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Review Article

Human Health Risks of Exposure to Environmental Per-and Poly-fluoroalkyl Substances (PFAS)

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Abstract

Due to their distinctive properties, per- and poly-fluoroalkyl substances (PFAS) are widely used in various products. The discovery of PFAS dates back to the middle of the twentieth century. The initial research focused on their commercial applications and non-stick properties. Concerns about the environmental and health effects of PFAS arose in the 1970s when their presence in human and animal blood samples sparked alarm. Significant studies have found PFAS in residents' blood near manufacturing facilities, highlighting the potential health risks. Industrial sites, fire-fighting foam, landfills, and wastewater treatment plants have been linked to PFAS contamination, and their chemical stability and resistance to degradation are responsible for their environmental persistence. Studies have linked PFAS exposure to adverse health effects in humans, including dysfunction of the immune system, liver and kidney damage, and an increased risk of certain cancers and developmental disorders. PFAS can cross the placenta and harm fetuses. PFAS exposure during pregnancy has been linked to miscarriages, lower birth weight, pre-eclampsia, and fecundity. Early PFAS exposure delays mammary gland development, while adult exposure causes liver toxicity, endocrine disruption, immune system dysfunction, cardiovascular, neurodevelopmental, and metabolic effects. Increased cholesterol levels, thyroid issues, gastrointestinal issues, liver damage, kidney cancer, testicular cancer, reproductive issues, breast cancer, decreased vaccine response, impaired immune function, and neurological problems are just a few of the metabolic effects of PFAS exposure. More research is required to understand the mechanisms and long-term health effects of PFAS exposure and develop preventive measures.

Keywords: *Adverse Effects of Prenatal Life; Causes of Miscarriages; Environmental Toxins; Epigenetic Changes; Polyfluoroalkyl Substances*

Abbreviations

AFFF: Aqueous Film-Forming Foam; EPA: Environmental Protection Agency; GI: Gastrointestinal; IBS: Irritable Bowel Syndrome; PFAS: Poly-Fluoroalkyl Substances; PFOA: Perfluorooctanoic Acid; PFOS: Perfluoro Sulfonic Acid; ppt: Parts Per Trillion; PTFE: Polytetrafluoroethylene

Introduction

Per- and poly-fluoroalkyl substances (PFAS) are a group of synthetic chemicals widely used in a variety of industrial and consumer products due to their unique properties, such as water and oil resistance, heat resistance, and surfactant characteristics, which make them popular in products such as non-stick cookware, waterproof fabrics, food packaging, and fire-fighting foams, among others. However, their widespread use has raised environmental and health concerns due to their persistence, mobility, and potential toxicity [1].

The discovery of PFAS dates back to the middle of the 20th century when scientists began to develop fluoropolymers composed of PFAS compounds. The discovery of polytetrafluoroethylene (PTFE) by Roy J. Plunkett, a DuPont chemist, in 1938 marked a significant advancement. PTFE is now commonly identified by its brand name, Teflon [2]. Initial research on PFAS centered on their commercial applications and unique non-stick properties. In the 1970s, however, studies revealing the presence of PFAS in the blood of humans and wildlife sparked concerns about the potential environmental and health effects of PFAS [3].

In 2003, the groundbreaking study conducted by Scott M. Bartell., *et al*. revealed the presence of PFAS in the blood of residents of West Virginia, United States, who lived near a PFAS manufacturing facility. The study identified potential health risks associated with exposure to these chemicals and found elevated levels of PFAS in the blood samples.[4]. The widespread use and persistence of PFAS in various industries resulted in the release of these chemicals into the environment. Multiple sources of PFAS contamination have been identified, including industrial sites, fire-fighting foam, landfills, and wastewater treatment facilities. Due to their chemical stability and resistance to degradation, PFAS can persist in the environment for extended periods after release [5].

In the early 2000s, the recognition of PFAS as a significant human health risk gained prominence. In 2006, the U.S. Environmental Protection Agency (EPA) issued a health advisory for two widely used PFAS compounds: perfluorooctanoic acid (PFOA) and perfluoro sulfonic acid (PFOS). The Environmental Protection Agency (EPA) established a health advisory level of 70 parts per trillion (ppt) for PFOA and PFOS in drinking water, recognizing their potential adverse health effects on humans [6].

Discussion

PFAS exposure and environmental sources

Numerous studies have established conclusive links between PFAS exposure and adverse human health effects. Several studies have shed light on the harmful effects of PFAS on various organ systems and health outcomes.

In a 2013 study, Philippe Grandjean and Esben Budtz-Jrgensen analyzed data from a large cohort of Faroe Islands children exposed to PFAS through contaminated drinking water. The study found associations between prenatal PFAS exposure and impaired immune response, neurodevelopmental delays, and adverse thyroid hormone levels [7]. Further, in 2018, Kyle Steenland., *et al*. examined the association between occupational PFAS exposure and the incidence of kidney cancer in individuals with PFAS exposure. Individuals with higher levels of PFAS exposure had a higher risk of developing kidney cancer, providing further evidence of the carcinogenic potential of PFAS [8].

As new research emerges, the current understanding of PFAS toxicity in humans continues to evolve. It is well-established that PFAS can accumulate in the human body and have a long half-life, resulting in prolonged exposure and potential health risks. In scientific studies, multiple biological processes, including hormone regulation, immune function, liver function, and reproductive health, are impacted by PFAS. Increasing evidence also links PFAS exposure to an increased risk of certain cancers, cardiovascular diseases, and developmental disorders in children [9,10].

Environmental contamination by PFAS can occur through multiple pathways and sources. Some of the primary sources of PFAS contamination are depicted in figure 1.

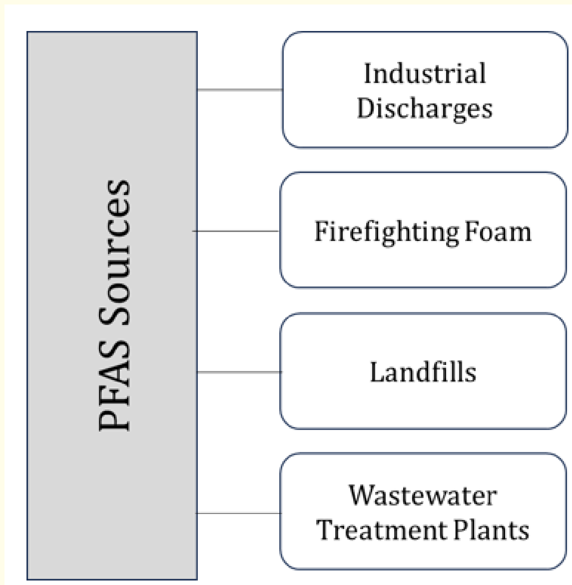

Figure 1: *PFAS sources.*

- Industrial discharges: Industries producing PFAS-containing products, such as textiles, electronics, and fire-fighting foam, can release PFAS into the environment through manufacturing processes or waste disposal [11].
- Fire-fighting foam: A significant source of PFAS contamination is using aqueous film-forming foam (AFFF) in fire-fighting and fire-training exercises. AFFF contains high levels of PFAS, and improper disposal or accidental releases can lead to environmental contamination [12].
- Landfills: Landfills that receive waste from industries or products containing PFAS can contribute to releasing PFAS into soil and water systems, leading to potential contamination of nearby areas [13].
- Wastewater treatment plants: PFAS can enter wastewater treatment plants through industrial discharges or domestic sewage. Conventional treatment methods may not effectively remove PFAS, releasing PFAS-contaminated water into rivers and lakes [14].

Chemical structure, physicochemical properties, absorption pathway, and adverse health effects of PFAS

PFAS are a class of synthetic chemicals distinguished by the attachment of fluorine atoms to carbon chains. PFAS has a carbon backbone with multiple fluorine atoms attached to each carbon atom. The length of the carbon chain and the type and arrangement of the functional groups can vary, resulting in a wide variety of PFAS compounds [15]. The chemical structure of PFAS is given in figure 2.

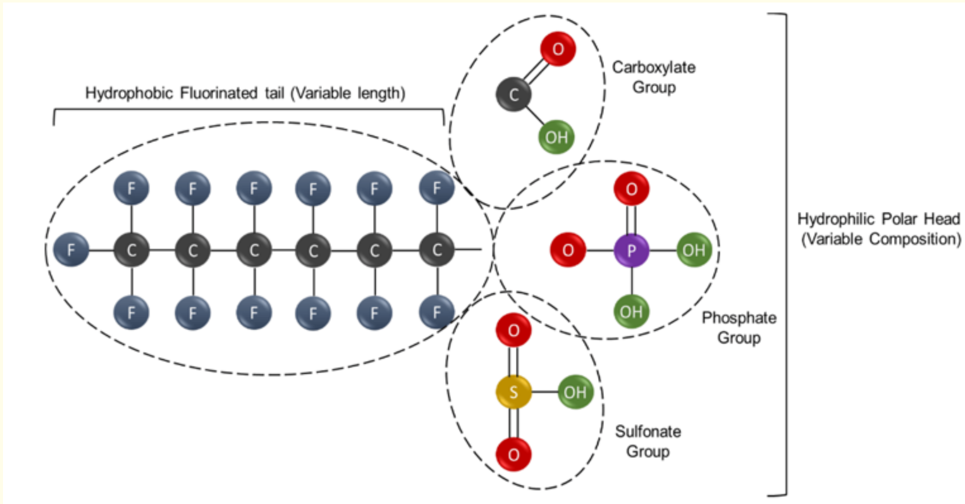

Figure 2: *Chemical structure of PFAS (Panieri., et al. 2022).*

PFAS exhibit several unique physicochemical properties contributing to their widespread use and persistence in the environment. Some key characteristics of PFAS are presented in table 1.

Properties	Description	Reference
Chemical Stability	PFAS compounds are highly stable due to the strong carbon-fluorine bonds, making them resistant to degradation by natural processes.	[16]
Hydrophobicity	PFAS are generally hydrophobic, meaning they repel water and have low solubility. However, certain PFAS, such as perfluorinated carboxylic acids, can be more water-soluble than others.	[17]
Lipophilicity	PFAS have a high affinity for fat- or lipid-based substances. This property contributes to their bioaccumulation potential in organisms and their ability to partition into fatty tissues.	[18]

Table 1: *Key characteristics of PFAS.*

PFAS can be absorbed through the gastrointestinal tract and enter the bloodstream following ingestion. Absorption of PFAS in the human body depends on the specific compound, route of exposure, and individual characteristics. Once absorbed, PFAS can spread throughout the body, including to the liver, kidneys, and thyroid gland [19].

Adverse health effects associated with PFAS exposure have been documented in scientific literature. Some of the notable health effects include:

- Endocrine disruption: PFAS can disrupt hormone regulation in the body, leading to potential effects on reproductive health, thyroid function, and growth and development [20].

- Immune system effects: Exposure to PFAS has been associated with immune system dysfunction, such as decreased antibody response, impaired immune cell function, and increased susceptibility to infections [21].
- Liver and kidney damage: Exposure to PFAS has been linked to liver toxicity, including abnormalities in liver enzymes and liver damage. In addition, certain PFAS compounds have been linked to kidney damage and diminished kidney function [22].
- Cancer risk: Certain PFAS compounds have been categorized as probable or possible human carcinogens, and evidence links them to kidney, testicular, and liver cancer [23].

Significantly, the extent and severity of adverse health effects may vary based on the specific PFAS compound, duration of exposure, and concentration. Ongoing research elucidates the full spectrum of health effects and their underlying mechanisms.

PFAS and pregnancy outcomes

It has been discovered that PFAS compounds can cross the placenta and be absorbed by the developing fetus. Studies have shown that PFAS can cross the placenta from the mother's bloodstream to the fetus's bloodstream, potentially exposing the fetus to these chemicals during crucial stages of development [24,25]. Exposure to PFAS during pregnancy has been associated with various adverse pregnancy outcomes. Some of the notable effects include:

a. Miscarriages: Several studies have reported an increased risk of miscarriage in pregnant women with higher levels of exposure to PFAS. Elevated PFAS concentrations in maternal serum have been associated with an increased risk of spontaneous abortion [26,27].

b. Lower birth weight: Prenatal exposure to PFAS has been linked to reduced birth weight in infants. Higher levels of PFAS in maternal serum or cord blood have been associated with decreased birth weight and a higher likelihood of small-for-gestational-age infants [28,29].

c. Pregnancy-induced pre-eclampsia, hypertension, and increased blood pressure: Some evidence suggests that PFAS exposure during pregnancy may be associated with an increased risk of pregnancy-induced conditions such as pre-eclampsia and hypertension. Elevated PFAS levels in maternal serum correlate with higher blood pressure and a higher incidence of pre-eclampsia [30,31].

d. Effects on time-to-pregnancy (Fecundity): Studies have shown that PFAS exposure may affect fecundity, which is the ability to conceive. Prolonged time-to-pregnancy and reduced fertility rates have been observed in couples with higher PFAS exposure levels [32,33].

Prenatal exposure to PFAS may have latent effects on health outcomes in adulthood. Although research is ongoing, some studies have suggested that early-life PFAS exposure may have long-term health effects. These effects may include altered immune function, metabolic alterations, and later-life susceptibility to certain diseases [34,35].

Notably, the precise mechanisms by which PFAS exert their effects on pregnancy outcomes are still being elucidated, and additional research is required better to comprehend the underlying processes and potential preventive measures.

Adverse effects of PFAS exposure

Studies have suggested that early-life exposure to PFAS may disrupt normal mammary gland development. Animal studies have shown delayed mammary gland development in offspring exposed to PFAS during critical periods of development, which may have implications for breast health later in life [36,37].

The long-term effects of PFAS exposure in adult life are still being studied, but some potential health effects have been identified. Research indicates that specific body structures have a higher propensity for PFAS absorption. For example, PFAS compounds have been found to accumulate in liver tissue and the kidneys, lungs, and blood [38,39]. Exposure to PFAS has been associated with various adverse health effects in humans (Table 2).

Health Effects	Description	References
Liver Toxicity	PFAS exposure has been linked to liver damage, including hepatotoxicity and altered liver function. Elevated PFAS levels have been associated with increased liver enzymes and hepatocellular injury.	[40,41]
Endocrine Disruption	Certain PFAS compounds have been shown to interfere with endocrine system function. They can disrupt hormone regulation and may lead to adverse reproductive and developmental effects and potential impacts on the thyroid gland.	[42,43]
Immune System Dysfunction	PFAS exposure has been associated with immune system dysregulation. Studies have reported alterations in immune response, including decreased antibody production, suppressed immune function, and increased susceptibility to infections.	[44,45]
Cancer	Some epidemiological studies have suggested a potential association between PFAS exposure and certain types of cancer, such as kidney and testicular cancer. However, further research is needed to establish a definitive causal relationship.	[46,47]
Cardiovascular Effects	Emerging evidence suggests that PFAS exposure may be associated with cardiovascular health risks. Elevated PFAS levels correlate with an increased risk of hypertension, elevated cholesterol levels, and a higher incidence of cardiovascular disease	[48,49].
Neurodevelopmental Effects	Prenatal and early-life exposure to PFAS has been linked to neurodevelopmental effects in children. Studies have reported associations between PFAS exposure and altered cognitive function, behavioral problems, and impaired neurodevelopment.	[50,51]

Table 2: *Adverse health effects in humans due to PFAS exposure.*

Metabolic effects of PFAS exposure

PFAS exposure has been associated with various metabolic effects and potential health consequences:

- Increased cholesterol levels: Studies have indicated a positive association between PFAS exposure and elevated cholesterol levels and other lipids in the blood. Higher concentrations of PFAS compounds have been linked to increased total cholesterol, LDL cholesterol, and triglycerides [52,53].
- Thyroid dysfunction: Certain PFAS compounds, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), have been found to interfere with thyroid hormone homeostasis. They can disrupt thyroid function by affecting hormone synthesis, binding, and transport, potentially leading to hypothyroidism or altered thyroid hormone levels [54,55].
- Gastrointestinal tract disorders: Some studies have reported a potential association between PFAS exposure and gastrointestinal (GI) tract disorders, including irritable bowel syndrome (IBS) and other functional GI disorders. However, more research is needed to establish a definitive causal link [56,57].
- Liver damage: PFAS exposure has been linked to liver damage and hepatotoxicity. Elevated levels of PFAS compounds have been associated with increased liver enzymes, inflammation, and hepatic injury [58,59].
- Kidney cancer: While the evidence is still evolving, some epidemiological studies have suggested a potential association between PFAS exposure and kidney cancer. However, further research is required to establish a conclusive relationship [60,61].

- Testicular cancer: Limited evidence suggests a possible link between PFAS exposure and testicular cancer. However, more research is needed to determine the nature of this association [62,63].
- Reproductive effects: PFAS exposure has adverse effects on male reproductive health. Studies have reported reduced sperm count, impaired sperm motility, and alterations in reproductive hormones [64,65].
- Breast cancer: Although the evidence is currently limited and conflicting, some studies have suggested a potential association between PFAS exposure and an increased risk of breast cancer. Further research is needed to establish a definitive link [66,67].
- Reduced vaccine response: Prenatal and childhood exposure to PFAS has been associated with reduced antibody response to vaccines, potentially compromising the effectiveness of immunization [68,69].
- Impaired immune function: PFAS exposure has been linked to immune system dysregulation. Studies have reported alterations in immune response, including reduced antibody production, suppressed immune function, and increased susceptibility to infections [70,71].
- Neurological effects: Some emerging evidence suggests a possible association between PFAS exposure and neurological effects, including cognitive impairment, neurodevelopmental disorders, and neurodegenerative diseases such as dementia, Parkinson's disease, and Alzheimer's disease. However, more research is needed to establish a conclusive relationship [72,73].

Epigenetic changes

Changes in gene expression that are not caused by alterations in the DNA sequence but rather by chemical modifications of the DNA or associated proteins are referred to as epigenetics. Multiple studies have examined the potential epigenetic effects of PFAS exposure. Some research suggests that PFAS exposure may be linked to epigenetic alterations, specifically DNA methylation patterns. DNA methylation is a frequent epigenetic modification involving adding a methyl group to DNA, which can influence gene expression. Concerning PFAS exposure, alterations in DNA methylation patterns have been observed in numerous studies.

For instance, Zhang., *et al*. (2013) examined the DNA methylation patterns in a population exposed to PFAS. They discovered alterations in the DNA methylation levels of specific genes involved in biological processes [74]. Winquist., *et al*. (2019) reported associations between PFAS exposure and DNA methylation modifications in placental tissue [75].

Political and public health factors influencing PFAS research

A thorough examination of the political and public health factors influencing research on the relationship between PFAS and human health reveals several vital insights. The direction of PFAS research is significantly influenced by political factors such as policy decisions and regulations. Various stakeholders influence these decisions, including policymakers, industry representatives, and advocacy groups [76]. Concerns about potential conflicts of interest and bias in scientific studies can sometimes be raised when the industry is involved in setting research agendas [77].

Public health factors, such as public perception and advocacy, also play a significant role in PFAS research. Increased public awareness of PFAS contamination and its potential health effects has prompted increased advocacy for research and policy modifications. The significance of effective risk communication strategies [78] is exemplified by the fact that public perceptions and concerns can impact policymaking and research priorities. Engagement and participation of the public in the research process are essential to ensuring that studies address community concerns and meet public health needs [79].

Emerging health concerns associated with PFAS exposure have shaped the research agenda significantly. Scientists have focused on comprehending the effects of PFAS exposure on human health and identifying potential health risks. [80] Health surveillance and epidemiological studies have contributed to understanding PFAS-related health outcomes, including associations with various diseases and conditions. Collaborative research efforts have emphasized the need for multidisciplinary approaches, data sharing, and knowledge exchange to address the complex challenges of PFAS research [81].

Political factors, industry influence, public perception and advocacy, and emerging health concerns affect PFAS health research. Understanding these factors is crucial for directing research and developing evidence-based PFAS exposure mitigation policies.

Current practices and laws to reduce or eliminate environmental PFAS

Existing regulations and practices to reduce or eliminate environmental PFAS are crucial for mitigating the risks associated with these persistent pollutants. Multiple measures have been taken to regulate PFAS and safeguard the environment and human health. These practices and laws involve various factors, such as regulations, advisories, source control, waste management, and international efforts.

The Environmental Protection Agency (EPA) has established regulations and exposure limits for PFAS to minimize exposure and control their release into the environment. These regulations include drinking water, air emissions, and the disposal of materials containing PFAS [82]. In addition, the EPA issues health advisories for PFAS in drinking water to guide water utilities and guarantee the safety of drinking water supplies [83].

Source control and remediation of PFAS contamination are essential for preventing additional environmental contamination. PFAS contamination is managed by identifying contamination sources, implementing remediation strategies, and developing effective treatment technologies [84]. Understanding the sources and pathways of PFAS release is necessary to implement targeted control measures.

Global prohibitions and restrictions on PFAS compounds have been enacted to reduce their use and limit their environmental impact. These regulatory actions aim to eliminate the production and use of particular PFAS chemicals, such as perfluorooctanoic acid (PFOA) and perfluoro octane sulfate (PFOS) [85]. These prohibitions and restrictions reflect global efforts to reduce perfluorinated alkyl substances (PFAS) use and transition to safer alternatives.

Waste management strategies for PFAS-containing waste are also crucial to prevent their release into the environment. Proper handling, treatment, and disposal of PFAS-containing materials are essential to minimize the potential for contamination. These strategies involve identifying appropriate waste management facilities, implementing containment measures, and developing protocols for safe disposal [86].

International efforts and collaborations play a significant role in addressing the global challenges associated with PFAS. Cooperation between countries and organizations aims to share knowledge, establish guidelines, and develop harmonized approaches for managing PFAS contamination. These efforts facilitate information exchange, data sharing, and coordination of research and regulatory activities [87].

Regulations, advisories, source control, waste management, and international collaborations reduce or eliminate environmental PFAS. PFAS contamination, ecosystems, and human health depend on these efforts.

Current practices and laws to reduce or eliminate environmental PFAS

Efforts to reduce or eliminate environmental PFAS involve various procedures and regulations to minimize contamination and mitigate health risks. These measures include:

- Regulatory actions: Regulatory agencies set limits on PFAS concentrations in water, air, and consumer products [82]. For example, the United States Environmental Protection Agency (EPA) has established drinking water health advisories for certain PFAS compounds [83].

- Source control and treatment: Efforts focus on identifying and reducing PFAS sources, such as industrial discharges, and implementing effective treatment technologies to remove PFAS from contaminated sites [88].
- Phase-out and substitution: Some jurisdictions have implemented bans or restrictions on specific PFAS compounds, encouraging the use of safer alternatives [89].
- Waste management: Proper management and disposal of PFAS-containing waste, including incineration or containment, aim to prevent further environmental contamination [90].

Future perspectives and research on PFAS and environmental exposure reduction

Future research and perspectives on PFAS are essential for understanding these contaminants and developing strategies to mitigate their impact on the environment and human health. Current scientific investigations and emerging research foci shed light on the future of PFAS research and potential solutions.

The need for precise and sensitive measurements drives the constant evolution of analytical methods for PFAS detection. Advanced analytical techniques, such as high-resolution mass spectrometry and non-targeted screening methods, enhance the capacity to detect and quantify PFAS in diverse environmental matrices [91].

Assessing the health effects of PFAS exposure is an active area of research, with a particular emphasis on elucidating the mechanisms of toxicity and its effects on various organ systems. Current knowledge suggests that exposure to PFAS may result in adverse health effects, including developmental and reproductive disorders, immune system dysfunction, and cancer [92].

Sustainable alternatives to per- and poly-fluoroalkyl substances (PFAS) are gaining interest as researchers and industries seek to reduce their reliance on these persistent chemicals. This shift includes developing and evaluating alternative materials and technologies with comparable functionality but without the environmental and health risks posed by PFAS [93].

In PFAS research and management, risk communication and public engagement play a crucial role. Effective communication strategies, including clear and accessible information, stakeholder participation, and community engagement, are essential for building trust, informing decision-making, and ensuring the public understands the risks and mitigation measures associated with PFAS [94].

Future perspectives and PFAS research generally include improvements in analytical techniques, the evaluation of health effects, sustainable solutions, and risk communication. By addressing these issues, scientists, decision-makers, and stakeholders can help develop strategies to reduce PFAS's risks to the environment and public health.

Conclusion

Due to their unique properties, PFAS are widely used in industries and consumer products. However, research has revealed their use's environmental and health risks. PFAS can persist in the environment and contaminate soil, water, and wildlife. As PFAS has been linked to adverse effects on the endocrine and immune systems, liver and kidney damage, and an increased risk of cancer, health advisories, and regulations have been established to limit exposure. Exposure to PFAS during pregnancy can result in adverse pregnancy outcomes. The physicochemical properties of PFAS contribute to their persistence and accumulation in organisms, resulting in adverse effects on numerous organ systems. Although more research is required to comprehend the mechanisms of PFAS toxicity fully, it is evident that these chemicals have significant negative impacts on human health. The development of preventive measures is essential. Overall, the findings presented in this manuscript underscore the critical need for continued research, regulation, and mitigation strategies to address the environmental impact and health risks associated with PFAS exposure. By advancing knowledge of per- and poly-fluoroalkyl substances (PFAS), science, medicine, and society can reduce their use, develop safer alternatives, and protect human health and the environment.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

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