especially, human populations are at greater risk near industrial sites, firefighting training areas and military installations, where PFAS have been used extensively. Owing to their persistence, mobility and resistance to degradation, PFAS are frequently detected in drinking water sources worldwide and pose long-term health risks to affected communities.[38]

Dietary exposure is also a significant contributor to human body burdens of PFAS. Persistent exposure to PFAS can lead to accumulation in plant-derived products via contaminated irrigation water and soil-root uptake and to biomagnification in the food chain, resulting in higher concentrations of PFAS in fish and seafood.[39] Food packaging materials containing PFAS can transfer these substances directly into food, particularly during heat treatment and with high-fat foods, thereby increasing the total dietary content of PFAS.

In addition to ingestion, exposure to contaminated indoor environments and dietary snack products is another pathway. PFAS have been detected in indoor air, house dust and a variety of household products, including stain-resistant textiles, cleaning agents, water-repellent clothing and personal care products. These exposures occur via incidental dust ingestion, inhalation of airborne particles and dermal contact, though the relative contributions of each pathway vary by compound and use pattern.[40]

Bioaccumulation and biomagnification further complicate human exposure to PFAS, as these substances have been detected in human blood, breast milk and other tissues due to their resistance to metabolism and slow elimination from the body. These characteristics lead to persistent and enhanced accumulation in internal organs over time, even under low-level environmental exposures.[41] Studies mapping PFAS occurrence across multiple environmental media reinforce the ubiquity of these chemicals and the diversity of potential human exposure pathways, reporting measurable PFAS levels in water, food, indoor dust, air and consumer products. This broad presence supports the concept that daily cumulative human exposure arises from multiple overlapping sources.[42]

Overwhelming evidence indicates that although drinking water and diet often represent the largest quantified exposures to PHFC substances, inhalation and dermal pathways, particularly in occupational or high-use settings, can contribute to enhanced body burden. Notably, exposure varies with age and exposure behaviour; for example, young children may receive higher PFAS doses relative to body weight due to hand-to-mouth behaviour and greater dust ingestion.[38]

## Tissue uptake and protein binding

Unlike many persistent organic pollutants that preferentially accumulate in adipose tissue, PFAS exhibit a distinct toxicokinetic profile, with a strong affinity for proteins rather than lipids. After ingestion, PFAS are efficiently absorbed in the gastrointestinal tract and rapidly distributed via the systemic circulation, where they bind extensively to serum proteins, particularly albumin and liver fatty acid–binding proteins.[43] This strong protein binding governs the preferential accumulation of PFAS in highly perfused organs, particularly the liver, kidneys and immune-related tissues. Experimental and human biomonitoring studies consistently show elevated PFAS concentrations in hepatic tissue, reflecting both active uptake by hepatocytes and limited metabolic transformation.[44] Renal accumulation is similarly pronounced, as PFAS are filtered by the kidneys and then substantially reabsorbed in the proximal tubules via organic anion transporters.[45]

In addition to the liver and kidneys, PFAS have been detected in immune organs such as the spleen and thymus, supporting growing evidence that these compounds may interfere with immune function.[46] The distribution pattern can be summarised as follows:

> Ingestion → systemic circulation → protein-bound transport → organ-specific retention, with limited redistribution to adipose tissue compared to other hydrophobic pollutants.

The exceptional persistence of PFAS in the human body is largely explained by their resistance to biotransformation and their strong binding to plasma and tissue proteins, which limits renal elimination. As a result, many legacy PFAS compounds have biological half-lives ranging from several years to decades in humans.[47] Long-chain PFAS analogues such PFOA, PFOS and perfluorohexane sulfonate (PFHxS) have been detected to persist in human serum for many years, with meta-analyses of exposed populations reporting typical half-lives of approximately 2.7 to 5.1 years for PFOA, 3.4 to 5.7 years for PFOS and 2.8 to 8.5 years for PFHxS.[1] National biomonitoring data also report similar persistence, noting that long-chain PFAS may circulate in human blood for 3 to 9 years or more, whereas short-chain PFAS molecules such as perfluorobutanoic acid (PFBA) and perfluorobutane sulfonic acid (PFBS) are eliminated more rapidly, often within days to weeks after exposure stops. This prolonged retention leads to cumulative internal organ exposure even when external environmental concentrations are relatively low.[48]

Overall, the unique protein-binding behaviour of PFAS distinguishes them from other environmental contaminants and underpins their long-term bioaccumulation in humans. Understanding these mechanisms is critical for interpreting biomonitoring data, assessing health risks and developing effective exposure-reduction strategies.[46]

## Competitive interaction in biological processes

PFAS can compete with endogenous ligands at critical biological binding sites, thereby disrupting normal physiological signalling pathways. Due to their structural similarity to fatty acids, several PFAS can bind to fatty acid transport proteins and fatty acid–binding proteins, which play central roles in lipid transport, storage and energy homeostasis.[48] By occupying these sites, PFAS may alter the cellular uptake and intracellular trafficking of natural fatty acids, thereby disrupting lipid metabolism pathways in the body.

PFAS analogues have also been shown to interact with nuclear hormone receptors, including PPARs, oestrogen receptors, thyroid hormone transport proteins and androgen receptors. Activation or inhibition of these receptors by PFAS can modify gene expression patterns involved in metabolic regulation, endocrine signalling and cellular differentiation.[49] In particular, PFAS-mediated activation of PPAR-α has been linked to altered lipid metabolism and energy balance, whereas interference with thyroid hormone signalling may affect foetal growth and nervous system development.[49]

This competitive binding behaviour disrupts hormonal homeostasis by reducing the availability of endogenous hormones at their target receptors or transport proteins. Several epidemiological and experimental studies have linked PFAS exposure to altered circulating levels of thyroid hormones, sex steroids and metabolic hormones, suggesting endocrine-disrupting potential even at environmentally relevant concentrations.[50] Such disruptions are of particular concern during sensitive life stages, including foetal development, infancy and adolescence, when hormonal signalling is critical for normal growth and organ maturation.

In addition to adverse endocrine effects, PFAS-induced competition for protein-binding sites may influence metabolic programming and developmental processes. By perturbing lipid and hormone signalling pathways, PFAS exposure has been linked to changes in body weight regulation, glucose metabolism and developmental timing.[51] These mechanistic insights support growing evidence that PFAS can exert long-term biological effects through subtle but persistent interference with protein-mediated processes.

Taken together, PFAS's ability to compete with endogenous molecules for key protein-binding sites is a central mechanism underlying their metabolic, endocrine and developmental toxicity. This mode of action helps explain the observed associations between PFAS exposure and chronic health outcomes, despite relatively low external exposure levels.[52]

## Cell signalling and genetic expression

In addition to competitive protein binding, PFAS can directly interfere with cellular signalling pathways and gene regulation, thereby altering fundamental biological processes. PFAS can modulate intracellular signalling cascades involved in metabolism, inflammation, oxidative stress and cell proliferation. These effects are largely mediated through interactions with transcription factors and nuclear receptors that regulate gene expression.[53] One of the most well-characterised mechanisms is PFAS-induced activation of PPARs, particularly PPAR-α and PPAR-γ. Activation of these receptors alters the transcription of genes involved in lipid metabolism, fatty acid oxidation, glucose homeostasis and energy balance.[53] Sustained modulation of these pathways may contribute to the metabolic dysregulation observed in populations exposed to PFAS.

PFAS analogues have also been shown to influence mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signalling pathways, which are critical for cell survival, differentiation and immune responses. Disruption of these pathways can alter cellular responses to external stimuli and impair the regulation of apoptosis and proliferation.[54] Such signalling perturbations may underlie associations between PFAS exposure and immune dysfunction or altered tissue development.

At the genomic level, PFAS exposure has been linked to changes in gene expression profiles and epigenetic modifications, including DNA methylation and histone modifications. These changes can alter transcriptional activity without changing the DNA sequence, potentially leading to long-lasting biological effects even after external exposure decreases.[55] Emerging evidence suggests that PFAS-induced epigenetic alterations

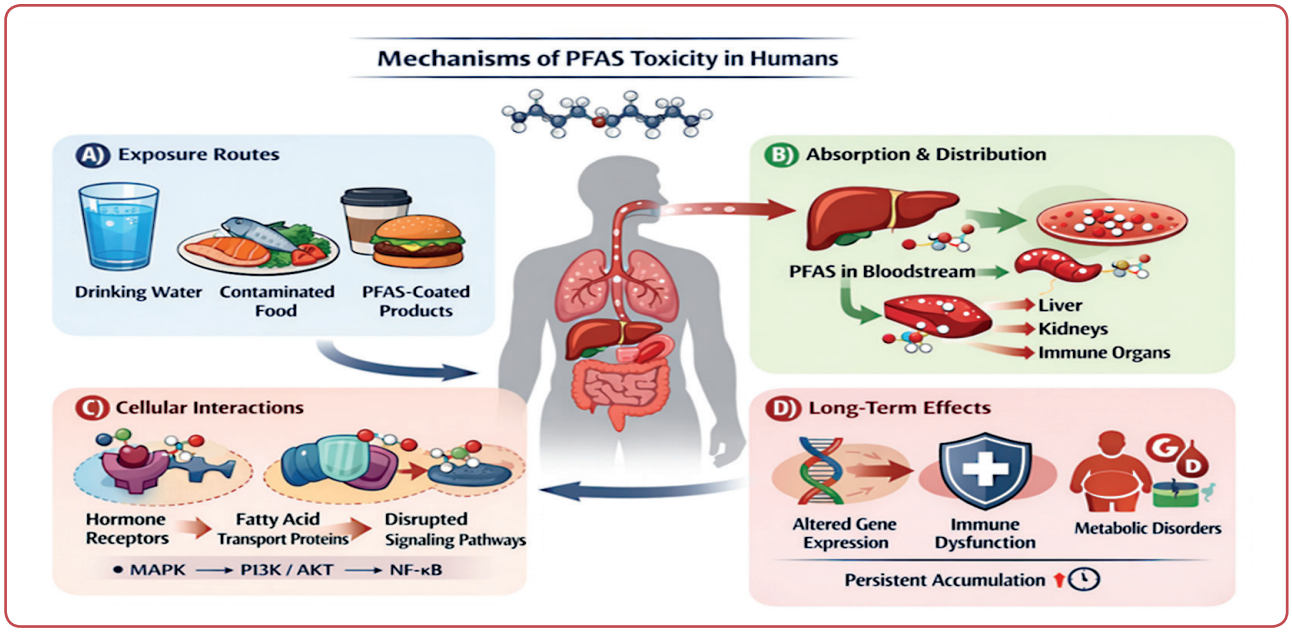


*Figure 3: Diagrammatic representation of the various toxicity sources and mechanisms involved in human perfluoroalkyl and polyfluoroalkyl substances (PFAS)-associated risk*

may contribute to developmental programming and disease susceptibility later in life.

In addition, PFAS can induce oxidative stress and inflammatory signalling, thereby activating redox-sensitive transcription factors, including nuclear factor κB (NF-κB). Activation of these pathways may promote low-grade chronic inflammation, which has been implicated in metabolic disorders, immune dysregulation and other adverse health outcomes.[54]

Collectively, disruption of cell signalling networks and gene expression appears to be a critical mechanism through which PFAS exert systemic and long-term biological effects. These molecular alterations provide mechanistic support for epidemiological associations between PFAS exposure and metabolic, immune and developmental outcomes, underscoring the importance of molecular-level investigations for PFAS risk assessment (Figure 3).

## PFAS compounds as food contaminants

PFAS molecules can enter the human food supply through several key environmental and industrial pathways. Agricultural water and soil contaminated with PFAS, whether from polluted irrigation sources, biomass amendments, or atmospheric deposition, can lead to plant uptake and accumulation in crops.[13] Contaminated animal feed and grazing areas result in the transfer and biomagnification of PFAS in livestock and poultry, contributing to elevated levels in meat and dairy products. In addition, PFAS can migrate from food packaging into food, particularly when packaging is heated or when food comes into direct contact with PFAS-treated materials.[14, 15]

A simplified pathway for PFAS movement through the food system is as follows:

Soil → Water → Environment → Plants → Foods → Humans

Global evidence indicates that seafood and fish are among the most significant dietary sources of PFAS, particularly in regions with industrial contamination of water bodies.[16] Animal-derived foods, such as meat, eggs and dairy, also contain measurable concentrations of PFAS, though levels vary by region and livestock exposure.[17] Plant-derived foods generally have lower PFAS levels, yet irrigation with contaminated water

and soil accumulation can still contribute to human intake.[18] Consumer behaviour and food processing further influence PFAS dietary exposure. Ultra-processed foods and those packaged in fluorinated materials may increase PFAS intake compared with minimally processed foods, underscoring the role of packaging and processing in dietary exposure pathways.[17]

*Table 4: Perfluoroalkyl and polyfluoroalkyl substances (PFAS)-linked health effects on immunity, carcinogenesis and reproduction in humans*

| Health domain | Observed adverse effects | Mechanism |
|---|---|---|
| Immune system | Reduced vaccination response and increased susceptibility to viral and bacterial infections | NF-κB signalling modulation, altered cytokines and chronic immune suppression |
| Cancer | Kidney, testicular and some other cancers | Genotoxicity, epigenetic changes, oxidative stress |
| Reproduction and fertility | Reduced fertility, altered sex hormones and pregnancy complications | Endocrine disruption, interference with gametogenesis, placental transfer and foetal ailments |

# Health hazards associated with PFAS analogues

PFAS analogues have been linked to a wide range of adverse health outcomes in humans (Figure 4). Scientific evidence from epidemiological studies, animal models and mechanistic research indicates that chronic exposure to PFAS can affect multiple organ systems and physiological pathways. The severity and type of health effects often depend on exposure level, duration, chemical type and the life stage at which exposure occurs.[56]

## Liver toxicity

PFAS molecules accumulate preferentially in the liver due to strong binding to hepatic transport and fatty acid–binding proteins. Chronic exposure is associated with elevated liver enzymes (ALT, AST), hepatic steatosis and altered lipid metabolism. Activation of PPAR-α by PFAS may contribute to hepatic hypertrophy and dysregulation of cholesterol synthesis, leading to long-term metabolic consequences.[57] Long-term consequences of PFAS exposure are linked to hepatomegaly or enlargement of the liver due to lipid accumulation, non-alcoholic fatty liver disease (NAFLD), altered lipid metabolism via PPAR-α activation. It also causes oxidative stress and altered cholesterol metabolism- Increased liver enzyme levels: ALT and AST.[4]

## Thyroid disorders

PFAS analogues can interfere with thyroid hormone transport proteins, such as thyroxine-binding globulin. and compete for binding to thyroid hormone receptors. Epidemiological studies have linked PFAS exposure to hypothyroidism, altered T3/T4 ratios and autoimmune thyroid disease, particularly in populations with prenatal or early postnatal exposure.[58] Children and pregnant women are particularly susceptible because thyroid hormones are critical for foetal brain development, postnatal growth and learning.

## Dyslipidaemia and cardiovascular risk

PFAS exposure has been consistently associated with elevated total cholesterol, LDL cholesterol and triglyceride levels. Mechanistically, PFAS-mediated activation of PPAR-α alters lipid metabolism, while chronic low-grade inflammation may contribute to atherosclerotic risk.[59]

## Developmental and reproductive effects

Prenatal and early postnatal exposure to PFAS chemicals is associated with intrauterine growth retardation and low birth weight, delayed motor and cognitive development and impaired immune responses. PFAS compounds can cross the placenta

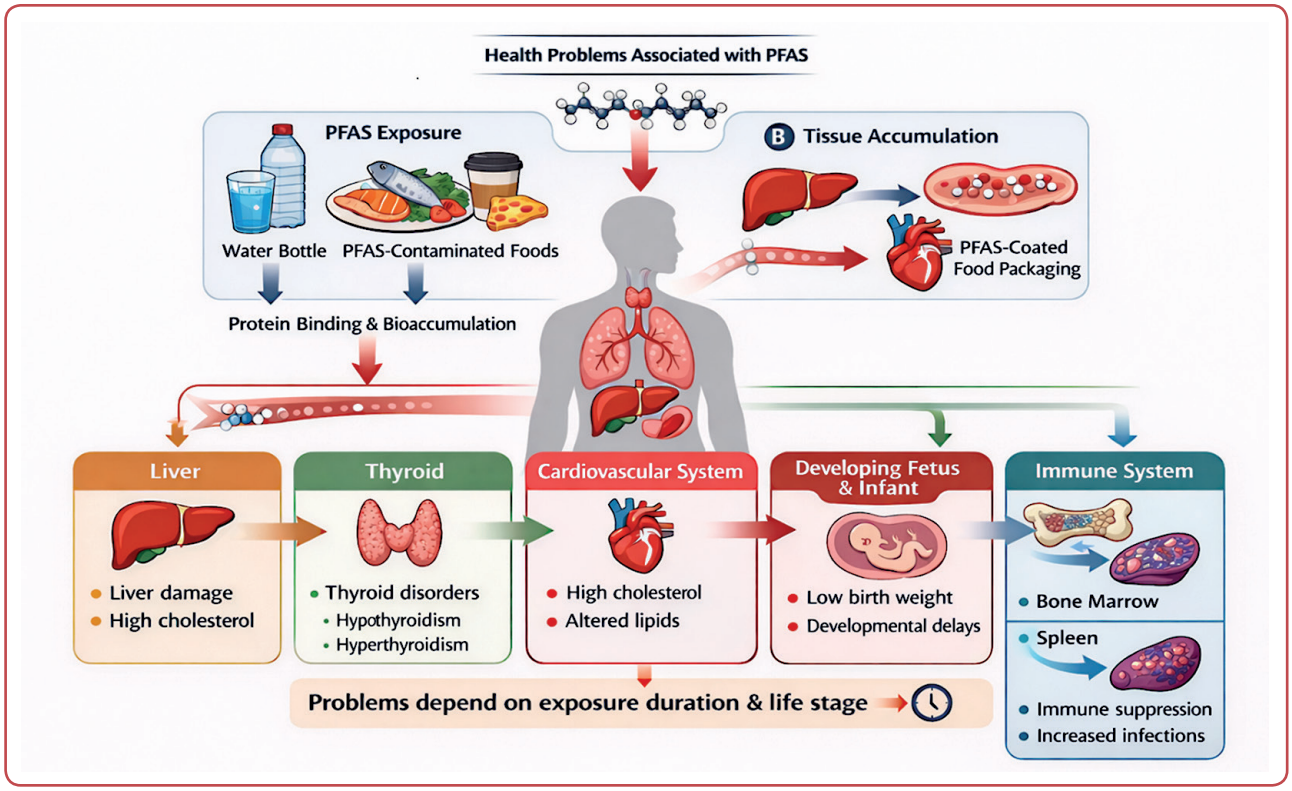


*Figure 4: Diagrammatic representation of the various health problems and purported mechanisms involved in perfluoroalkyl and polyfluoroalkyl substances (PFAS)-related risk in humans*

*Table 5: Examples of perfluoroalkyl and polyfluoroalkyl substances (PFAS) regulatory limits in developed countries*

| Country | Regulatory standard | PFAS analogues | Regulations |
|---|---|---|---|
| United States (EPA) | 0.004 µg/L (lifetime health advisory) | PFOA, PFOS | Apply to drinking water; non-enforceable advisory |
| European Union (EFSA) | 4.4 ng/kg body weight/week | Sum of PFOA and PFOS | Apply to drinking water; non-enforceable advisory |
| Canada (Health Canada) | 0.0002 mg/L | PFOA, PFOS | Drinking water guidelines |
| Sweden and Norway | Ban on certain long-chain PFAS | Multiple analogues | Includes PFOS-based firefighting foams |
| Australia | 0.07 µg/L | PFOA, PFOS | Drinking water guidelines |

*Note: Regulatory limits vary by chemical type, exposure pathway and national risk assessment frameworks. PFOA: perfluorooctanoic acid; PFOS: perfluorooctane sulfonate;*

and are secreted in breast milk, thereby exposing nursing infants to these compounds during critical developmental periods. Animal studies further support associations with impaired fertility and altered pubertal timing after chronic PFAS exposure.[56, 60]

## Impaired immunity, cancer and infertility

A few studies have shown that the adverse effects of PFAS compounds are associated with systemic impacts on the immune system, male and female reproductive health and carcinogenesis (Table 4). These effects are largely mediated by PFAS's

protein-binding properties, interference with endocrine functions and hormonal pathways and modulation of gene expression and are amplified in sensitive populations, including children, pregnant women and lactating women.[4, 56]

## Impaired immune response

PFAS exposure has been consistently linked to reduced vaccine-specific antibody responses, impaired immune cell function and altered cytokine signalling. Epidemiological studies have documented lower antibody titres to routine vaccines (eg diphtheria, tetanus and measles) among children with higher serum PFAS concentrations. Mechanistically, PFAS can modulate NF-κB signalling and the expression of immune mediators, leading to chronic low-grade immune suppression and increased susceptibility to infection.[61]

## Cancer risk

Chronic exposure to PFAS has been linked to increased risk of kidney and testicular cancers, among other malignancies. Potential mechanisms include genotoxicity, epigenetic modifications, oxidative stress and dysregulation of hormonal and growth pathways. Although risk varies by PFAS type and exposure level, evidence from highly exposed populations shows statistically significant associations with cancer incidence, underscoring the need for continuous monitoring and risk assessment.[62]

## Infertility and reproductive effects

PFAS are endocrine-disrupting chemicals that can interfere with reproductive hormones, follicular development and spermatogenesis. Women exposed to elevated PFAS levels have shown longer time-to-pregnancy, reduced fertility and higher rates of pregnancy complications, while men may show reduced sperm quality and altered testosterone levels.[63, 64] PFAS can cross the placental barrier, thereby exposing the developing foetus and contributing to adverse long-term reproductive and developmental outcomes.

## Vulnerable populations

Children and pregnant women are particularly susceptible due to ongoing immune system development, rapid hormonal changes and foetal exposure. Prenatal exposure may result in altered organogenesis, impaired immune system development and increased susceptibility to diseases later in life.[56]

## Transplacental passage and foetal effects of PFAS analogues

PFAS analogues cross the placental barrier, resulting in direct prenatal exposure of the developing foetus. Studies measuring matched maternal and umbilical cord serum concentrations consistently show that multiple PFAS congeners, including PFOA and PFOS isomers, are detectable in cord blood at substantial levels, indicating efficient transplacental transfer during pregnancy. Transfer efficiency varies by compound, but cord-to-maternal serum ratios for many PFAS typically range from ~0.3 to ~0.7, indicating that a significant fraction of the maternal body burden is transferred to the foetus.[65]

Once transferred across the placenta, PFAS compounds have been linked in epidemiological studies to adverse foetal outcomes. Maternal PFAS exposure during early pregnancy has been associated with lower birth-weight z-scores and shorter gestational age, particularly in populations with nutritional vulnerabilities, such as low folate status.[66] These associations align with broader evidence that prenatal PFAS exposure may impair foetal growth and development, although effect sizes and specific outcomes vary by compound and cohort.[67] Potential mechanisms underlying these effects include endocrine disruption. For example, PFAS may interfere with thyroid hormone physiology during pregnancy, which is critical for normal foetal development.[68] Maternal PFAS exposure has also been associated with preterm birth and altered foetal growth parameters in some studies, though results vary by PFAS congener and population studied.[67] Evidence on postnatal effects continues to accumulate. Some studies suggest that early-life PFAS exposure may have persistent effects on health outcomes beyond birth, including potential alterations in immune development and increased risks of chronic conditions in later-life. For instance, emerging reports link prenatal PFAS exposure to higher blood pressure in adolescence, although more research is needed to confirm and understand these findings.[69]

# The need for evidence-based regulation

The findings of this review strongly indicate that PFAS exposures pose widespread and persistent

environmental and human health risks, necessitating science-based regulatory frameworks for decision-making. Effective regulation depends on rigorous risk assessment, enforceable exposure limits, substitution with safer chemicals and continuous environmental and biomonitoring programs. Despite growing awareness, regulatory approaches vary widely across countries, reflecting differences in scientific capacity, risk perception and industrial dependence on PFAS-containing products.[70]

## Risk assessment and exposure limits

Establishing evidence-based limits for PFAS in drinking water, food and consumer products is critical to protect public health. Risk assessment frameworks typically integrate:

- Toxicokinetic and toxicodynamic data: serum half-life and bioaccumulation in different organ systems.
- Population exposure assessments: dietary, occupational, environmental.
- Robust health endpoints: including liver toxicity, endocrine disruption, developmental effects and cancer risk.

Regulatory bodies, such as the U.S. Environmental Protection Agency (EPA), European Food Safety Authority (EFSA) and Health Canada, have developed guidelines for drinking water PFAS concentrations, but these limits differ substantially between jurisdictions. For example, the EPA's health advisory level for PFOS is 0.004 µg/L, while EFSA recommends a tolerable weekly intake of 4.4 ng/kg body weight (Table 5).[71-73]

## The lowest maximum acceptable levels of PFSA compounds in food, water and the environment, as set by Health Canada and WHO

Health Canada has established precautionary drinking water guidance values for PFAS compounds to protect public health, particularly for PFOS and PFOA. Under the Guidelines for Canadian Drinking Water Quality, Health Canada's maximum acceptable concentrations (MACs) for PFOS and PFOA are 0.0006 mg/L (0.6 µg/L) and 0.0002 mg/L (0.2 µg/L), respectively, reflecting risks from lifetime exposure. In addition, screening values have been set for other PFAS, including PFHxS and PFBS. A new interim objective of 30 ng/L has been recommended for the sum of 25 PFAS in drinking water, with an emphasis on maintaining concentrations "as low as reasonably achievable" (ALARA) in water intended for human consumption.[74] For environmental media such as biosolids, interim standards are being developed (eg < 50 µg/kg PFOS in commercial biosolids) to limit PFAS transfer to agricultural soils and food chains.[75]

At the global level, WHO has been working to incorporate PFAS analogues into its Guidelines for Drinking-Water Quality, particularly for well-studied legacy compounds such as PFOS and PFOA, but has not yet finalised firm international numerical standards due to an ongoing review of health effects and exposure data.[3] WHO's efforts highlight the complexity of establishing global benchmarks given varying toxicological evidence and analytical challenges and the organisation continues to evaluate PFAS-associated health risks and prioritise key compounds for future guidance.[76]

## Replacement and green chemistry

Where feasible, substituting legacy PFAS with safer alternatives is recommended. This approach requires rigorous safety testing of replacement compounds to prevent regrettable substitutions, as some short-chain PFAS may retain persistence and bioactivity.[77] Several short-chain PFAS and alternative fluorinated surfactants have been introduced:

- ADONA- Replacement surfactant used by DuPont.
- F-53B- Chinese PFOS substitute.
- Short-chain PFAS (C4-C6)- Lower bioaccumulation but still persistent.

However, many replacements show similar environmental persistence, raising concerns.[78-80]

## Environmental and food monitoring

Continuous monitoring of water, soil, crops and animal products is essential for assessing regulatory effectiveness and for detecting emerging contamination hotspots. Integrating human biomonitoring data, including serum PFAS levels, provides critical information on population-level exposure and helps refine risk management strategies.[47]

## Global regulatory landscape

Despite growing evidence, global regulation remains uneven. Some countries have banned or restricted the manufacture and use of long-chain

PFAS, while others lack enforceable limits. Harmonised global standards are urgently needed, given the persistent, bioaccumulative and transboundary nature of PFAS analogues.[81]

## Predicted implications with and without regulations

The long-term outcomes of PFAS exposure in populations are strongly shaped by the presence or absence of regulatory interventions. Modelling studies and empirical data indicate that without effective regulations, PFAS analogues will continue to accumulate in the environment, increasing dietary exposure, sustaining internal body burdens and amplifying human health risks.[4, 82] Conversely, evidence-based regulation and mitigation strategies can substantially reduce environmental contamination, human exposure and associated health burdens.

### Without regulations:

- Increasing environmental contamination: Persistent PFAS analogues in water, soil and microbiota will continue to accumulate from industrial releases, agricultural runoff and improper waste disposal.[82, 83]
- Rising food safety risks: Contamination of crops, livestock and seafood will increase, posing a chronic risk of dietary exposures.[82]
- Higher healthcare burdens: Long-term exposure is expected to escalate incidences of liver disease, thyroid disorders, metabolic dysfunction, impaired immunity, reproductive issues and certain cancers.[82]

### With regulations:

- Cleaner water and soil: Enforcing PFAS discharge limits and environmental remediation reduces environmental concentrations.[83]
- Reduced food contamination: limiting PFAS use in food packaging and monitoring agricultural sources minimises dietary intake.[84]
- Improved public health outcomes: Reduced exposure lowers the prevalence of chronic diseases associated with PFAS, particularly among vulnerable populations such as children and pregnant and nursing women.[85]

## Summary

PFAS analogues pose a significant environmental and public health challenge because of their chemical stability, resistance to degradation and persistent bioactivity. Their strong carbon-fluorine bonds make them highly stable in soil, water and living organisms, leading to widespread contamination and cumulative internal exposure in humans. PFAS can enter the food chain through contaminated water, animal feed and migration from food packaging, ultimately reaching humans through dietary intake, direct water consumption and environmental contact. This widespread exposure underscores the urgent need to understand both the molecular behaviour and ecological fate of these compounds to develop effective mitigation strategies.

At the biological level, PFAS analogues exhibit distinctive toxicokinetic properties. Unlike many organic pollutants that accumulate in adipose tissue, PFAS preferentially bind to plasma and liver proteins, thereby promoting long-term persistence in the human body. Their interactions with nuclear receptors, fatty acid transport proteins and intracellular signalling pathways disrupt hormone regulation, lipid metabolism, immune function and developmental programming in the cells. This molecular interference contributes to a spectrum of adverse health outcomes, including liver toxicity, dyslipidaemia, thyroid dysfunction, impaired immunity, developmental delays and reproductive disorders. Importantly, vulnerable populations, such as pregnant women and children, face disproportionately higher risks due to critical windows of development and heightened sensitivity to endocrine and immune disruption.

From an environmental and public health perspective, the absence of regulatory interventions is likely to worsen these challenges. Without regulatory controls and standards, PFAS would continue to accumulate in soil, drinking water, rivers, lakes, oceans and food systems, perpetuating long-term exposure and increasing the burden of chronic diseases. Conversely, evidence-based regulation, including enforceable limits in drinking water and food, replacement with safer alternatives and comprehensive environmental monitoring, has the potential to significantly reduce human exposure and associated health risks. Countries that have implemented PFAS bans or

restrictions demonstrate measurable reductions in environmental concentrations and biomonitoring indicators, underscoring the efficacy of proactive policy measures.

Despite growing scientific knowledge about PFAS analogues, global regulations remain uneven and the health effects of many emerging short-chain PFAS molecules and replacement chemicals remain incompletely understood. Furthermore, although most studies have focused on individual PFAS compounds, humans are often exposed to complex mixtures and the cumulative effects of these mixtures remain poorly characterised. Addressing these challenges requires a multidisciplinary approach that integrates toxicology, environmental science, epidemiology and public policy research. Priorities include longitudinal biomonitoring, assessment of combined chemical exposures, evaluation of emerging PFAS substitutes and development of remediation technologies capable of effectively removing PFAS analogues from water, soil and food systems.

## Conclusion

PFAS compounds are a class of persistent environmental contaminants whose chemical resilience and biological activity make them a global concern for ecosystems and human health. Effective management requires a comprehensive understanding of exposure pathways, molecular mechanisms and population-level impacts, along with robust, evidence-based regulatory interventions. Reducing PFAS exposure through regulatory limits, safer alternatives and ongoing monitoring can substantially mitigate long-term health risks, protect food systems and safeguard public health. Continued research, international collaboration and policy harmonisation are critical to addressing the persistent challenges posed by PFAS and to ensuring sustainable, safe environments for future generations.

## Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. For this review, the literature was sourced from *Scopus, PubMed, Web of Science, Google Scholar, Medline* and *Sci-Hub*. Therefore, the ethics approval was not required in this paper.

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