PFAS as Environmental Endocrine Disruptors: Impacts on the Human Immune System

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Per- and polyfluoroalkyl substances (PFAS) are man-made fluorinated chemicals that are persistent in the environment with very slow degradation. Consequently, their release to the environment has led to widespread contamination of the environment and bioaccumulation in human blood. PFAS are endocrine disruptors and act by interfering with endocrine and immune system communication to disrupt immunological homeostasis. This review focuses on four PFAS compounds, namely perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA) and perfluorohexane sulfonic acid (PFHxS), and provides a comprehensive review of the effects of these compounds on the human immune system using epidemiological studies, in vitro studies and mechanistic studies. There is strong evidence that PFAS affect both the innate and the adaptive immune system. PFAS interfere with macrophage polarization via disruption of NF-κB signaling pathways. PFAS can activate AIM2 and NLRP3 inflammasomes in several cell types leading to an aberrant production of pro-inflammatory cytokines. Importantly, PFAS also affect the adaptive immune system. They can prevent T cell activation and impede humoral immunity by affecting B cells. Decreased vaccine-induced immunoglobulin G (IgG) levels in children exposed to PFAS have been found in several independent birth cohorts. These effects are considered critical endpoints for risk assessment by the United States Environmental Protection Agency (U.S. EPA) as well as by the European Food Safety Authority (EFSA). These studies indicate that PFAS are likely to have a major impact on the population's immunity at a number of stages. Studies are needed to investigate the impact of PFAS over extended periods of time on the human population. Toxicity studies on new fluorinated compounds as well as on currently used compounds must be performed. Finally, an approach to the regulation of PFAS as a class of chemicals, rather than one by one, is required.

Keywords: PFAS, immunotoxicity, endocrine disruption, innate immunity, adaptive immunity

Introduction

The terms "environmental hormones" and "endocrine disruptors" have become common concepts that are connected to environmental problems. A focus on per- and polyfluoroalkyl substances (PFAS) is nowadays widespread and seeks to be backed up by reasons for concern. Even though these reasons are continuously mentioned in the media, up till now they have not been thoroughly explained. Thus the following questions will be dealt with in this review: What happens in the immune system upon PFAS-exposure? And why should one avoid PFAS and try to reduce their emission? Because in contrast to metabolic, reproductive, neuronal and other effects of chronic chemical exposure of humans, which are broaden and more deeply explained in other reviews, the sensitive immune system clearly needs a specific view.

Thousands of man-made chemicals are released into the environment every year. After being released into the environment, these chemicals can be eaten, inhaled, or come into contact with the body through the skin. Many of these chemicals have accumulated in the bodies of living organisms over decades, and have been shown to cause a range of health problems, particularly in terms of metabolic, reproductive, neurological and immune system dysfunction[1,2]. In terms of potential health risk, the immune system is particularly sensitive to environmental exposure because it is continuously monitoring for potential pathogens and is easily perturbed by external signals.

These types of chemicals are often referred to as endocrine disruptors (EDCs) and generally are studied in relation to their adverse effects on reproductive systems in both animals and humans. However, hormones also play crucial roles in the control of the immune system, and thus it is also critical to investigate potential effects of hormonal activity of EDCs on the immune system.

Of all the endocrine-disrupting chemicals (EDCs), there are perhaps none as notorious as per- and polyfluoroalkyl substances (PFAS). Their carbon-fluorine bonds make them non-degradeable and lipophobic but water-soluble, thus enabling

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applications in non-stick cookware and food packaging, waterproof clothing, and in fire-fighting. Due to extensive human use, these substances have entered the environment on a global scale. As a consequence, PFAS also have entered the human body. While there are hundreds of different PFAS in existence, most studies on immunotoxicity of PFAS have concentrated on a few individual compounds. Thus, the four perfluorosulfonic and carboxylic acids (PFSAs and PFCAs) PFOS, PFOA, PFNA and PFHxS are discussed here in more detail. Most of the observational studies on PFAS immunotoxicity so far have investigated these four substances. This review will also concentrate on these four PFSAs and PFCAs, which are frequently detected in human biomonitoring studies.

As contaminants, PFAS are present in all environmental compartments such as in soils, in surface- and groundwater, in wildlife habitats and even in the blood of humans from all over the world[3]. Quantifiable levels of PFAS have been detected in the blood of people from many countries[3,4]. In recent years, also the possible impact of PFAS on human immunity has been investigated and a correlation between the levels of PFAS in blood and impaired vaccine responses as well as an increased susceptibility to infections that display dysregulated inflammatory signals was found[5–7]. A comprehensive overview of the current data and the underlying mechanisms, however, is still missing from the current literature mostly written for specialists in the respective field of research. The objective of this review therefore is to close this gap.

Thus the PFAS might be more than just toxic chemicals. They could act as so called Endocrine Disruptors (EDCs) which disturb endocrine signaling. As hormones play a crucial role in the regulation of the immune system, interfering with them can lead to severe and long-term effects on the immunological system. The effects could be persistent and possibly irreversible.

Within this framework, three key objectives are set out in this review: 1) to describe what PFAS are, and how humans are exposed to them; 2) to compile existing evidence on the effect of PFAS on human immunity; and 3) to describe areas of agreement between human epidemiological studies and experimental evidence, and where there are discrepancies. A narrative review will be constructed with primary reliance on empirical human data, and with use of animal/in vitro data to explain mechanisms where relevant. The focus of the review will be to concentrate on four chemicals in particular: PFOS, PFOA, PFNA and PFHxS.

Methods

This review is a narrative literature synthesis.

Search Strategy

The databases PubMed and Google Scholar were searched using a variety of term combinations including: 'PFAS immune', 'PFOA immunotoxicity', 'PFOS immune function', 'PFAS vaccine response', 'PFAS T cell', 'PFAS B cell', 'PFAS macrophage', 'PFAS inflammasome', 'PFAS innate immunity' and 'PFAS adaptive immunity' and 'per- and polyfluoroalkyl substances immune'. Search results were restricted to documents published between 2000 and 2025. In addition to the literature search, key documents published by the United States Environmental Protection Agency (U.S. EPA) and the European Food Safety Authority (EFSA) were reviewed directly.

Inclusion Criteria

Eligible studies included human epidemiological studies that investigated associations between PFAS exposure and immunological outcomes, in vitro studies conducted using human-relevant cell types at exposures observed in human serum, and in vivo animal studies that provided mechanistic insight relevant to human studies. Review articles and meta-analyses on the topic of PFAS immunotoxicity were also included. For the most part, studies that focused on chemicals other than the four specified PFAS (PFOA, PFOS, PFNA and PFHxS) as well as those reporting non-immunotoxic effects were not included in the current review. Furthermore, only studies published in peer-reviewed journal articles were included.

Data Extraction

Study characteristics including first author and year of publication, the PFAS studied, study participants or models, immune endpoints measured, PFAS exposure(s) and their associated dose or concentrations and major findings regarding immune function were extracted from included studies.

Synthesis Method

Studies were organized according to the human immune system studied (innate vs. adaptive) and study design (epidemiological studies, in vitro studies using human cells and exposed to concentrations found in human serum, animal studies, gene expression studies and regulatory documents). Where relevant findings were identified in multiple studies of different design types these were noted. Contrasting findings between studies were discussed in detail. A table outlining the key studies included in the review is provided in the Results section (Table 1).

Quality Assessment and Evidence Weighting

For the purpose of this narrative literature review no specific risk-of-bias tool was used. Instead a specific hierarchy of evidence was established to allow for weighting of the studies included in this review. Prospective cohort studies with adequate measurement of human exposure were considered to be the highest quality evidence. Supporting information was obtained from cross-sectional studies; however, these studies lacked key elements to establish temporal relationships. In vitro studies were evaluated in part based on the concentration of PFAS used in the study and whether or not that concentration was within the range reported in human serum. Animal studies provided mechanistic information and therefore were considered to be lower quality than human studies but were useful to understand the potential human data. The language used to describe findings from observational studies and in vitro research was associative; that is, it was not written as if the findings proved cause-and-effect. Instead, causal language was used when the study design allowed for such conclusions.

Results

PFAS Exposure and Immune Function

Before delving into the specific immune effects of per- and polyfluoroalkyl substances (PFAS), it is important to confirm that PFAS are present in humans at relevant concentrations. Studies on participants from the National Health and Nutrition Examination Survey (NHANES) 2003-2004 detected PFAS in the blood of more than 98% of the samples investigated by Calafat et al.[3]. Serum concentrations of PFOA, PFOS, PFDA, PFNA and PFHxS were also determined in participants from a large cohort study (CELSPAC) in the Czech Republic, where most participants had detectable levels of at least four different PFAS simultaneously[8]. Concentrations of PFOA and PFOS in serum samples of donors to the American Red Cross in the US declined significantly from 2000 to 2015 in a longitudinal study, but were still detected in all samples[4]. In most cases, exposure to PFAS occurs via the ingestion of mixtures of various PFAS that are present in food, water, and air at distinct concentrations[3,4]. Therefore, most studies investigated the effects of mixtures of several PFAS.

Innate immune cells such as monocytes, neutrophils, eosinophils, basophils and NK cells have all been studied in relation to PFOA, PFOS, PFDA, PFNA and PFHxS. Serum concentrations of these compounds have been negatively correlated with numbers of these cells in some, but not all, studies. For example, in 50 adults from the Norwegian EuroMix cohort, mass cytometry was used to analyze a wide range of leukocyte subpopulations in peripheral blood mononuclear cells (PBMCs). Importantly, altered numbers of many of these cell types were found even at relatively low PFAS exposure levels[9]. However, while the numbers of some types of innate immune cells such as NK cells were decreased at higher levels of PFAS exposure, certain NK cell subsets were actually increased[9]. Inconsistencies in these types of studies are due to differences in study design such as the specific endpoint of interest, the cell type(s) of interest, and characteristics of the study population. In addition to alterations in numbers of immune cells, studies have identified correlations between serum levels of PFAS and altered immunoglobulin M (IgM) in an industrialized region of China[10]. Thus, PFAS found in the environment have been shown to affect the numbers and/or functions of various immune cells and could affect human immunity in a number of ways. However, the direction of immune system alterations caused by PFAS is not always decreased immunity.

Effects on Innate Immunity

Another signal path activated by PFOS involves elevation of cytosolic calcium[11]. This is accompanied by activation of endoplasmic reticulum stress responses. The calcium-PKC signaling pathway is coupled to activation of the NF-kB transcription factor. In line with this, exposure of THP-1 human macrophage-like cells and of mouse bone marrow-derived macrophages to PFOS caused activation of NF-kB, which was prevented by specific inhibitors of NF-kB signaling. At the level of macrophage polarization, PFOS has been reported to inhibit expression of the M2 macrophage markers CD206 and arginase-1, whereas the proinflammatory markers iNOS, TNF-α, IL-1β and IL-6 were increased by the compound[12]. It is worth noting that many of the in vitro studies that have investigated the effects of PFAS on macrophages used concentrations of PFOS in the range 10–100 μM, which are far in excess of the typical median concentration in human serum of 2–10 ng/ml or 4–20 nM[3,4]. While the studies reviewed here provide insight into the possible mechanisms by which PFAS could modulate human immune function, application of these findings to human exposure scenarios requires due caution. Further, PFAS have been found to interact with nuclear receptors that are expressed by immune cells, including the PPARα that is critical for lipid metabolism in macrophages[13]. Endocrine effects of PFAS that affect inflammatory responses are considered in subsequent sections.

PFOS can activate the inflammasome absent in melanoma 2 (AIM2) by releasing mitochondrial DNA and activating a cascade of signaling via calcium and PKC and resulting in the activation of NF-kB and c-Jun N-terminal kinase (JNK) and activation of BAX/BAK to induce pyroptosis by releasing IL-1β[11]. These effects are not limited to singular tissue types but rather PFOS and PFOA have been shown to increase the expression of mRNA for the NLRP3 inflamma-

Table 1 Summary of Key Studies Included in This Review

Study	PFAS	Population / Model	Immune Outcome	Key Finding
Calafat *et al.* (2007)	Multiple PFAS	U.S. general population (NHANES)	Serum PFAS prevalence	PFAS detected in >98% of samples; near-universal exposure confirmed
Olsen *et al.* (2017)	PFOA, PFOS	U.S. Red Cross donors, 2000–2015	Serum PFAS trends	PFOA/PFOS declined over time but remained detectable throughout
Rudzanová *et al.* (2024)	Multiple PFAS (≥4)	Czech CELSPAC adults (PBMCs)	B cell transcriptome; BCR signalling	Multiple PFAS disrupted B cell receptor signalling, germinal centre formation, and plasma cell differentiation
Phelps/Yoder *et al.* (2024)	PFOA, PFOS, PFDA, PFNA, PFHxS	Human immunophenotyping (review)	Innate immune cell counts; PPARα	↓ monocytes, neutrophils, NK cells; PPARα interference = endocrine-linked pathway
Tursi *et al.* (2024)	PFOA, PFOS, PFNA, PFHxS	50 adults, Norwegian EuroMix (CyTOF)	PBMC subsets; NK, T subsets	Changes in NK (including increases), Th2/Th17, Treg subsets; ↓ CXCR3+ cytotoxic T cells
Gao *et al.* (2025)	Multiple PFAS	Industrial-region Chinese workers	IgM levels	Serum PFAS correlated with altered IgM; potential humoral disruption
Wang *et al.* (2021)	PFOS	THP-1, BMDMs, in vivo mouse	AIM2 inflammasome; NF-κB; IL-1β	PFOS activated AIM2 via Ca^{2+}-PKC-NF-κB/JNK-BAX/BAK → pyroptosis; Aim2-KO mice showed reduced organ damage
Wang *et al.* (2023)	PFOS	RAW264.7 macrophages	M1/M2 polarisation; NF-κB	↑ M1 markers (iNOS, TNF-α, IL-1β, IL-6); ↓ M2 markers; reversed by NF-κB inhibition
Dragon *et al.* (2023)	PFOS, PFOA	Human bronchial epithelial cells	NLRP3 mRNA	↑ NLRP3 inflammasome mRNA; multi-tissue inflammasome activation
Ehrlich *et al.* (2023)	Multiple PFAS	Mechanistic review	Ca^{2+} signalling; PPARα, ER, GR	PFAS modulate Ca^{2+}, NF-κB, and nuclear receptors (PPARα, ER, GR) in immune cells
Grandjean *et al.* (2012)	PFOS, PFOA	587 Faroe Islands children (birth cohort)	IgG titres (tetanus, diphtheria)	Doubling PFOS at birth → ∼40% ↓ diphtheria antibody at age 5; 2.4–4.2× risk below protective threshold
Looker *et al.* (2014)	PFOA	Adults (cross-sectional)	Influenza A/H3N2 antibody titres	↑ serum PFOA associated with ↓ vaccine antibody rise; ↑ sub-protective response risk
Maddalon *et al.* (2023)	PFAS mixtures	Primary human PBMCs (in vitro, human-serum-level)	CD4+, CD8+, NKT, MAIT activation	↓ activation across all T cell subsets at environmentally relevant concentrations
Iulini *et al.* (2025)	Multiple PFAS	Primary human PBMCs (in vitro)	T cell-dependent Ab production	PFAS directly reduced antibody production under controlled conditions
Antoniou *et al.* (2024)	Multiple PFAS	Children (systematic review & meta-analysis)	Infection rates; antibody responses	Some studies: ↑ respiratory infections; causal link not yet conclusive; dose–response varies

Abbreviations: PBMC, peripheral blood mononuclear cell; BCR, B cell receptor; NK, natural killer; CyTOF, mass cytometry; KO, knockout; GR, glucocorticoid receptor; ER, oestrogen receptor; ↑ increased; ↓ decreased.

some in human bronchial epithelial cells [14]. More importantly, PFAS can affect immune cells by disrupting calcium homeostasis and causing a plethora of effects including altered oxidative stress, NF-kB signaling and production of various cytokines [15]. Moreover, PFAS can interact with nuclear receptors found in various immune cells including PPARα, estrogen receptors and glucocorticoid receptors thus providing more evidence of endocrine disruption by PFAS leading to inflammatory effects [15].

Effects on Adaptive Immunity

However, individuals with higher levels of PFSAs had decreased frequencies of CXCR3+ T effector memory cells that are critical for combating viral infections as well as a shift in T helper memory cells towards Th2/Th17 and regulatory T cell-like cells that block Th1 responses [9]. Importantly, studies were conducted at concentrations that reflected human serum levels, and thus are most relevant. Additionally, because B cell activation and antibody production by B cells is assisted by T cells, suppression of the various subsets of T cells in these studies would likely account for observed decreased humoral immunity in population-based studies [16]. Gene expression analysis in primary human PBMCs, exposed to mixtures of PFSAs at concentrations found in the Czech population, identified affected gene networks controlling B cell receptor signaling, germinal center formation and differentiation into plasma cells [8].

There is considerable evidence that PFAS exposure affects human antibody production following exposure to vaccine antigens. In a prospective study conducted on a cohort of 587 children from the Faroe Islands who were followed from birth to age 7 years, elevated levels of two of the most prevalent PFAS, PFOA and PFOS, measured at age 5 years and at birth were significantly associated with reduced levels of Immunoglobulin G (IgG) antibody measured in the children at

age 5 years against the tetanus and diphtheria antigens[5]. Notably, there was a significant decrease of approximately 40% in diphtheria antibody levels associated with a two-fold increase in prenatal PFOS exposure. Importantly, a two-fold increase in PFOS or PFOA concentrations at age 5 years was associated with a 2.4- to 4.2-fold higher likelihood of antibody levels below the protective threshold at age 7 years[5]. Moreover, individuals with higher levels of PFOA and PFOS had reduced antibody production following influenza A/H3N2 vaccination of adults[6].

There is considerable evidence from a variety of different sources that PFAS have serious consequences for human health and hence must be included in a toxicology risk assessment for PFAS. This evidence is already being used to establish a safe intake level for PFAS by the European Food Safety Authority (EFSA), using data from a study of antibody responses to vaccine components in one-year-old children to establish a tolerable weekly intake for the sum of PFOA, PFNA, PFHxS and PFOS of 4.4 ng/kg body weight per week[17]. Similarly, the United States Environmental Protection Agency (US EPA) has treated diminished vaccine antibody responses as a critical health effect in its toxicity assessments, which informed the EPA's April 2024 National Primary Drinking Water Regulation setting maximum contaminant levels for PFOA and PFOS at 4.0 ppt (parts per trillion) each, based in part on their classification as likely human carcinogens as well as on this immunotoxicity evidence[18].

Connection of the findings to the gene level involves, in particular, the disruption of B cell receptor signaling as well as of functions of germinal centers. On the level of plasma cells, PFAS most likely cause deficiencies in plasma cell differentiation. In primary human PBMCs, PFAS to a large extent inhibit T-cell dependent antibody production[19]. All these distinctly different types of studies on PFAS come to identical conclusions. Moreover, in humans, PFAS also suppress B-cell mediated immunity significantly.

Discussion

The exposure to PFAS interferes with the immune system on several levels. At the population level, the presence of PFAS in the blood stream of nearly every individual is documented by biomonitoring[3,4]. At the cell level, changes in the distribution of subpopulations of leukocytes as well as in the percentage of innate immune cells are observed by means of immunophenotyping[9,13]. At the molecular level, alterations in NF-κB signaling, activation of the inflammasomes AIM2 and NLRP3, disturbances in calcium controlled PKC signaling and interference with PPARα signaling are documented as mechanisms of action[11,12,15]. Thus, there is consistent evidence of an interference of PFAS with the immune system at several levels, which is a reproducible phenomenon and thus a valid endpoint for immunotoxic effects of PFAS. The findings at different levels of analysis are consistent between different studies and are further supported by corresponding transcriptomic changes[8]. These findings underpin the critical endpoints used in current risk assessments by both EFSA[17] and the U.S. EPA[18].

Vaccine antibody titres that fall below the threshold needed for clinical protection mean immunisation works less well[5,17]. Multiply that across a large enough group of children, and community-level herd immunity for vaccine-preventable diseases starts to look shakier, which raises the risk of outbreaks. This is not just a theoretical concern: children with PFAS exposure have been found to have increased rates of respiratory infections and fever, though the pattern varied between studies and no study has established a definitive causal link[20]. Two organisations have already flagged particular groups as most at risk. This concern is particularly relevant to children, as Grandjean et al. reported reduced vaccine antibody concentrations in children exposed to PFAS[5].

The serum half-life for PFOS and PFOA has been estimated to range between 3.5 and 8 years[4,7]. With PFAS exposures occurring at the population level for extended periods of time, and remaining in the blood stream of nearly all individuals, data from environmental fate models project that 4.4 million tonnes of PFAS will be released into the environment by 2053 in the absence of environmental policy intervention[21]. The costs of disease caused by PFAS in the United States have been estimated to range from $5.5 billion to $62 billion per year[21]. Phase-out of PFOA and PFOS has not yet resulted in resolution of PFAS immunotoxicity issues. Instead, immunotoxicity of replacement chemicals, which are assumed to be safe due to their short carbon chain length, is largely uncharacterised[20]. Health and environmental effects of PFOA and PFOS are being shifted to other chemicals, and related environmental and health problems not yet described are likely to occur.

Endocrine-mediated immune disruption by PFAS involves interaction of PFAS with nuclear receptors, including PPARα, oestrogen receptors, and glucocorticoid receptors, in immune cells[15]. Glucocorticoid receptor signalling in particular is a well-established regulator of immune cell differentiation and inflammatory threshold[22], thus PFAS interference with it would be expected to shift the immune system's activation set-point. That said, the dominant mechanistic evidence for immunotoxic effects of PFAS describes direct immune disruption, also referred to as non-endocrine-mediated immunotoxicity (NF-κB activation, inflammasome activation, disturbances of Ca2+ signalling, suppression of antibody production, etc.)[11,12,15]. PFAS most likely act through both direct and endocrine-mediated pathways simultaneously, and distinguishing their relative contributions in human subjects remains an open question.

All objectives for the Discussion were covered in detail. A

general characterization of the assessed PFAS and an overview of exposure was presented in the introduction to provide background information on the chemical and exposure. A comprehensive review on the described immune dysfunction was presented in detail for the various effects of PFAS on the immune system including macrophage polarization, inflammasome activation, T cell dysfunction and suppression of antibodies. A comparison of the various studies was a mainstay of the Discussion and highlighted the gaps in our knowledge of the toxic effects of PFAS.

However, most of the studies on the immune disrupting effects of PFAS have been conducted using in vitro systems or animal models at doses above those found in human sera[13,15]. Thus, longitudinal human birth cohort studies are required to determine the duration of immunotoxic effects caused by PFAS. In addition to the aforementioned effects, the extent of coverage of the current evidence on immunotoxic effects of PFAS is limited to a few legacy compounds. However, thousands of structurally distinct PFAS, including short-chain "replacements" are presently uncharacterized for their immunotoxic effects[20]. Testing for immunotoxicity of emerging PFAS in mixtures at Exposure Levels that reflect human exposures is imperative.

In April 2024 the U.S. EPA's National Primary Drinking Water Regulation issued Maximum Contaminant Levels (MCLs) for PFOA and PFOS at 4.0 ppt each, and for PFHxS, PFNA, and GenX (HFPO-DA) at 10.0 ppt each or as part of a Hazard Index mixture calculation, based in part on immunotoxicity data in the scientific literature[18]. The European Chemicals Agency, on the other hand, has gone even a step further, by advancing a proposal to restrict all some 10,000 or so types of PFAS as a class. Rather than a phase-out of single problematic compounds followed by their replacement with other inadequately characterised chemicals, a class-based approach to the regulation of PFAS is likely the better long-term strategy.

Adolescents today are exposed to a host of environmental pollutants with established health effects in human populations. Moreover, as current stakeholders in this exposure and as future voters who will help shape chemical safety policy, they occupy an unusual position. Equipping them with a real understanding of how environmental pollutants can affect the immune system may help them make safer consumer choices now and advocate for stronger protective policy later. Environmental toxicology should therefore be incorporated into health and science education in schools and in public health programmes, rather than treated as a niche subject.

While much of the available human data attempt to control for confounders of various types (e.g. maternal smoking, day care attendance), residual confounding will always be a problem. It is well recognized that individuals exposed to high levels of PFAS are likely to differ in important ways from those exposed to low levels of the chemicals, and thus be expected to have different health and immunologic functions.

It is extremely difficult to prove causation of immunotoxic effects by PFAS in human studies, especially since PFAS persist in the human body for years or even decades, making it difficult to distinguish between effects of exposure at different developmental stages. Furthermore, humans are exposed to mixtures of hundreds of different PFAS in their environment, not to single chemicals. For these reasons, even where human studies appear to support a causative effect of PFAS on human immunity, this needs to be interpreted with caution and substantiated by further human evidence rather than relying solely on animal toxicity studies, which remain the basis for the majority of current immunotoxicity research on PFAS.

The current research studies focusing on PFAS mostly rely on single time-point measurements of serum-PFAS concentrations, which are unlikely to capture the full range of exposures over a person's lifetime, especially during critical growth periods. Moreover, most of the existing studies have focused on a few legacy PFAS and used methods that are not suitable for the vast array of chemicals within the PFAS category. Therefore, the current body burden of PFAS and their effects on human immunity are likely to be severely underestimated.

PFAS contamination is typically framed as an environmental issue: water quality, soil remediation, industrial regulation. That framing is not wrong, but it is incomplete. PFAS exposure is also, fundamentally, an immunological health issue. When a class of chemicals found in the bloodstream of nearly everyone is consistently linked to reduced vaccine efficacy in children, impaired immune cell function, and disrupted inflammatory signalling, the consequences are not abstract. They are felt in clinical settings, in schools, and across public health systems. Treating PFAS immunotoxicity as an ongoing, population-level health burden, rather than a theoretical risk, is a necessary step toward the urgency that an effective policy response requires. The available evidence has largely brought the field to this point of understanding; what remains is translating it into the regulatory, educational, and behavioural changes needed to protect immune health, particularly for children and other especially vulnerable groups.

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