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Per- and Poly-fluoroalkyl Substances in the Food Chain: A Review of Exposure Pathways and Long-term Health Consequences

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Abstract

The pervasive presence of per- and poly-fluoroalkyl substances (PFAS) in the food chain poses significant threats to human health and ecosystem integrity due to their persistence, bioaccumulation potential, and widespread environmental contamination. This review summarizes current evidence on the pathways of PFAS exposure through dietary and environmental routes and examines their long-term health implications. There is an urgent need to consolidate existing knowledge to inform regulatory actions, risk assessments, and public health interventions aimed at reducing PFAS exposure. This review covers the primary exposure pathways of PFAS, including contaminated irrigation water, soil, and food processing materials, as well as bioaccumulation in aquatic and terrestrial food webs. It discusses the chemical properties influencing PFAS behavior, such as chain length and functional groups, and details the mechanisms of bioaccumulation and bioavailability across species. The health consequences of PFAS exposure are thoroughly examined, including links to cancer, metabolic and endocrine disorders, reproductive and developmental issues, and immunotoxicity. Clinical and epidemiological studies highlighting associations with cardiovascular mortality, type 2 diabetes, dyslipidemia, and reduced bone density are summarized. The review also addresses the heightened vulnerability of certain populations, such as pregnant women and children, and evaluates global exposure patterns. Finally, current mitigation strategies—ranging from regulatory measures and technological innovations to sustainable agricultural practices—are assessed for their effectiveness in reducing PFAS contamination. Future research should prioritize longitudinal studies on emerging PFAS compounds and their mixtures, particularly their effects during critical developmental windows. There is also a need to develop more sensitive and standardized methods for detecting PFAS in complex matrices and to evaluate the long-term efficacy of remediation technologies in real-world settings. Ultimately, interdisciplinary efforts are essential to bridge existing knowledge gaps and support evidence-based policies that safeguard public health and the environment.

Keywords: Bioaccumulation, Dietary exposure, Food chain, Health effects, Mitigation strategies, Per- and poly-fluoroalkyl substances, Regulatory policies

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Introduction

The presence of PFAS in the food chain has emerged as a significant concern due to their persistence, bioaccumulation potential, and associated health risks [1-7]. Recent literature underscores the complexity of exposure pathways and the long-term health consequences stemming from chronic low-level exposure to these chemicals [8-14]. A primary focus of current research is identifying and mapping the pathways through which PFAS enter the human diet. Melnyk et al. [15] conducted extensive evidence mapping and scoping review to elucidate these pathways, emphasizing the importance of dietary exposure routes. Their study highlights that PFAS contamination can occur at multiple points along the food chain, including environmental contamination of soil and water, uptake by crops, and accumulation in terrestrial and aquatic organisms that are subsequently consumed by humans. This comprehensive approach underscores the multifaceted nature of exposure, involving environmental matrices such as irrigation water and soil, which serve as reservoirs for PFAS, thereby facilitating transfer into food products.

The contamination of terrestrial food chains is particularly concerning, as demonstrated by Bonato et al. [16], who reviewed the long-term health impacts of chronic low-level PFAS exposure through diet. Their findings suggest that persistent environmental contamination leads to bioaccumulation in crops and livestock, which then becomes a direct source of human exposure. This pathway is compounded by the chemical stability of PFAS, often termed 'forever chemicals,' which resist degradation and persist in the environment for extended periods. The review emphasizes that such contamination not only affects food safety but also poses ongoing health risks to populations consuming contaminated products. Further elucidating the environmental aspects, the analysis by Melnyk et al. [15] and others indicates that

PFAS can infiltrate various environmental compartments, impacting ecosystems and food safety simultaneously [17]. The contamination of water sources used for irrigation and drinking is a critical concern, as it facilitates the transfer of PFAS into crops and animals. The review by Brown et al. [18] highlights that irrigation water and soil contaminated with PFAS are significant exposure sources, raising regulatory concerns about the safety of agricultural practices and the need for monitoring and remediation strategies.

The health implications of dietary PFAS exposure are increasingly documented [19-25]. Studies reviewed by Fenton et al. [26] reveal associations between long-chain PFAS exposure and adverse health outcomes, including kidney cancer and mortality. Specifically, a review of 6 published studies found that exposure to long-chain PFAS compounds correlates with increased risks of kidney-related health issues, with risk ratios ranging from 1.07 to higher values, indicating a measurable increase in health risks [26]. These findings are corroborated by long-term epidemiological studies that link PFAS exposure to chronic health conditions, emphasizing the importance of understanding exposure duration and chemical persistence. Emerging research also points to the vulnerability of early life stages to PFAS exposure. The review by Eze et al. [27] discusses how prenatal and early childhood exposure to PFAS can have latent health effects, with the placenta identified as a target tissue for chemical accumulation. This suggests that exposure during critical developmental windows may predispose individuals to health issues later in life, including immune dysregulation and metabolic disturbances. Such findings highlight the importance of considering vulnerable populations in risk assessments and regulatory policies.

The ongoing phase-out of certain long-chain PFAS compounds, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), has been examined for its impact on environmental and human health [28-33]. Revisiting these chemicals, Wee and Aris [34] discusses how their reduction influences the concentrations of perfluoroalkyl acids in the environment and food products. While phase-out efforts have led to decreased levels of some PFAS in certain matrices, the persistence of these chemicals and the emergence of alternative compounds continue to pose challenges [34]. Overall, the literature underscores that PFAS contamination in the food chain is a complex issue involving multiple environmental and biological pathways. The persistence of these chemicals in soil, water, and biota facilitates ongoing exposure, which is associated with significant long-term health risks, including cancer, immune dysfunction, and developmental effects. The evidence mapping by Melnyk et al. [15] provides a foundational understanding of these pathways, emphasizing the need for integrated monitoring, risk assessment, and regulatory strategies to mitigate exposure and protect public health.

In summary, the current body of research highlights the critical importance of understanding and addressing the pathways through which PFAS enter the food chain. The long-term health consequences of such exposure are profound, necessitating continued investigation into environmental contamination, bioaccumulation, and health outcomes. As efforts to phase out certain PFAS compounds progress, ongoing vigilance is essential to manage emerging risks associated with persistent and bioaccumulative chemicals in the environment and food supply.

Exposure Pathways

The pathways through which PFAS enter the food chain are multifaceted (Table 1). One of the primary routes is through contaminated irrigation water or soil, which can lead to the uptake of PFAS by crops. Brown et al. [18] highlighted that the consumption of vegetables irrigated with PFAS-impacted water poses a significant exposure risk, particularly for vulnerable populations such as young children. The study estimated that daily dietary exposure to individual PFASs from vegetables could exceed health risk thresholds, emphasizing the importance of monitoring irrigation sources. Another critical pathway is the bioaccumulation of PFAS in aquatic organisms. Cheng et al. [35] noted that fish and other seafood can accumulate PFAS from contaminated water, which then enter the human diet. The ingestion of contaminated fish is a well-documented route of exposure, particularly in regions where fishing is a primary food source. Additionally, PFAS can be transferred to food through contaminated agricultural inputs, such as biosolids used as fertilizers. Scearce et al. [36] discussed how the application of PFAS-laden sewage sludge in agricultural practices creates a direct pathway for these contaminants to enter the food chain. This highlights the need for stringent regulations regarding the use of biosolids in agriculture.

Dietary intake

- Animal-derived foods: PFAS are commonly found in animal-derived foods such as fish, meat, and dairy products. These substances accumulate in the tissues of animals, particularly in protein-rich tissues like the liver and kidneys, due to their affinity for proteins. Carnivorous fish, for example, tend to have higher PFAS levels compared to omnivorous fish [37].

- Aquatic products: Seafood, including fish and shrimp, is a significant source of PFAS exposure. These substances bioaccumulate in aquatic food webs, making seafood a primary dietary source of PFAS for humans [38].

- Food processing and packaging: PFAS can migrate from food contact materials into food, especially in items with higher fat content. This migration is a notable source of PFAS contamination in processed foods [37].

Environmental and chemical factors

- Drinking water: PFAS contamination in drinking water is a well-documented exposure route. The US EPA has set a maximum contamination limit for PFAS in drinking water, highlighting its

Table 1: Primary dietary exposure pathways of PFAS.

Pathway category	Specific source	Key PFAS compounds	Notable findings/risks
Aquatic foods	Fish, seafood, shellfish	PFOS, PFOA, long-chain	High bioaccumulation in carnivorous species; major source of human dietary exposure
Animal-derived foods	Meat, dairy, eggs (liver/kidneys)	PFOS, PFOA, PFNA	Accumulates in protein-rich tissues; dairy can be a significant exposure route
Plant-derived foods	Leafy vegetables, crops	Various, depending on water/soil	Uptake via contaminated irrigation water and soil; higher in leafy greens
Processed foods	Food packaging, grease-resistant paper	Short-chain replacements	Migration from packaging into food, especially high-fat content products
Drinking water	Public supply, private wells	PFOA, PFOS, PFHxS, PFBS	A direct and significant exposure route; exceeds proposed maximum contamination limit in many samples

significance as an exposure pathway [39].

- Soil and air: PFAS can also be present in soil and air, contributing to their presence in the food chain through agricultural practices and atmospheric deposition [39].

- Chemical properties: The chain length and functional groups of PFAS significantly impact their bioaccumulation potential. Long-chain PFAS ($C \geq 7$) and those with sulfonic groups tend to accumulate more in organisms due to their higher stability and affinity for proteins [37]. Short-chain PFAS, however, are more bioavailable in certain conditions, such as in the rhizosphere soil of plants [40].

While dietary intake is the primary route of PFAS exposure, it is important to consider the broader environmental context. PFAS are ubiquitous in the environment, and their persistence means they can be found in various media, including air, water, and soil. This widespread presence complicates efforts to mitigate exposure, as PFAS can enter the food chain through multiple pathways. Additionally, the interaction of PFAS with dietary components, such as fats and proteins, can modulate their toxicity and bioavailability, further influencing human health outcomes [41-45].

Bioaccumulation and Bioavailability

PFAS are persistent environmental pollutants that bioaccumulate and biomagnify in both aquatic and terrestrial food webs, posing significant risks to human health. These substances are resistant to environmental degradation and can be found in various consumer products and industrial applications. Their accumulation in food webs is a result of their chemical properties, which allow them to persist and concentrate as they move up the trophic levels [46-50]. This accumulation has been documented in various ecosystems, with implications for both wildlife and human health. Different species exhibit varying levels of PFAS bioaccumulation. For instance, carnivorous fish tend to accumulate more PFAS than omnivorous fish, and poultry metabolize PFAS more rapidly than mammals [37]. In plants, the lipid and protein content in tissues play a significant role in PFAS accumulation, with leafy vegetables showing higher bioavailability due to their high-water demand [40]. Enterohepatic circulation, this biological process significantly influences the bioaccumulation of PFAS in organisms. For example, PFOS and its alternatives are reabsorbed in the liver and gallbladder, affecting their distribution and excretion [51].

Aquatic food webs

- PFAS are prevalent in aquatic environments, where they accumulate in organisms such as fish and aquatic invertebrates. Studies have shown that PFAS concentrations are higher in apex predators like the white shark, indicating biomagnification through the food web [52].

- In freshwater systems, PFAS have been detected in all food web compartments, with aquatic insects showing significant accumulation. This suggests that PFAS can move through the food web from primary producers to higher trophic levels [53].

- The bioaccumulation and biomagnification of PFAS in aquatic food webs are influenced by factors such as the chemical structure of PFAS, with long-chain PFAS showing higher potential for biomagnification [54].

Terrestrial food webs

- In terrestrial ecosystems, PFAS have been found to accumulate in soil, plants, and wildlife. For instance, high concentrations of PFAS were detected in the liver of bank voles, which are part of the terrestrial food web [55].

- The movement of PFAS through terrestrial food webs can be complex, involving multiple pathways such as ingestion of contaminated soil and water, and consumption of contaminated prey [56].

- Terrestrial food webs can also be influenced by nearby aquatic systems, as seen in studies where PFAS were transferred from aquatic to terrestrial organisms, such as tree swallows feeding on aquatic invertebrates [56].

While the accumulation and biomagnification of PFAS in food webs are well-documented, there are still gaps in understanding the full extent of their impact, particularly in terrestrial ecosystems. The complexity of PFAS chemistry and their diverse sources make it challenging to fully assess their environmental and health implications [57-60]. Further research is needed to develop effective strategies for monitoring and mitigating PFAS exposure in both ecosystems and human populations.

Health Consequences

The long-term health consequences of PFAS exposure are a growing concern (Table 2). Epidemiological studies have linked PFAS exposure to various adverse health outcomes, including reproductive and developmental issues. Chambers et al. [61] compiled evidence indicating that long-chain PFAS compounds, such as PFOA and PFOS, are associated with decreased fertility, reduced fetal growth, and pregnancy complications. The persistence of these compounds in the environment raises concerns about their long-term effects on human health. Moreover, recent research has suggested that short-chain PFAS, which are increasingly used as replacements for long-chain variants, may also pose reproductive risks. Although they are less bioaccumulative, their mobility and persistence in aquatic ecosystems warrant further investigation into their health impacts [61]. The need for high-quality epidemiological studies to assess the reproductive health effects of short-chain PFAS is critical, as current data remain inconsistent. PFAS exposure has also been linked to metabolic disorders, including obesity and endocrine disruption. Pezeshki et al. [62] highlighted the connection between PFAS in drinking water and the incidence of obesity, particularly during critical growth phases. The disruption of hormonal functions due to PFAS exposure can lead to

Table 2: Health consequences associated with chronic PFAS exposure.

Health outcome category	Specific conditions/effects	Key PFAS implicated	Vulnerable populations
Cancer	Kidney cancer, testicular cancer	PFOA, PFOS	General population, highly exposed communities
Metabolic and endocrine	Dyslipidemia, type 2 diabetes, obesity	PFOA, PFOS, PFNA, PFUnDA	Adults, younger populations (early-onset)
Reproductive and developmental	Reduced fertility, low birth weight, preterm birth	PFOA, PFOS	Pregnant individuals, fetuses, infants
Immunotoxicity	Reduced vaccine response, increased infection risk	PFOS, PFOA	Children, immunocompromised individuals
Cardiovascular	Hypertension, ischemic heart disease	PFOA, PFOS	Adults with high exposure
Skeletal	Reduced bone mineral density	PFOS	Adolescents, young adults

various health issues, including thyroid dysfunction and reproductive abnormalities.

- Cardiovascular health: PFAS exposure has been linked to several cardiovascular risk factors, including dyslipidemia, hypertension, glucose intolerance, and obesity. These factors contribute to an increased risk of cardiovascular diseases such as atherosclerosis and vascular disease. The National Academies of Sciences, Engineering, and Medicine recommend clinical follow-up for individuals with high PFAS blood levels, emphasizing the need for screening for dyslipidemia [63].

- Reproductive and female health: PFAS have been associated with reproductive system disorders and pregnancy-related diseases in females. The disruption of the hypothalamic-pituitary-gonadal axis and hormonal imbalances are key mechanisms through which PFAS affect female health. There is also evidence suggesting that PFAS exposure may influence autoimmune disorders, which are more prevalent in women, although further research is needed to substantiate these findings [64].

- Developmental and pediatric health: PFAS exposure can impact the growth, learning, and behavior of infants and children. There is a potential risk of developmental issues, including delays in motor and cognitive development, which can affect learning abilities and social interactions. During pregnancy, PFAS exposure has been linked to fetal growth retardation, low birth weight, and preterm birth [65].

- Immune system and cancer risk: PFAS exposure is associated with immunotoxicity, potentially leading to decreased antibody responses and increased susceptibility to infections. There is evidence linking PFAS to an increased risk of certain cancers, including kidney, breast, and testicular cancer, although the evidence is more limited for some cancer types [66].

- Metabolic and endocrine effects: PFAS can disrupt endocrine function, affect thyroid and pancreatic health, and increase the risk of metabolic disorders such as type 2 diabetes [67]. These substances have also been associated with liver and kidney damage, further complicating metabolic health [68].

- Vulnerable populations: Susceptible populations, such as pregnant individuals, newborns, the elderly, and those with pre-existing health conditions, are at greater risk of adverse effects from PFAS exposure. These groups may experience enhanced toxicity due to physiological changes that reduce resilience to environmental exposures [69].

Prenatal exposure

Prenatal exposure to PFAS has been linked to various developmental and reproductive health consequences in children. These synthetic chemicals, found in numerous consumer products, are persistent in the environment and can cross the placental barrier, leading to prenatal exposure. Research indicates that such exposure can affect fetal growth, hormone levels, and long-term health outcomes, although findings are sometimes inconsistent. The section details the specific developmental and reproductive health consequences associated with prenatal PFAS exposure.

- Fetal growth and birth outcomes: Prenatal exposure to PFAS has been associated with lower birth weight. For instance, exposure to PFOA was linked to a reduction in birth weight in infants, suggesting significant implications for children's health during critical developmental periods [70]. Some studies have reported mixed findings, with prenatal PFAS exposure also linked to excess adiposity and higher weight in childhood, indicating complex relationships between PFAS exposure and growth trajectories [71].

- Hormonal disruptions: PFAS exposure has been shown to disrupt fetal sex hormone homeostasis, which could lead to reproductive and developmental abnormalities. For example, exposure to PFAS mixtures was associated with altered levels of estradiol and progesterone in infants, with sex-specific differences observed in hormone levels. The disruption of hormone levels due to PFAS exposure may have long-term implications for reproductive health, although further research is needed to fully understand these effects [72].

- Obesity and adiposity: Prenatal exposure to PFAS has been linked to an increased risk of obesity in adolescence. Higher prenataland perfluorononanoic acid (PFNA) exposures were associated with a greater risk of obesity in children aged 16 to 20 years, supporting the classification of PFAS as obesogenic substances [73]. The relationship between PFAS exposure and adiposity is complex, with some studies indicating negative associations with body mass index in early life but positive associations in later childhood and adolescence [74].

- Neurodevelopmental effects: There is evidence suggesting that prenatal PFAS exposure may be associated with neurodevelopmental disorders, including impairments in executive function and performance IQ, particularly in boys. However, the evidence is mixed, with some studies reporting no significant associations between PFAS exposure and behavioral difficulties in children [75].

Affecting the immune system

PFAS are synthetic chemicals that have been shown to adversely affect the immune system, increasing the risk of infections. These substances are persistent in the environment and bioaccumulate in human tissues, leading to widespread exposure. The immunotoxic effects of PFAS are primarily characterized by immunosuppression, which can manifest as reduced vaccine efficacy and increased susceptibility to infections. The mechanisms through which PFAS exert these effects include modulation of immune cell signaling, alteration of immune cell populations, and suppression of key immune responses.

Mechanisms of immunotoxicity

- Modulation of cell signaling: PFAS can interfere with cell signaling pathways, such as NF-κB and PPARs, which are crucial for immune responses. This interference can lead to altered immune cell function and reduced ability to respond to pathogens [76].

- Alteration of immune cell populations: Exposure to PFAS has been associated with changes in the distribution and function of immune cells, including natural killer cells, T helper cells, and cytotoxic T cells. These changes can skew immune responses and impair the body's ability to fight infections [77].

- Suppression of neutrophil function: PFAS have been shown to suppress the neutrophil respiratory burst, a critical component of the innate immune response that involves the production of reactive oxygen species to kill pathogens. This suppression can increase susceptibility to infections [78].

Impact on vaccine efficacy and infection risk

- Reduced vaccine efficacy: Epidemiological studies have documented that PFAS exposure is associated with reduced antibody

responses to vaccines, such as those for measles, mumps, rubella, diphtheria, and tetanus. This reduction in vaccine efficacy can lead to increased vulnerability to these diseases [79].

- Increased susceptibility to infections: PFAS exposure has been linked to a higher incidence of infections, particularly respiratory infections in children. This increased risk is likely due to the immunosuppressive effects of PFAS, which weaken the body's defense mechanisms against pathogens [80].

Studies have shown that PFAS often occur as mixtures in the environment, and their combined effects on the immune system are not simply additive. Different PFAS mixtures can differentially affect immune responses, with some mixtures impacting T-cell responses and others affecting B-cell responses. The sensitivity of immune responses to PFAS can vary depending on the specific PFAS compounds and their concentrations. This variability underscores the complexity of PFAS immunotoxicity and the need for further research to understand these interactions.

Clinical Studies

PFAS are synthetic chemicals that have been linked to a range of long-term health consequences through various clinical studies. These substances are known for their persistence in the environment and the human body, leading to widespread exposure and potential health risks. The research highlights several adverse health outcomes associated with PFAS exposure, including cancer, metabolic disorders, immune system effects, and developmental issues.

A study by Biggeri et al. [81] investigated the impact of PFAS contamination in a large Italian area between 1980 and 2018 revealed significant findings regarding all-cause and cause-specific mortality. During the 34-year period from 1985 (assumed start of contamination) to 2018 in three provinces of the Veneto Region (northern Italy), the resident population of the 'red area' experienced 51,621 observed deaths compared to 47,731 expected deaths (Figure 1). This resulted in an age- and sex-standardized mortality ratio of 108, with a 90% confidence interval (CI) of 107 to 109, indicating a statistically significant increase in overall mortality. The research provided the first formal demonstration of an association between PFAS exposure and mortality from cardiovascular disease. Specifically, raised mortality was observed for heart diseases and ischemic heart disease. The study also found evidence of increased mortality from malignant neoplastic diseases. Consistent with previously reported data, the findings reinforced the association of PFAS exposure with kidney cancer and testicular cancer. In summary, the study identified a higher overall mortality rate in the PFAS-contaminated 'red area' of Italy, with specific increases linked to cardiovascular diseases (including heart and ischemic heart diseases) and malignant neoplastic diseases, particularly kidney and testicular cancers.

A register-based study by Xu et al. [82], conducted in Ronneby, Sweden, investigated the association between exposure to high levels of PFAS through drinking water and the risk of Type 2 diabetes among adults. The study found an elevated risk of Type 2 diabetes when comparing individuals with 'ever-high' PFAS exposure to those with 'never-high' exposure. The hazard ratio was 1.18, with a 95% CI of 1.03 to 1.35, after adjusting for age and sex. Similar elevated hazard ratio was observed when comparing 'early-high' exposure (hazard ratio 1.12, 95% CI 0.98 to 1.50) or 'late-high' exposure (hazard ratio 1.17, 95% CI 1.00 to 1.37) to 'never-high' exposure, also adjusted for age and sex. Adjusting for the highest-achieved education level attenuated these estimates, meaning the association became slightly weaker, but the direction of the associations remained consistent, indicating a persistent link between PFAS exposure and Type 2 diabetes risk. Individuals aged 18 to 45 years showed even higher hazard ratios, suggesting an increased susceptibility to PFAS-related health effects at younger ages and a higher risk of early-onset diabetes. Elevated hazard ratios were also identified among those who had resided in areas with heavily contaminated water for specific durations. For 1 to 5 years of exposure, the hazard ratio was 1.26 (95% CI 0.97 to 1.63). For 6 to 10 years of

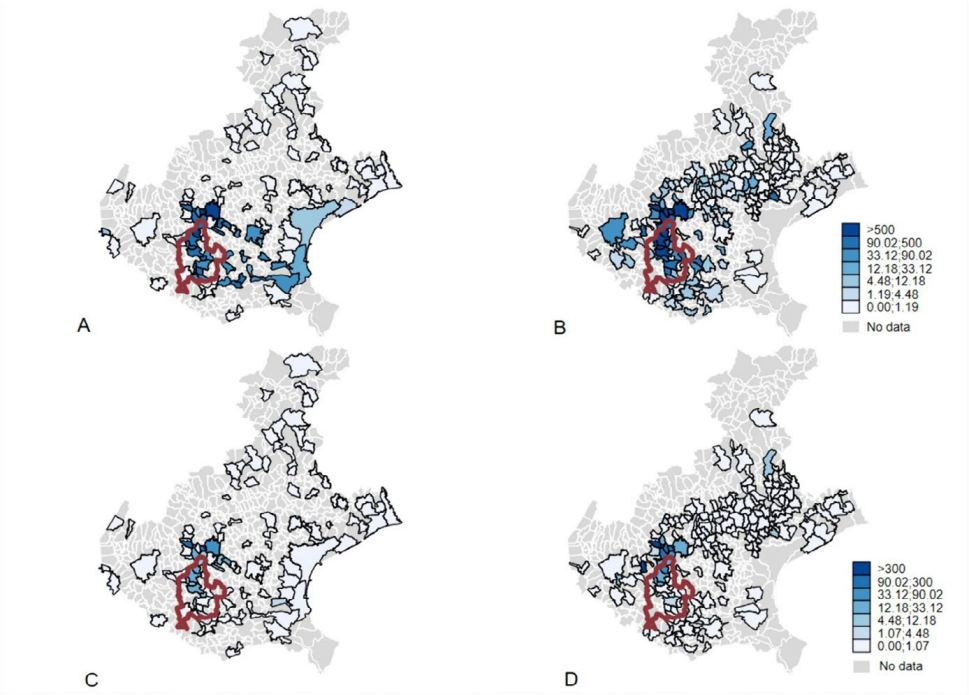

Figure 1: Map of concentrations (ng/L) of perfluorooctanoic acid (**A** and **B**) and perfluorooctanesulfonic acid (**C** and **D**) in the surface water (**A** and **C**) and groundwater (**B** and **D**) of the municipalities of the Veneto Region (northern Italy). A red outline indicates the red area. July 2013 to June 2015 [81].

exposure, the hazard ratio was 1.25 (95% CI 0.80 to 1.94). In summary, the study indicates an increased risk of Type 2 diabetes following long-term high PFAS exposure via drinking water, particularly highlighting a greater risk for early-onset diabetes in younger individuals.

A study by Dunder et al. [83] analyzed data from 864 elderly individuals (50.1% women) from the prospective investigation of the vasculature in Uppsala seniors' study from Uppsala Sweden, with measurements taken three times between 2001 and 2014. At baseline (age 70), the mean total cholesterol was 5.55 mmol/L, low-density lipoprotein cholesterol was 3.50 mmol/L, high-density lipoprotein cholesterol was 1.53 mmol/L, and triglycerides were 0.12 mmol/L. Over the 10-year period, total cholesterol showed no significant change, while triglycerides and low-density lipoprotein cholesterol increased, and high-density lipoprotein cholesterol decreased. Plasma levels of certain PFAS, including Perfluoroheptanoic acid (PFHpA), PFOA, PFOS, and PFOS, decreased from age 70 to 80, whereas levels of perfluorohexane sulfonic acid (PFHxS), PFNA, Perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) increased. The study found positive associations between changes in plasma levels of six out of eight investigated PFAS and changes in plasma lipid levels, even after adjusting for factors like sex, body mass index changes, smoking, physical activity, and statin use. Specifically, changes in plasma levels of PFUnDA, PFOA, PFNA, PFHpA, and PFDA were positively associated with changes in total cholesterol. PFUnDA had the most significant effect on total cholesterol; a one-unit increase in PFUnDA (ng/mL) was linked to a 0.79 mmol/L increase in plasma total cholesterol. Changes in PFOA, PFNA, PFHpA, and PFDA levels were also positively associated with changes in plasma triglycerides. A one-unit increase in PFDA or PFNA levels (ng/mL) was associated with a 0.55 mmoL/L increase in plasma triglycerides. Only the change in plasma levels of PFUnDA was positively associated with changes in plasma low-density lipoprotein cholesterol. Changes in plasma levels of PFUnDA, PFOS, PFOA, PFNA, and PFDA were positively associated with changes in plasma high-density lipoprotein cholesterol (Figure 2). This longitudinal study, spanning 10 years and involving three measurements of both plasma PFAS and lipid levels, provides strong evidence for positive associations between changes in six different PFAS and changes in total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. These findings support the idea that PFAS exposure plays a role in human lipid metabolism.

A study by Beglarian et al. [84] investigated the associations between individual PFAS and PFAS mixtures with longitudinal changes in bone mineral density in Hispanic adolescents and young adults. The primary findings indicate a significant association between perfluorooctanesulfonic acid exposure and lower bone mineral density. PFOS in Adolescents: In the Study of Latino Adolescents at Risk of Type 2 Diabetes (SOLAR) cohort, baseline plasma perfluorooctanesulfonic acid was significantly associated with longitudinal changes in bone mineral density. Specifically, each doubling of perfluorooctanesulfonic acid was linked to an average −0.003 g/cm^2 difference in the change in trunk bone mineral density per year over the follow-up period (95% CI: −0.005, −0.0002). These associations with perfluorooctanesulfonic acid were also observed in the Southern California Children's Health Study young adult cohort. Each doubling of plasma perfluorooctanesulfonic acid was associated with an average −0.032 g/cm^2 difference in total bone mineral density at baseline (95% CI −0.062, −0.003). However, the longitudinal associations in this cohort were not statistically significant. The study did not find significant associations between other individual PFAS and bone mineral density outcomes. The associations of the PFAS mixture with bone mineral density outcomes were primarily negative, although these findings were not statistically significant. The findings suggest that perfluorooctanesulfonic acid exposure is linked to lower bone mineral density during adolescence and young adulthood, which are critical periods for bone development. This could have significant implications for future bone health and increase the risk of osteoporosis in adulthood. In summary, the study highlights perfluorooctanesulfonic acid as a particular concern for bone health, demonstrating an inverse relationship with bone mineral

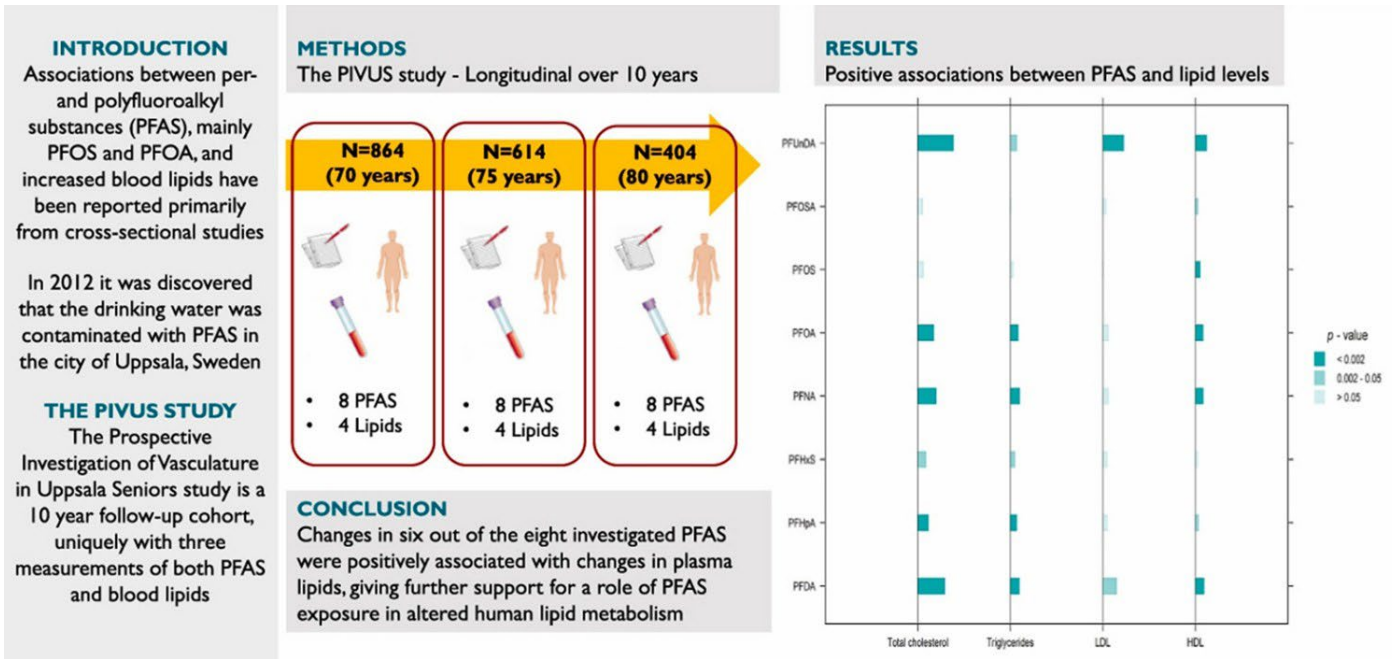

Figure 2: Plasma levels of PFAS are linked to dyslipidemia [83].

density in both adolescent and young adult populations, particularly in Hispanic individuals.

A study by Sonne et al. [85] investigated exposure to PFAS and their association with immune suppression, particularly in an Indigenous Arctic community, and placed these findings within a global context. Between September 21 and October 2, 2015, 22 anonymous Inuit adults (12 male, 10 female) from Ittoqoortoormiit were enrolled in the study. These participants were from full-time or part-time hunter families. Of the enrolled participants, 14 completed food frequency and lifestyle questionnaires. These indicated that the primary source of PFAS exposure was the consumption of ringed seals and polar bears. Polar bears and ringed seals are crucial year-round food sources, with peak consumption occurring during the springtime hunt. Muscle tissue samples from 17 randomly selected ringed seals and polar bears (collected in 2018 to 2019) showed mean PFAS concentrations of 3.15 ng/g wet weight for ringed seals (range: 1.93 to 6.35) and 15.28 ng/g wet weight for polar bears (range: 7.93 to 13.31). The European Food Safety Authority (EFSA) sets the tolerable weekly intake for PFASs at 4.4 ng/kg bodyweight for non-pregnant adults. Monte Carlo simulations estimated that 231 (66%) of 350 people exceeded this tolerable weekly intake when consuming only ringed seal. This proportion increased to 322 (92%) of 350 people when polar bear consumption was included, due to the 5- to 6-fold higher PFAS concentrations in polar bears. Less than 15% of the Ittoqoortoormiit population remained below the safe intake level when consuming polar bear alone. This indicates that polar bear meat is a major contributor to long-term PFAS exposure and immune suppression risks. When comparing blood serum PFAS concentrations with EFSA's toxic thresholds for immune deficiency, 305 (86%) of 350 people in the Ittoqoortoormiit Inuit population fell into the most severe risk category (>31.9 ng/mL). This finding demonstrates a strong correlation between estimated exposure and actual bioaccumulation in blood, as well as the associated risks of immune suppression. Country-wide average values from global studies revealed that blood serum PFAS concentrations were generally higher in European countries, North America, the Arctic, and Australia compared to South America, Africa, and mainland Asia. The highest concentrations were found in people from the US, Canada, Greenland, Faroe Islands, Denmark, Iceland, Norway, Sweden, the UK, Spain, Poland, and Australia. All these high-exposure countries fall within the EFSA moderate-risk and high-risk categories. Specifically, Sweden, the Faroe Islands, Denmark, the UK, and Australia were in the high-risk category (>17.5 to 31.9 ng/mL), while the USA, Canada, Iceland, Norway, Spain, Poland, Greece, Malaysia, and Taiwan were in the moderate-risk category (>9.5 to 17.5 ng/mL). Populations in South America, Europe, Africa, and Asia generally showed low risk (0.7 to 9.5 ng/mL). The study noted a lack of data for India, South and Central America, Africa, Russia, and large parts of Asia, highlighting a need for more research in these regions. In summary, the study found that the Inuit population in East Greenland experiences extremely high PFAS exposure, primarily from consuming marine mammals like polar bears and ringed seals. This exposure significantly exceeds safety thresholds and places a large majority of the population in the severe risk category for immune suppression. Globally, Arctic and developed nations show higher PFAS levels, underscoring the widespread nature of this contamination and the urgent need for comprehensive risk assessment and mitigation strategies.

A study by Smalling et al. [86] conducted a national reconnaissance to assess human exposure to PFAS in residential tapwater, comparing unregulated private-well and regulated public-supply sources, and evaluating associated health implications. At least 1 PFAS was detected in 30% of the tapwater samples collected across the US. The study estimated that at least one PFAS could be detected in approximately 45% of US drinking-water samples. Modeled results indicated that on average, at least one PFAS is detected in about 45% of US drinking-water samples. The number of individual PFAS observed in samples ranged from 1 to 9, with a median of 2. Seventeen different PFAS were detected at least once, with PFBS, PFHxS, and PFOA being the most frequently observed, appearing in approximately 15% of samples. The number of individual PFAS observed ranged from 1 to 9, with a median of 2. Cumulative PFAS concentrations (sum of detected PFAS) ranged from 0.348 to 346 ng/L, with a median of 7.00 ng/L. Across the US, PFAS profiles and estimated median cumulative concentrations were similar between private wells and public-supply tap water. Specifically, median cumulative PFAS concentrations were comparable between public-supply (median = 7.1 ng/L) and private-well (median = 8.2 ng/L) point-of-use tap water. One PFAS was detected in 20% of private-well samples and 40% of public-supply samples. No differences were observed in estimated median concentrations of individual PFAS or the number of detected individual PFAS between public-supply and private-well point-of-use tap water samples when considering only PFAS with >5% detections. Benchmark screening approaches indicated that potential human exposure risk was primarily driven by PFOA and PFOS when detected. Newly proposed maximum contaminant levels for PFOA (4 ng/L) and PFOS (4 ng/L) were exceeded in 6.7% and 4.2%, respectively, of all tap water samples. When considering only detected PFAS, these exceedances rose to 48% and 70% for PFOA and PFOS, respectively, in all tap water samples. For private-well tap water samples where PFAS were detected, proposed maximum contaminant levels for PFOA and PFOS were exceeded in 63% and 67%, respectively. The proposed hazard index of 1 for the sum of the toxicity quotient for PFBS, PFNA, PFHxS, and GenX was exceeded in 4.6% of collected tap water. The study found that 124 samples overall had a cumulative toxicity quotient greater than 1, indicating a high probability of aggregated risk from observed PFAS with available benchmarks. Cumulative toxicity quotient values were higher in private-well tap water samples compared to public-supply. PFAS detection probabilities varied spatially, with limited temporal variation in concentrations or numbers of PFAS detected. The probability of not detecting PFAS above detection limits ranged from approximately 25% in urban centers or areas with known PFAS contamination history to over 75% in rural areas. Cumulative PFAS concentrations and the number of detected compounds increased with surrounding developed land and decreased with increasing distance from probable sources. However, the distance to probable sources was not a strong predictor for individual PFAS concentrations. In summary, the study highlights that PFAS contamination is a national concern, present in both private and public tap water across the US at comparable levels. A significant portion of samples exceeded proposed regulatory limits, indicating potential human health risks, particularly from PFOA and PFOS. The findings underscore the critical need for continued monitoring and assessment of cumulative health risks, especially in unregulated private-wells and for mixtures of PFAS and co-occurring contaminants.

A study by Grandjean et al. [87] investigated the association between PFAS concentrations in plasma and the severity of COVID-19 outcomes in a Danish cohort. Plasma-PFAS concentrations were generally higher in males, older subjects, and individuals of Western European origin. However, the presence of chronic disease did not appear to be associated with PFAS levels, though kidney disease showed a tendency for higher plasma concentrations. The predominant PFAS

found in plasma was PFOS, with an average concentration of 6.1 ng/mL (median, 4.7 ng/L), contributing approximately 69% of the total PFAS concentrations. Other quantified PFASs generally had average concentrations below 1 ng/mL. Elevated plasma-perfluorobutanoic acid concentrations were significantly associated with an increased risk of more severe COVID-19 outcomes. The unadjusted odds ratio for increasing severities of the disease with perfluorobutanoic acid was 2.19 (95% CI, 1.39 to 3.46). For hospitalized patients, the fully adjusted odds ratio for progressing to intensive care or death was 5.18 (1.29, 20.72) when based on plasma samples taken at or up to one week before diagnosis. This association remained significant even after adjusting for factors like sex, age, comorbidities, national origin, sampling location, and time. None of the other PFAS showed a similar strong association with disease severity. In some cases, other PFAS, such as PFHxS, appeared to be associated with a lower risk, though this tendency weakened when considering samples closer to diagnosis. More severe COVID-19 outcomes were more frequently observed in males, older subjects, and individuals with chronic disease. There was no significant difference in disease severity based on national origin. The study concluded that increased plasma- perfluorobutanoic acid concentrations are linked to a greater severity of COVID-19 prognosis. This finding persisted after adjusting for various confounding factors. Although perfluorobutanoic acid is present in relatively low concentrations in plasma, it is known to accumulate in the lungs and is an immunotoxic substance, suggesting it may contribute to COVID-19 severity. The results highlight a need for further investigation into how elevated exposures to environmental immunotoxicants might worsen SARS-CoV-2 outcomes.

While the evidence from these studies underscores the significant health risks posed by PFAS, it is important to consider the complexity and variability of these effects. The persistence and bioaccumulative nature of PFAS, combined with their widespread use, make it challenging to fully understand their long-term health impacts. Additionally, the variability in individual susceptibility and exposure levels can lead to differing health outcomes. Further research is needed to elucidate the mechanisms of PFAS toxicity and to develop effective strategies for mitigating exposure and associated health risks.

Mitigation Strategies

Addressing the PFAS contamination in the food chain requires a multifaceted approach. Remediation efforts, such as the use of carbon-based materials for PFAS sequestration in soil, have shown promise in reducing the bioavailability of these contaminants [88]. Additionally, improving agricultural practices and monitoring the use of contaminated irrigation sources are essential steps in mitigating exposure risks. Public health initiatives aimed at raising awareness about PFAS contamination and its health implications are also crucial. As consumers become more informed, there may be increased demand for transparency regarding the presence of PFAS in food products.

- Regulatory measures: Legislation plays a pivotal role in controlling PFAS contamination. New laws aim to limit PFAS production and establish acceptable levels in food and water, balancing environmental protection with food sustainability [89, 90]. International proposals suggest restricting PFAS as a group, particularly in food contact materials, to mitigate human exposure [91].

- Technological innovations: Advanced analytical methods for PFAS detection in food and water matrices are crucial for monitoring and managing contamination levels [89]. Technological solutions such as advanced filtration systems, adsorbents, and high-temperature incineration are being developed to remove PFAS from the environment [90]. Biochar, derived from organic materials, is highlighted as a cost-effective adsorbent for PFAS removal in agricultural systems, offering a scalable and economically feasible remediation technology [92].

- Sustainable practices: The use of biomaterials, such as carbohydrate-based polymers, is being explored as a green chemistry approach for PFAS removal, providing a renewable and biodegradable alternative to traditional chemical treatments [90]. In agricultural contexts, strategies include the use of biochar for soil and water filtration, and the careful management of PFAS-containing materials like biosolids and composts to prevent contamination [92, 93]. Source control measures, such as reducing the use of PFAS-containing pesticides and managing wastewater and biosolid applications, are essential to minimize PFAS introduction into agroecosystems [93].

- Risk mitigation in food systems: Understanding the bioaccumulation and biomagnification of PFAS in food webs is critical for assessing human health risks. Strategies such as selective consumption and pre-cooking treatments can help mitigate these risks [94]. Continuous monitoring and research are necessary to address the challenges posed by PFAS in marine and terrestrial food chains, with a focus on developing effective biodegradation methods and improving ecosystem management [95].

While these strategies offer promising avenues for mitigating PFAS contamination, challenges remain. The complexity of PFAS compounds and their widespread use necessitate ongoing research and innovation. Additionally, the transition to fluorine-free alternatives in non-essential applications is advocated to reduce reliance on PFAS. The effectiveness of these strategies depends on coordinated efforts across regulatory, technological, and practical domains to protect human health and the environment.

Conclusion

The current research on PFAS underscores their widespread environmental persistence and bioaccumulative potential, with diverse and significant long-term impacts on human health. Epidemiological evidence consistently links PFAS exposure, particularly to legacy compounds such as PFOA and PFOS, with increased risks of specific cancers, notably kidney and testicular cancers, supported by robust cohort and case-control studies demonstrating dose-response relationships. However, associations with other cancer types, including breast, ovarian, and thyroid cancers, remain less consistent and warrant further investigation. The literature indicates that PFAS-related carcinogenesis likely operates through non-genotoxic mechanisms including metabolic dysregulation, endocrine disruption, and epigenetic alterations, although mechanistic clarity is still evolving.

Reproductive and developmental toxicities emerge as critical concerns associated with PFAS exposure. Studies document adverse effects on female fertility, pregnancy outcomes, and early childhood development, including reduced birth weight, preterm birth, and neurodevelopmental impairments. Male reproductive health is also affected, with evidence of hormonal disruptions, impaired sperm quality, and epigenetic modifications. Vulnerable populations such as pregnant women, infants, and children demonstrate heightened susceptibility, emphasizing the need for targeted research and protective measures. Despite these findings, heterogeneity in exposure assessment, study designs, and outcome definitions complicates definitive causal inferences, and data on emerging PFAS compounds and mixtures remain limited.

Exposure assessment techniques have advanced considerably, with high-throughput serum quantification and metabolomics offering improved characterization of internal doses and biomarkers. Nonetheless, challenges persist due to the vast chemical diversity of PFAS, difficulties in measuring aggregate exposures, and variability in exposure routes, particularly in underrepresented communities and occupational settings. Mechanistic and toxicological studies complement epidemiological findings by elucidating pathways such as immune suppression, endocrine disruption, oxidative stress, and receptor-mediated effects, yet species differences and limited data on newer PFAS constrain translation to human health risk assessment.

In conclusion, the current evidence base substantiates significant health risks from PFAS exposure, particularly for certain cancers and reproductive and developmental outcomes, with vulnerable populations disproportionately affected. However, critical knowledge gaps remain concerning the health effects of emerging PFAS, exposure mixtures, long-term low-dose impacts, and mechanistic pathways. Addressing these gaps through coordinated, multidisciplinary research efforts, improved exposure assessment, and longitudinal studies is essential to inform regulatory policies and public health interventions aimed at mitigating the adverse health burden of PFAS exposure.

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Conflict of Interest

None.

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