Public Health Risks Associated with Per- and Polyfluoroalkyl Substances in Drinking Water: Current Knowledge and Research Gaps

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Abstract: Per- and polyfluoroalkyl substances (PFAS) represent a critical public health challenge due to their widespread contamination of drinking water systems and established links to adverse health outcomes. This review synthesizes current scientific understanding of PFAS-related health risks while identifying critical research gaps that limit effective public health protection. PFAS contamination stems from diverse point and non-point sources, with global distribution patterns reflecting both historical industrial use and long-range environmental transport. Established health effects include increased cancer risk, cardiovascular disease, immune dysfunction, and developmental disorders, with children, pregnant women, and occupationally exposed groups representing particularly vulnerable populations. Current regulatory frameworks, while evolving rapidly, remain incomplete due to limited toxicological data for thousands of PFAS compounds and uncertainties regarding mixture effects. Critical research gaps include inadequate toxicological characterization of emerging PFAS, limited understanding of sensitive exposure windows, challenges in exposure assessment methodology, and uncertainties in risk assessment approaches. Treatment technologies show variable efficacy across different PFAS compounds, with cost and waste management challenges limiting widespread implementation. Priority research needs include long-term epidemiological studies, mechanistic toxicology research, improved analytical methods, and development of safer alternatives. Addressing these knowledge gaps requires sustained research investment, international collaboration, and adaptive regulatory approaches that can respond to emerging scientific evidence while protecting public health.

Keywords: PFAS, drinking water, public health, environmental contamination, toxicology, risk assessment, water treatment, regulatory policy

INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) represent one of the most pressing environmental and public health challenges of the 21st century (Sunderland *et al.,* 2019). Often referred to as "forever chemicals" due to their extraordinary environmental persistence, PFAS comprise a diverse class of synthetic organofluorine compounds that have been widely used in industrial and consumer applications since the 1940s (Buck *et al.,* 2011). The unique carbon-fluorine bonds that make these substances so useful in manufacturing, providing water, oil, and stain resistance, also render them virtually indestructible in natural environments and the human body (Krafft & Riess, 2015).

The scope of PFAS contamination has become increasingly apparent over the past two decades. These substances are now ubiquitous in drinking water systems worldwide, detected in public water supplies serving millions of people across developed and developing nations alike (Glüge *et al.,* 2020). In the United States alone, recent nationwide sampling efforts have revealed PFAS contamination in drinking water systems serving over 200 million Americans, with concentrations often exceeding newly established regulatory limits (Andrews & Naidenko, 2020; Hu *et al.,* 2016). The global nature of this contamination reflects both the widespread historical use of PFAS and their capacity for long-range environmental transport through atmospheric and hydrologic pathways (Cousins *et al.,* 2019).

From a public health perspective, PFAS present a particularly concerning exposure scenario. Unlike many environmental contaminants that degrade over time, PFAS accumulate in human tissues and remain detectable in blood serum for years following exposure (Olsen *et al.,* 2007). Epidemiological studies have linked PFAS exposure to a range of adverse health outcomes, including increased cancer risk, cardiovascular disease, immune system dysfunction, and developmental disorders (Fenton *et al.,* 2021; Steenland *et al.,* 2018). The evidence base continues to expand, with new studies regularly identifying previously unrecognized health effects and vulnerable populations (Rappazzo *et al.,* 2017).

The regulatory response to PFAS contamination has evolved rapidly but remains incomplete. In April 2024, the U.S. Environmental Protection Agency established the first-ever national drinking water standards for six PFAS compounds, marking a significant milestone in environmental health protection (U.S. EPA, 2024). However, thousands of PFAS compounds remain unregulated, and substantial gaps persist in our understanding of their individual and cumulative health risks (Wang

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et al., 2017). This regulatory lag reflects deeper scientific uncertainties about dose-response relationships, mixture effects, and the long-term consequences of chronic low-level exposure (Kwiatkowski *et al.,* 2020).

Current knowledge of PFAS health risks is characterized by both significant advances and critical gaps. While strong evidence exists for certain health outcomes, particularly for legacy compounds like perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), substantial uncertainties remain regarding newer PFAS compounds, sensitive exposure windows, and vulnerable populations (Boronow *et al.,* 2019; Grandjean & Budtz-Jørgensen, 2013). These knowledge gaps have profound implications for risk assessment, regulatory decision-making, and public health protection strategies.

This review synthesizes current scientific understanding of PFAS-related health risks in drinking water while critically examining the research gaps that limit effective public health response. By identifying priority areas for future investigation and highlighting policy implications of existing knowledge, this analysis aims to inform evidence-based approaches to PFAS management and protection of public health. The urgency of this challenge demands both immediate action based on current evidence and sustained research investment to address fundamental knowledge limitations that constrain our ability to protect communities from PFAS exposure.

PFAS CONTAMINATION IN DRINKING WATER SYSTEMS

Sources of Contamination

PFAS contamination in drinking water systems originates from diverse anthropogenic sources, reflecting the widespread historical use of these compounds across multiple industries (Lindstrom *et al.,* 2011). Point sources represent the most significant contributors to high-level contamination events, with industrial facilities, military installations, and airports serving as primary release sites (Hu *et al.,* 2016). Manufacturing facilities that produced or used PFAS in their operations have created substantial groundwater plumes that continue to migrate toward drinking water sources decades after initial releases (Cordner *et al.,* 2019).

Military installations present a particularly concerning contamination source due to the extensive use of aqueous film-forming foams

(AFFF) containing PFAS for firefighting training and emergency response activities (Anderson *et al.,* 2016). These facilities often exhibit extremely high PFAS concentrations in groundwater and surface water, with some sites recording levels exceeding 100,000 ng/L, orders of magnitude above regulatory limits (Schultz *et al.,* 2004). The legacy of military PFAS use has resulted in contamination at hundreds of sites across the United States, affecting both on-base water supplies and surrounding communities.

Airports represent another critical point source category, with firefighting foam use and fuel-related activities contributing to widespread contamination (Filipovic *et al.,* 2015). Commercial airports routinely used PFAS-containing foams for training exercises and emergency response, creating persistent contamination plumes that migrate through groundwater systems (Baduel *et al.,* 2017). The proximity of many airports to urban areas increases the potential for drinking water system impacts.

Non-point sources contribute to more diffuse but geographically extensive contamination patterns. Wastewater treatment plants serve as significant PFAS release points, as conventional treatment processes are largely ineffective at removing these compounds (Gao *et al.,* 2020). Municipal wastewater contains PFAS from diverse sources including household products, industrial discharges, and urban runoff, with treated effluent and biosolids serving as ongoing contamination sources (Munoz *et al.,* 2017).

Agricultural applications of biosolids and the use of PFAS-containing pesticides and fertilizers contribute to rural contamination patterns (Ye *et al.,* 2018). The practice of applying municipal biosolids as agricultural fertilizer has inadvertently distributed PFAS across agricultural landscapes, with subsequent leaching into groundwater and surface water systems (Sepulvado *et al.,* 2011).

Atmospheric deposition represents a globally significant transport mechanism, enabling PFAS contamination of remote areas far from direct sources (Dreyer *et al.,* 2009). Volatile PFAS precursors can undergo long-range atmospheric transport before degrading to persistent perfluoroalkyl acids, contributing to background contamination levels in pristine environments (Ellis *et al.,* 2004). This atmospheric pathway helps explain the global distribution of PFAS contamination, including detection in Arctic

environments and remote mountain lakes (Stock *et al.,* 2007).

Global Distribution and Prevalence

The global distribution of PFAS in drinking water systems reflects complex interactions between historical use patterns, environmental transport processes, and regional industrial activities (Glüge *et al.,* 2020). Developed countries with extensive industrial histories generally exhibit higher contamination levels, particularly in regions with significant chemical manufacturing, military installations, or firefighting foam use (Gobelius *et al.,* 2018).

In the United States, comprehensive monitoring efforts have revealed widespread PFAS contamination across diverse geographic regions and water system types. The Third Unregulated Contaminant Monitoring Rule (UCMR3) detected PFAS in approximately 4% of public water systems tested between 2013-2015, affecting an estimated 16.5 million people (Hu *et al.,* 2016). However, subsequent studies using lower detection limits suggest contamination may be far more prevalent, with some analyses indicating detectable PFAS in over 40% of tested water systems (Andrews & Naidenko, 2020).

European monitoring programs have similarly documented extensive PFAS contamination, with particularly high levels reported in industrial regions of Germany, the Netherlands, and Sweden (Ullah *et al.,* 2011). The European Environment Agency has identified PFAS contamination as a

priority concern, with member states reporting contamination at thousands of sites across the continent (EEA, 2019). Nordic countries have been particularly proactive in monitoring efforts, revealing widespread contamination even in relatively pristine environments (Filipovic *et al.,* 2015).

Contamination patterns in developing countries remain less well-characterized due to limited monitoring capacity and analytical resources (Li *et al.,* 2018). However, emerging evidence suggests significant PFAS contamination in rapidly industrializing regions, particularly in China and Southeast Asia where manufacturing activities have intensified (Pan *et al.,* 2018). Industrial facilities producing PFAS or PFAS-containing products have created substantial local contamination, with levels in some Chinese industrial areas exceeding those observed in historical contamination sites in developed countries (Wang *et al.,* 2016).

Urban versus rural contamination patterns reflect different source profiles and exposure pathways. Urban areas typically exhibit higher background contamination levels due to diverse diffuse sources, including wastewater discharges, urban runoff, and atmospheric deposition (Coggan *et al.,* 2019). Rural areas may experience lower background levels but can suffer severe point source contamination from agricultural biosolid applications or nearby industrial facilities (Munoz *et al.,* 2017).

Table 1: Global PFAS Contamination Levels in Drinking Water

Region/Country	PFOA Range (ng/L)	PFOS Range (ng/L)	Detection Frequency (%)	Key Sources
United States	<1 - 3,900	<1 - 7,000	4-45	Military, industrial, WWTP
Germany	<1 - 4,400	<1 - 2,100	15-25	Industrial, firefighting foam
Sweden	<1 - 1,200	<1 - 800	20-35	Military, WWTP, landfills
Netherlands	<1 - 2,800	<1 - 1,500	18-28	Industrial, WWTP
China	<1 - 8,600	<1 - 12,000	25-55	Manufacturing, industrial
Australia	<1 - 2,200	<1 - 3,400	12-22	Military, firefighting, WWTP

Environmental Fate and Transport

The environmental fate and transport of PFAS in aquatic systems is governed by their unique chemical properties, particularly their exceptional stability and diverse physicochemical characteristics across different chain lengths and functional groups (Ahrens & Bundschuh, 2014). The carbon-fluorine bonds that define PFAS

structure are among the strongest in organic chemistry, rendering these compounds resistant to conventional degradation processes including photolysis, hydrolysis, and biodegradation (Krafft & Riess, 2015).

In aquatic environments, PFAS exhibit complex transport behavior influenced by their amphiphilic

nature and varying chain lengths. Long-chain PFAS (≥8 carbons) demonstrate greater sorption to sediments and organic matter, while short-chain compounds remain more mobile in water phases (Ahrens *et al.,* 2010). This differential behavior creates distinct contamination profiles, with long-chain compounds tending to accumulate in sediment-rich environments while short-chain PFAS maintain higher mobility and persistence in groundwater systems (Higgins & Luthy, 2006).

Groundwater contamination represents a particularly challenging aspect of PFAS environmental fate, as these compounds can persist and migrate through aquifer systems for decades (Weber *et al.,* 2017). The high mobility of short-chain PFAS in groundwater, combined with their resistance to natural attenuation processes, results in persistent contamination plumes that can extend for kilometers from source areas (Houtz *et al.,* 2013). Hydrogeological factors including groundwater flow patterns, aquifer heterogeneity, and geochemical conditions influence PFAS transport rates and pathways (McKenzie *et al.,* 2015).

Surface water systems serve as important transport pathways for PFAS, facilitating widespread distribution through river networks and coastal environments (Yamashita *et al.,* 2005). PFAS released into surface waters can undergo downstream transport over hundreds of kilometers, contributing to contamination of drinking water intakes and aquatic ecosystems far from original sources (Möller *et al.,* 2010). Seasonal variations in flow patterns and precipitation can significantly influence PFAS transport and distribution in surface water systems (Munoz *et al.,* 2018).

Bioaccumulation and biomagnification processes in aquatic food webs contribute to ecological exposure pathways and potential human health risks through consumption of contaminated seafood and freshwater fish (Houde *et al.,* 2011). PFAS demonstrate protein binding affinity that facilitates bioaccumulation in fish tissues, with longer-chain compounds generally exhibiting higher bioaccumulation factors (Martin *et al.,* 2003). Food web magnification has been documented in various aquatic ecosystems, with predatory species often exhibiting the highest tissue concentrations (Conder *et al.,* 2008).

The interaction between PFAS and drinking water treatment processes represents a critical aspect of exposure pathway development. Conventional water treatment technologies, including coagulation, sedimentation, and chlorination, demonstrate limited efficacy for PFAS removal, allowing these compounds to persist through treatment and appear in finished drinking water (Appleman *et al.,* 2014). This treatment resistance necessitates specialized removal technologies and contributes to widespread drinking water contamination despite treatment efforts.

CURRENT KNOWLEDGE OF HEALTH EFFECTS

Established Health Outcomes

The epidemiological evidence linking PFAS exposure to adverse health outcomes has grown substantially over the past two decades, with the strongest evidence emerging from occupational cohorts and communities with high environmental exposure (Steenland *et al.,* 2018). The most comprehensive evidence comes from studies of workers at PFAS manufacturing facilities and residents near contaminated water supplies, particularly the C8 Health Project which studied communities affected by PFOA contamination from a DuPont manufacturing facility in West Virginia (Barry *et al.,* 2013).

Cancer Risks

Multiple epidemiological studies have identified associations between PFAS exposure and increased cancer incidence, with the strongest evidence for kidney and testicular cancers (Steenland *et al.,* 2018). The C8 Health Project, involving over 69,000 participants, found statistically significant associations between PFOA exposure and kidney cancer (RR = 1.58, 95% CI: 1.07-2.35) and testicular cancer (RR = 2.00, 95% CI: 1.02-3.93) (Barry *et al.,* 2013). Occupational cohort studies have similarly reported elevated cancer risks, with a meta-analysis of worker studies finding increased kidney cancer risk (RR = 1.58, 95% CI: 1.08-2.31) associated with PFOA exposure (Vieira *et al.,* 2013).

More recent studies have expanded cancer concerns to include liver cancer, with several investigations reporting associations between PFAS exposure and hepatocellular carcinoma (Girardi & Merler, 2019). A large-scale study of PFAS-exposed communities found increased liver cancer incidence associated with both PFOA and PFOS exposure, with dose-response relationships suggesting causality (Innes *et al.,* 2014). However, evidence for other cancer types remains more limited and inconsistent across studies.

Cardiovascular Effects

PFAS exposure has been consistently linked to cardiovascular disease risk factors and outcomes across multiple study populations (Steenland *et al.,* 2018). The most consistent finding involves elevated serum cholesterol levels associated with PFAS exposure, observed in both occupational and community-based studies (Fitz-Simon *et al.,* 2013). A comprehensive meta-analysis found significant associations between PFOA exposure and increased total cholesterol (β = 7.75 mg/dL per log ng/mL, 95% CI: 4.50-11.00) and LDL cholesterol (β = 6.12 mg/dL per log ng/mL, 95% CI: 3.10-9.15) (Frisbee *et al.,* 2010).

Hypertension represents another well-documented cardiovascular outcome associated with PFAS exposure. The C8 Health Project found increased hypertension risk associated with PFOA exposure (OR = 1.13, 95% CI: 1.05-1.22), with similar associations reported for PFOS exposure (Min *et al.,* 2012). More recent studies have identified associations with pregnancy-induced hypertension and preeclampsia, suggesting particular vulnerability during pregnancy (Wikström *et al.,* 2019).

Emerging evidence suggests associations between PFAS exposure and coronary artery disease, with several studies reporting increased risk of heart attack and coronary interventions (Shankar *et al.,* 2012). However, the evidence base for cardiovascular disease outcomes remains more limited than for cardiovascular risk factors, requiring additional longitudinal studies for definitive conclusions.

Immune System Impacts

PFAS exposure has been associated with various measures of immune system dysfunction, including reduced vaccine efficacy and increased susceptibility to infectious diseases (Granum *et al.,* 2013). Studies in both children and adults have found associations between PFAS exposure and reduced antibody responses to childhood vaccinations, including tetanus, diphtheria, and influenza vaccines (Grandjean *et al.,* 2012).

The most concerning immune system effects involve reduced vaccine efficacy in children. A longitudinal study of Faroese children found that PFAS exposure was associated with reduced antibody responses to tetanus and diphtheria vaccines, with antibody levels falling below protective thresholds more rapidly in highly exposed children (Grandjean *et al.,* 2012). Similar

findings have been reported for influenza vaccination, with PFAS-exposed individuals showing reduced and shorter-lived antibody responses (Looker *et al.,* 2014).

Autoimmune disease associations have also been reported, with studies finding increased risk of ulcerative colitis, rheumatoid arthritis, and autoimmune thyroid disease associated with PFAS exposure (Steenland *et al.,* 2018). However, these associations are based on limited studies and require replication in independent populations.

Liver Function and Hepatotoxicity

PFAS exposure has been consistently associated with altered liver function and hepatotoxicity markers across multiple study populations (Gallo *et al.,* 2012). Studies have reported associations between PFAS exposure and elevated liver enzymes, including alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT), suggesting hepatocellular damage (Gleason *et al.,* 2015). The consistency of these findings across diverse populations suggests liver toxicity as a sensitive endpoint for PFAS exposure assessment.

Non-alcoholic fatty liver disease (NAFLD) has emerged as a significant concern associated with PFAS exposure. Several studies have reported associations between PFAS exposure and increased NAFLD risk, with some investigations suggesting dose-response relationships (Jin *et al.,* 2020). The mechanisms underlying PFAS hepatotoxicity likely involve peroxisome proliferator-activated receptor (PPAR) activation and disruption of lipid metabolism pathways (Rosen *et al.,* 2017).

Developmental and Reproductive Effects

PFAS exposure during pregnancy has been associated with various adverse birth outcomes and developmental effects in offspring (Johnson *et al.,* 2014). The most consistent findings involve reduced birth weight and increased risk of low birth weight births associated with maternal PFAS exposure. A meta-analysis of birth weight studies found significant associations between PFOA exposure and reduced birth weight (β = -18.9 g per log ng/mL, 95% CI: -29.8 to -7.9) (Johnson *et al.,* 2014).

Preterm birth associations have been reported in several studies, though results remain somewhat inconsistent across populations (Darrow *et al.,* 2013). Some investigations have found increased preterm birth risk associated with PFAS exposure, while others report null or protective associations,

suggesting potential confounding factors or population-specific vulnerabilities.

Reproductive health effects in adults include associations with reduced fertility and altered reproductive hormone levels. Studies have reported longer time-to-pregnancy associated with PFAS exposure in both men and women, suggesting impacts on fertility (Bach *et al.,* 2015). Altered testosterone and estrogen levels have been observed in association with PFAS exposure, though the clinical significance of these changes remains uncertain.

Table 2: Summary of Established PFAS Health Effects

Health Outcome	Strength of Evidence	Key Studies	Risk Estimates	Vulnerable Populations
Kidney Cancer	Strong	C8 Project, occupational cohorts	RR: 1.58 (1.07-2.35)	Occupational workers
Testicular Cancer	Strong	C8 Project, occupational cohorts	RR: 2.00 (1.02-3.93)	Young men
Elevated Cholesterol	Very Strong	Multiple populations	β: +7.75 mg/dL per log unit	General population
Hypertension	Moderate	C8 Project, NHANES	OR: 1.13 (1.05-1.22)	Adults, pregnant women
Reduced Vaccine Response	Strong	Children's cohorts	2-fold reduction in antibodies	Children
Low Birth Weight	Strong	Multiple birth cohorts	β: -18.9 g per log unit	Pregnant women
Liver Enzyme Elevation	Strong	Multiple populations	Dose-dependent increases	General population

VULNERABLE POPULATIONS
Children and Adolescents
Children represent one of the most vulnerable populations to PFAS exposure due to developmental vulnerabilities, behavioral factors that increase exposure, and physiological characteristics that enhance absorption and retention (Rappazzo *et al.,* 2017). The developing immune, endocrine, and nervous systems during childhood create windows of heightened susceptibility to environmental toxicants, making early-life PFAS exposure particularly concerning from a public health perspective.

Developmental vulnerabilities in children stem from rapid cellular division and organ development, processes that can be disrupted by environmental chemicals at concentrations that may not affect mature systems (Grandjean *et al.,* 2008). PFAS exposure during critical developmental windows has been associated with altered growth patterns, with several studies reporting associations between early-life exposure and reduced childhood growth rates (Høyer *et al.,* 2015). The mechanisms underlying these growth effects likely involve disruption of growth hormone pathways and metabolic processes critical for normal development.

Neurodevelopmental impacts represent an emerging area of concern, with several studies reporting associations between PFAS exposure and behavioral problems in children. A longitudinal study found associations between prenatal PFAS exposure and increased hyperactivity and attention problems in school-age children, with effects persisting through adolescence (Ode, *et al.,* 2014). However, the evidence base for neurodevelopmental effects remains more limited than for other health outcomes, requiring additional research to establish causality.

Immune system vulnerability in children is particularly well-documented, with studies consistently finding associations between PFAS exposure and reduced vaccine efficacy (Grandjean *et al.,* 2012). Children's developing immune systems appear especially sensitive to PFAS-induced immunosuppression, with effects observed at exposure levels commonly encountered in the general population. The clinical significance of reduced vaccine responses includes increased susceptibility to vaccine-preventable diseases and potential for reduced herd immunity in highly exposed communities.

Behavioral factors that increase children's PFAS exposure include hand-to-mouth behaviors, increased dust ingestion, and dietary preferences that may include PFAS-contaminated foods

(Trudel, *et al.,* 2008). Children consume more water per unit body weight than adults, potentially increasing exposure through contaminated drinking water. Additionally, children's higher metabolic rates and lower body weight result in higher dose per kilogram exposures compared to adults at similar environmental concentrations.

Pregnant Women and Fetal Development
Pregnancy represents a critical exposure window for PFAS due to maternal-fetal transfer and potential impacts on fetal development (Johnson *et al.,* 2014). PFAS readily cross the placental barrier, resulting in fetal exposure throughout gestation, with some studies finding fetal serum concentrations approaching maternal levels (Apelberg *et al.,* 2007). The combination of maternal exposure and direct fetal exposure creates particular vulnerability during this sensitive developmental period.

Placental transfer efficiency varies among PFAS compounds, with shorter-chain compounds generally showing greater transfer rates (Kim *et al.,* 2011). Studies have documented significant correlations between maternal and cord blood PFAS concentrations, confirming substantial prenatal exposure across diverse populations. The persistence of PFAS in maternal tissues means that fetal exposure can continue throughout pregnancy, even in the absence of ongoing external exposure.

Pregnancy outcomes associated with PFAS exposure include reduced birth weight, altered gestational duration, and pregnancy complications (Johnson *et al.,* 2014). The most consistent finding involves reduced birth weight associated with maternal PFAS exposure, observed across multiple populations and geographic regions. A systematic review found consistent associations between PFOA and PFOS exposure and reduced birth weight, with effect sizes ranging from 11-31 grams per interquartile range increase in exposure.

Fetal growth restriction represents another concerning outcome, with several studies reporting increased risk associated with maternal PFAS exposure (Darrow *et al.,* 2013). The mechanisms underlying fetal growth effects likely involve disruption of placental function and fetal metabolic processes. Some studies have suggested that PFAS exposure may alter placental gene expression and hormone production, potentially contributing to adverse pregnancy outcomes.

Pregnancy-induced hypertension and preeclampsia have been associated with PFAS exposure in several studies, though results remain somewhat inconsistent (Wikström *et al.,* 2019). These conditions pose significant risks to both maternal and fetal health, potentially requiring early delivery and intensive medical management. The association with PFAS exposure suggests another pathway through which these chemicals may impact pregnancy outcomes.

Breastfeeding considerations present complex exposure scenarios, as PFAS are detected in breast milk and can contribute to continued infant exposure (Mogensen, *et al.,* 2015). However, the benefits of breastfeeding generally outweigh the risks associated with PFAS exposure, and current recommendations support continued breastfeeding even in areas with known PFAS contamination. Strategies to reduce maternal PFAS exposure during pregnancy and lactation remain important for minimizing infant exposure.

Occupationally Exposed Groups
Occupational exposure to PFAS represents some of the highest human exposures documented, with workers in PFAS manufacturing and use industries exhibiting serum concentrations orders of magnitude above general population levels (Olsen *et al.,* 2007). These highly exposed populations have provided critical information about PFAS health effects while highlighting the need for enhanced workplace protections and medical surveillance programs.

Firefighters and First Responders
Firefighters represent a particularly vulnerable occupational group due to extensive use of PFAS-containing aqueous film-forming foams (AFFF) and exposure to PFAS combustion products during fire suppression activities (Trowsdale *et al.,* 2022). Studies have documented elevated PFAS serum concentrations in firefighters compared to general population controls, with concentrations increasing with years of service and frequency of fire suppression activities (Graber *et al.,* 2021).

The sources of firefighter PFAS exposure are diverse, including direct contact with AFFF during training and emergency response, inhalation of combustion products containing PFAS precursors, and contaminated personal protective equipment (Peaslee *et al.,* 2020). Fire stations located at airports or military installations may experience additional exposure through environmental contamination from historical foam use.

Health outcomes in firefighters have been linked to PFAS exposure, with studies reporting

associations with cancer, cardiovascular disease, and reproductive health effects (Trowsdale *et al.,* 2022). The high cancer rates observed in firefighter populations may be partially attributable to PFAS exposure, though multiple occupational hazards likely contribute to elevated cancer risk. Recent studies have specifically examined PFAS exposure and cancer risk in firefighters, finding associations with kidney and testicular cancers consistent with general population studies.

Industrial Workers
Workers involved in PFAS manufacturing and processing represent the most highly exposed occupational group, with historical exposures often exceeding current general population levels by several orders of magnitude (Olsen *et al.,* 2007). Long-term cohort studies of workers at PFAS manufacturing facilities have provided critical evidence for PFAS health effects while documenting extremely high exposure levels and long elimination half-lives.

The DuPont Washington Works facility, which manufactured PFOA from 1951-2013, has been extensively studied, providing detailed information about occupational exposure patterns and health outcomes (Leonard *et al.,* 2008). Workers at this facility exhibited median PFOA serum concentrations of approximately 1,000 ng/mL during active employment, compared to general population levels typically below 5 ng/mL. Retirement studies found extremely long elimination half-lives, with PFOA concentrations remaining elevated years after exposure cessation.

Health outcomes in industrial workers include increased cancer risk, cardiovascular disease, and liver dysfunction (Steenland *et al.,* 2018). The high

exposure levels in these populations have enabled detection of health effects that might be difficult to observe in general population studies. However, the relevance of these findings to lower-level environmental exposures remains an important consideration for risk assessment.

Military Personnel
Military personnel face PFAS exposure through various sources, including contaminated drinking water at military installations, occupational use of AFFF, and environmental contamination at training and operational facilities (Anderson *et al.,* 2016). Hundreds of military installations worldwide have documented PFAS contamination, creating exposure scenarios for both active duty personnel and their families.

The extent of military PFAS contamination reflects decades of AFFF use for firefighting training and emergency response activities (Schultz *et al.,* 2004). Many military installations have documented extreme groundwater contamination, with some sites exceeding 100,000 ng/L for combined PFAS concentrations. This contamination affects both on-base drinking water supplies and surrounding civilian communities.

Health effects in military populations remain less well-studied than in other occupational groups, though emerging research suggests elevated PFAS serum concentrations and potential health impacts (Daly *et al.,* 2018). The transient nature of military populations and limited access to military health data present challenges for epidemiological research. However, ongoing studies are beginning to characterize exposure levels and health outcomes in military personnel.

Table 3: Vulnerable Population Exposure Characteristics

Population Group	Typical Serum PFAS Levels	Key Exposure Sources	Primary Health Concerns	Research Status
Children (0-12 years)	1-15 ng/mL	Drinking water, food, dust	Immune, growth, development	Moderate evidence
Pregnant Women	2-20 ng/mL	Drinking water, food	Birth outcomes, fetal development	Strong evidence
Firefighters	5-50 ng/mL	AFFF, combustion products	Cancer, cardiovascular	Growing evidence
Industrial Workers	50-5,000 ng/mL	Occupational exposure	Cancer, liver, cardiovascular	Strong evidence
Military Personnel	3-100 ng/mL	Contaminated water, AFFF	Multiple health effects	Limited evidence

TREATMENT AND REMEDIATION TECHNOLOGIES

Current Treatment Options
The treatment of PFAS-contaminated drinking water presents significant technical and economic

challenges due to the exceptional chemical stability and diverse physicochemical properties of these compounds (Appleman *et al.,* 2014). Conventional water treatment processes, including coagulation, flocculation, sedimentation, and chlorination, demonstrate minimal efficacy for PFAS removal, necessitating specialized treatment technologies specifically designed to address these persistent contaminants (Rahman *et al.,* 2014).

Granular Activated Carbon (GAC)

Granular activated carbon represents the most widely implemented technology for PFAS removal in drinking water treatment, offering effective removal for many PFAS compounds through adsorption mechanisms (Appleman *et al.,* 2014). GAC efficacy varies significantly among different PFAS compounds, with longer-chain compounds (≥8 carbons) generally showing better removal efficiency than shorter-chain compounds (Saeidi *et al.,* 2019). PFOA and PFOS, the most extensively studied PFAS, typically achieve >90% removal in properly designed GAC systems, though breakthrough can occur over time depending on influent concentrations and operational parameters.

The performance of GAC systems is influenced by multiple factors including carbon type, contact time, pH, temperature, and competing organic matter (McCleaf *et al.,* 2017). Natural organic matter can significantly reduce PFAS adsorption capacity through competitive sorption, requiring careful consideration of water quality characteristics in system design. Pre-treatment to remove competing organics may enhance GAC performance but adds system complexity and cost.

Carbon regeneration and replacement represent significant operational challenges for GAC systems treating PFAS-contaminated water. Traditional thermal regeneration processes may not completely remove PFAS from spent carbon, potentially leading to reduced capacity in regenerated media (Yu *et al.,* 2020). High-temperature regeneration (>800°C) may achieve better PFAS destruction but requires specialized facilities and creates concerns about atmospheric emissions of PFAS or degradation products.

Ion Exchange Resins

Ion exchange represents another established technology for PFAS removal, particularly effective for ionic PFAS compounds such as perfluoroalkyl sulfonates and carboxylates (Boyer *et al.,* 2016). Anion exchange resins demonstrate high affinity for anionic PFAS, with some specialized resins achieving >95% removal efficiency for PFOA and PFOS under optimal conditions. The selectivity of ion exchange resins can be tailored through resin selection, with some newer resins specifically designed for PFAS removal applications.

The performance of ion exchange systems is influenced by water chemistry parameters, particularly pH, ionic strength, and competing anions (McCleaf *et al.,* 2017). Sulfate and other multivalent anions can compete with PFAS for exchange sites, potentially reducing removal efficiency in waters with high ionic strength. Regular monitoring and optimization of operating conditions are essential for maintaining consistent performance.

Resin regeneration presents environmental challenges similar to those encountered with GAC systems. Conventional regeneration using salt solutions results in concentrated PFAS waste streams that require additional treatment or disposal (Woodard *et al.,* 2017). Some facilities have implemented disposal strategies involving high-temperature incineration, though concerns remain about destruction efficiency and potential atmospheric emissions.

Membrane Technologies

High-pressure membrane processes, including reverse osmosis (RO) and nanofiltration (NF), demonstrate effective PFAS removal through size exclusion and electrostatic repulsion mechanisms (Steinle-Darling & Reinhard, 2008). RO systems typically achieve >90% removal for most PFAS compounds, with performance influenced by membrane characteristics, operating pressure, and feed water quality. Nanofiltration shows variable performance depending on PFAS chain length and membrane molecular weight cutoff.

Membrane fouling represents a significant operational challenge in PFAS treatment applications, particularly when treating surface waters with high organic content (Tang *et al.,* 2006). Biofouling, organic fouling, and scaling can reduce membrane performance and increase maintenance requirements. Pre-treatment systems including media filtration and antiscalant addition may help mitigate fouling issues but add system complexity and cost.

Concentrate management presents a critical challenge for membrane-based PFAS treatment systems. The concentrated waste stream contains elevated PFAS levels and requires appropriate

disposal or additional treatment (Steinle-Darling & Reinhard, 2008). Some facilities have implemented concentrate treatment using advanced oxidation or incineration, though these approaches add significant costs and operational complexity.

Treatment Efficacy and Limitations
Removal Efficiency Variations
Treatment efficacy varies significantly among different PFAS compounds, creating challenges for comprehensive contamination management (Rahman *et al.,* 2014). Long-chain PFAS (C≥8) generally demonstrate higher removal rates across treatment technologies compared to short-chain compounds (C<8), which show greater mobility and treatment resistance. This differential removal creates shifting contamination profiles, with treated water potentially containing higher proportions of short-chain PFAS that may have comparable or unknown toxicological significance

PFAS precursors present additional treatment challenges, as many precursor compounds can transform to persistent perfluoroalkyl acids during or after treatment (Houtz & Sedlak, 2012). Some treatment processes may inadvertently promote precursor transformation, potentially increasing concentrations of regulated PFAS compounds in treated water. Monitoring programs must account for both parent compounds and potential transformation products to accurately assess treatment efficacy.

Mixture effects complicate treatment design and performance assessment, as real-world contamination typically involves multiple PFAS compounds with varying treatment responses (McCleaf *et al.,* 2017). Competitive sorption and interference effects can reduce removal efficiency for individual compounds when present in complex mixtures. Treatment systems must be designed to address the most challenging compounds while maintaining acceptable performance for the full spectrum of contamination.

Cost Considerations
The economic implications of PFAS treatment represent significant challenges for water utilities, particularly smaller systems with limited financial resources (Bartell *et al.,* 2010). Capital costs for PFAS treatment systems can range from hundreds of thousands to millions of dollars depending on system size and technology selection. GAC systems typically require lower initial investment

but may have higher long-term operating costs due to frequent media replacement requirements.

Operating costs are driven primarily by media replacement (GAC) or disposal (ion exchange, membranes), energy requirements, and specialized monitoring needs (Woodard *et al.,* 2017). PFAS-contaminated waste streams require specialized disposal methods, often involving high-temperature incineration at hazardous waste facilities, adding significant ongoing costs. Some utilities report PFAS treatment costs exceeding $1 million annually for large systems.

Cost-benefit analyses must consider both treatment costs and potential health benefits, though quantifying health benefits remains challenging due to uncertainties in dose-response relationships and long-term health outcomes (Bartell *et al.,* 2010). Economic evaluations suggest that PFAS treatment may be cost-effective in highly contaminated systems but may present challenges for systems with lower contamination levels.

Waste Management Challenges
The management and disposal of PFAS-containing waste streams from treatment processes represents one of the most significant challenges in PFAS remediation (Ross *et al.,* 2018). Spent GAC, regeneration wastes, ion exchange brines, and membrane concentrates all contain elevated PFAS concentrations requiring appropriate disposal methods. Traditional disposal methods including landfilling may not provide adequate containment for persistent PFAS compounds.

High-temperature incineration (>1000°C) represents the most widely accepted disposal method for PFAS-containing wastes, though concerns remain about destruction efficiency and formation of other fluorinated compounds (Ross *et al.,* 2018). Not all incinerators are equipped to handle PFAS wastes, limiting disposal options and potentially increasing costs. Monitoring of incineration processes and emissions is essential to ensure adequate PFAS destruction.

Alternative disposal methods including specialized landfills and deep well injection have been proposed but raise concerns about long-term containment and potential for future environmental release (Weber *et al.,* 2017). Research into PFAS destruction technologies, including advanced oxidation and electrochemical treatment, may provide future solutions for waste stream management but currently remain at pilot scale.

Emerging Treatment Technologies
Advanced Oxidation Processes

Advanced oxidation processes (AOPs) represent promising emerging technologies for PFAS destruction, offering potential for complete mineralization rather than physical separation (Singh *et al.,* 2019). Electrochemical oxidation, plasma treatment, and photochemical processes have demonstrated PFAS destruction capabilities under laboratory conditions, though full-scale applications remain limited. These technologies offer the advantage of destroying PFAS rather than concentrating them, potentially eliminating waste disposal challenges.

Electrochemical treatment using boron-doped diamond electrodes has shown particular promise for PFAS destruction, achieving >90% removal for PFOA and PFOS under optimized conditions (Schaefer *et al.,* 2017). The process involves direct electrochemical oxidation and indirect oxidation through generated hydroxyl radicals. Energy requirements remain high, potentially limiting applicability to highly contaminated waste streams rather than bulk water treatment.

Plasma-based treatment technologies offer potential for complete PFAS mineralization through high-energy radical reactions (Singh *et al.,* 2019). Laboratory studies have demonstrated effective PFAS destruction using various plasma configurations, though scale-up challenges and energy requirements may limit practical applications. Research continues into optimizing plasma conditions and reactor designs for improved efficiency and cost-effectiveness.

Bioremediation Approaches

Bioremediation represents an active area of research, though the exceptional stability of PFAS presents significant challenges for biological degradation approaches (Espana *et al.,* 2021). Most research has focused on biodegradation of PFAS precursors rather than terminal perfluoroalkyl acids, as the carbon-fluorine bonds in fully fluorinated compounds resist biological attack. Some studies have reported bacterial strains capable of defluorinating certain PFAS compounds under specific conditions.

Constructed wetlands and biofilters have been investigated for PFAS removal, primarily through sorption mechanisms rather than biodegradation (Sörengård *et al.,* 2019). While these systems may provide some PFAS removal, performance is generally lower than conventional treatment technologies and may be limited to specific compounds and conditions. Research continues into enhancing biological systems for PFAS treatment through bioaugmentation and genetic engineering approaches.

Phytoremediation using plants to remove PFAS from contaminated media has shown limited success, with most studies reporting low uptake rates and limited treatment depths (Espana *et al.,* 2021). Some plants may concentrate PFAS in tissues, potentially providing a removal mechanism, but disposal of contaminated plant material presents similar challenges to other PFAS wastes.

Point-of-Use vs. Centralized Treatment

Point-of-use (POU) treatment systems offer an alternative approach for PFAS removal, particularly in areas with limited centralized treatment options or for high-risk individuals seeking additional protection (Crone *et al.,* 2019). Residential-scale GAC and RO systems can provide effective PFAS removal, though performance monitoring and maintenance requirements may challenge typical homeowner capabilities. The effectiveness of POU systems depends heavily on proper installation, maintenance, and media replacement schedules (Crone *et al.,* 2019). Many residential systems are not specifically designed for PFAS removal, potentially providing inadequate protection. Third-party certification programs are developing standards for POU PFAS treatment systems, though implementation remains limited.

Cost-effectiveness comparisons between POU and centralized treatment depend on contamination levels, population served, and local infrastructure conditions (Post *et al.,* 2017). POU systems may be more cost-effective for small, highly contaminated systems, while centralized treatment generally offers better economics for larger populations. Hybrid approaches combining centralized pre-treatment with POU polishing may offer optimal solutions in some circumstances.

Table 4: PFAS Treatment Technology Comparison

Technology	PFAS Removal Efficiency	Capital Cost	Operating Cost	Waste Management	Maturity Level
GAC	80-99% (long-chain)	Moderate	High	Incineration/disposal	Commercial
Ion Exchange	85-99% (ionic PFAS)	Moderate	High	Regeneration/disposal	Commercial
Reverse Osmosis	90-99% (most PFAS)	High	Moderate	Concentrate disposal	Commercial
Nanofiltration	70-95% (variable)	Moderate	Moderate	Concentrate disposal	Commercial
Electrochemical	90-99% (destruction)	High	Very High	Minimal	Pilot/Demo
Plasma Treatment	95-99% (destruction)	Very High	Very High	Minimal	Research

RESEARCH GAPS AND KNOWLEDGE LIMITATIONS

Toxicological Data Gaps

The vast number of PFAS compounds in commercial use and environmental detection presents perhaps the most significant challenge in toxicological assessment and risk characterization (Wang *et al.,* 2017). Current estimates suggest over 4,700 PFAS compounds have been identified globally, yet toxicological data exists for fewer than 1% of these substances (Glüge *et al.,* 2020). This massive data gap creates substantial uncertainties in risk assessment and regulatory decision-making, as regulators must often rely on read-across approaches and structural activity relationships rather than compound-specific toxicity data.

Limited Data on Emerging PFAS Compounds

The regulatory focus on legacy compounds such as PFOA and PFOS has inadvertently created knowledge gaps for newer PFAS alternatives that have entered commercial use as replacements for regulated substances (Wang *et al.,* 2013). Short-chain PFAS, including perfluorobutanoic acid (PFBA) and perfluorobutane sulfonic acid (PFBS), have limited toxicological characterization despite widespread environmental detection and evidence of greater mobility in water systems. Emerging evidence suggests that short-chain PFAS may exhibit different toxicological profiles compared to longer-chain compounds, potentially involving different target organs and mechanisms of action (Gomis *et al.,* 2018).

Fluorotelomer compounds and other PFAS precursors represent another significant data gap, as these substances can transform to persistent perfluoroalkyl acids in environmental and biological systems (Houtz & Sedlak, 2012). The toxicological assessment of precursor compounds must consider both direct effects of the parent compound and indirect effects from transformation products. This complexity is compounded by variable transformation rates and pathways that depend on environmental conditions and biological factors.

Ultra-short chain PFAS (C≤3) have received even less toxicological attention despite their high mobility and potential for widespread exposure (Brendel *et al.,* 2018). Trifluoroacetic acid (TFA), a terminal degradation product of many PFAS precursors, is detected globally in precipitation and surface waters but lacks comprehensive toxicological evaluation. The assumption that ultra-short chain compounds are less toxic due to reduced bioaccumulation may not account for potential acute effects or impacts on sensitive populations.

Long-term Chronic Exposure Effects

Current toxicological studies predominantly focus on relatively short exposure durations, creating uncertainty about the health effects of lifelong low-level PFAS exposure typical of environmental scenarios (Fenton *et al.,* 2021). The extremely long elimination half-lives of PFAS in humans (ranging from 2-10 years for major compounds) suggest that chronic exposure scenarios may result in continued bioaccumulation and potential for delayed health effects not captured in shorter-term studies.

Carcinogenicity assessment represents a particular challenge, as the latency period for many cancers may exceed the duration of available epidemiological studies (Steenland *et al.,* 2018). While some studies have identified associations between PFAS exposure and certain cancer types, the relatively recent recognition of widespread

environmental exposure means that populations exposed from early life are only now reaching ages where cancer incidence typically peaks. Long-term follow-up of existing cohorts and establishment of new birth cohorts will be essential for characterizing lifetime cancer risks.

Neurodegenerative diseases represent another area where long-term exposure effects remain poorly characterized. Given the potential for PFAS to cross the blood-brain barrier and evidence of developmental neurotoxicity, concerns exist about potential contributions to adult-onset neurodegenerative conditions (Johansson *et al.,* 2008). However, the long latency periods for these conditions and limited historical exposure data create substantial challenges for epidemiological investigation.

Mixture Toxicology and Interactions

Real-world PFAS exposure invariably involves complex mixtures of multiple compounds, yet toxicological assessment typically focuses on individual chemicals (Bil *et al.,* 2021). The potential for synergistic, antagonistic, or additive interactions among PFAS compounds remains poorly understood, creating uncertainties in risk assessment for environmentally relevant exposure scenarios. Mixture effects may be particularly important given the similar mechanisms of action shared by many PFAS compounds. Interactions between PFAS and other environmental contaminants represent an additional layer of complexity in mixture toxicology assessment (Sunderland *et al.,* 2019). PFAS exposure often occurs in the context of co-exposure to other persistent organic pollutants, heavy metals, and endocrine disrupting compounds. These complex exposure scenarios may result in cumulative or interactive effects that exceed predictions based on individual chemical assessments.

The dose-additivity assumption commonly used in mixture risk assessment may not be appropriate for PFAS given their diverse molecular structures and potential for different mechanisms of action (Bil *et al.,* 2021). Some PFAS may act through common pathways (e.g., PPAR activation), supporting additivity assumptions, while others may involve independent mechanisms requiring more complex mixture modeling approaches.

EXPOSURE ASSESSMENT LIMITATIONS

Analytical Challenges for Ultra-trace Detection

The analytical challenges associated with PFAS detection and quantification create significant limitations in exposure assessment and environmental monitoring (Reiner *et al.,* 2021). PFAS analysis requires specialized analytical methods using liquid chromatography tandem mass spectrometry (LC-MS/MS), with method detection limits that may not be adequate for detecting health-relevant concentrations of all compounds. The lack of analytical standards for many PFAS compounds limits the ability to detect and quantify the full spectrum of environmental contamination.

Method validation and quality assurance present ongoing challenges in PFAS analysis, with interlaboratory variability and matrix effects potentially affecting data quality (Reiner *et al.,* 2021). The development of standardized analytical methods and certified reference materials remains incomplete for many PFAS compounds, creating uncertainty in exposure assessment and regulatory compliance monitoring.

Non-target screening approaches offer potential for detecting unknown PFAS compounds but remain technically challenging and require specialized expertise (Schymanski *et al.,* 2014). The identification of unknown peaks in environmental samples requires extensive analytical chemistry expertise and may miss compounds that don't ionize well or co-elute with other substances. Total fluorine measurements provide complementary information but cannot identify specific compounds or their toxicological relevance.

Temporal Variability in Exposure

PFAS exposure levels can vary significantly over time due to changing source contributions, environmental transport processes, and individual behavior patterns (Goosey & Harrad, 2011). Drinking water concentrations may fluctuate seasonally or in response to changes in source water quality, industrial discharges, or water treatment operations. Single-point exposure measurements may not adequately represent long-term average exposures relevant to chronic health risk assessment.

Biomonitoring approaches using serum or urine measurements provide integrated exposure information but are influenced by recent exposure patterns and individual elimination kinetics (Bartell *et al.,* 2010). The long elimination half-lives of PFAS mean that serum concentrations reflect exposure integrated over several years,

potentially obscuring recent changes in exposure or short-term high-level exposures.

Historical exposure reconstruction presents particular challenges for epidemiological studies, as PFAS contamination was not widely recognized until the 1990s and systematic environmental monitoring began even later (Lindstrom *et al.,* 2011). Modeling approaches can provide estimates of historical exposure but require assumptions about past use patterns, environmental fate, and population behavior that introduce substantial uncertainty.

Multiple Exposure Pathway Integration
PFAS exposure occurs through multiple pathways including drinking water, food, dust, and consumer products, with relative pathway contributions varying among individuals and populations (Sunderland *et al.,* 2019). Integrating exposure across multiple pathways requires data on contamination levels in different media, consumption patterns, and pathway-specific absorption rates. Limited data availability for many pathways creates uncertainty in total exposure estimates.

Food pathway exposure assessment is complicated by limited contamination data for many food categories and variability in PFAS concentrations within food groups (Trier *et al.,* 2011). Seafood, meat, and dairy products may contain elevated PFAS levels depending on environmental contamination and production practices, but systematic monitoring data remains limited. The potential for bioaccumulation in food webs creates additional complexity in exposure modeling.

Consumer product exposures are difficult to quantify due to proprietary product formulations and variability in PFAS content among similar products (Trier *et al.,* 2011). Personal care products, textiles, food packaging, and household items may all contribute to PFAS exposure, but product-specific contamination data and exposure modeling approaches remain limited.

EPIDEMIOLOGICAL STUDY LIMITATIONS
Sample Size and Statistical Power
Many epidemiological studies of PFAS health effects are limited by small sample sizes that may lack adequate statistical power to detect health effects, particularly for rare outcomes such as specific cancer types (Steenland *et al.,* 2018). The relatively recent recognition of PFAS as a health concern means that large, well-characterized cohorts with long-term follow-up remain limited. Cancer studies are particularly challenging due to the long latency periods required and the need for large study populations to detect elevated risks.

Effect modification by age, sex, genetics, or other factors may require even larger sample sizes to detect and characterize adequately (Fenton *et al.,* 2021). Vulnerable populations such as children or pregnant women may be underrepresented in study populations, limiting the ability to assess health effects in these critical groups. The potential for differential effects across populations requires large, diverse study populations for adequate assessment.

Rare health outcomes require particularly large study populations or specialized study designs to achieve adequate statistical power (Steenland *et al.,* 2018). Birth defects, specific cancer subtypes, and rare autoimmune conditions may require consortium approaches or registry-based studies to accumulate sufficient cases for analysis.

Exposure Misclassification
Exposure assessment in epidemiological studies often relies on surrogate measures or single-point measurements that may not accurately represent relevant exposure windows (Bartell *et al.,* 2010). Drinking water measurements may not account for temporal variability, residential mobility, or exposures from other pathways. Biomarker measurements reflect integrated exposure over different time periods depending on the biological matrix and compound elimination kinetics.

Critical exposure windows for health effects may not coincide with available exposure measurements, creating potential for exposure misclassification (Fenton *et al.,* 2021). Developmental effects may be most sensitive to in-utero or early childhood exposures, while cancer effects may depend on exposures occurring decades before diagnosis. The long elimination half-lives of PFAS complicate exposure window assessment, as current biomarker levels reflect integrated historical exposure.

Geographic mobility and changes in contamination sources over time can create additional exposure misclassification (Steenland *et al.,* 2018). Individuals may have lived in multiple locations with different PFAS contamination levels, making it difficult to assign appropriate exposure estimates for epidemiological analysis. Historical changes in contamination levels at specific locations add additional complexity to exposure assessment.

Confounding Factors and Study Design

PFAS exposure is often correlated with other environmental and lifestyle factors that may independently affect health outcomes, creating potential for confounding in epidemiological studies (Fenton *et al.,* 2021). Socioeconomic status, diet, other environmental exposures, and lifestyle factors may all be associated with both PFAS exposure and health outcomes. Adequate control for confounding requires detailed information on potential confounders that may not be available in all studies.

Occupational cohort studies, while providing high exposure contrasts, may be subject to healthy worker effects and confounding by other occupational exposures (Steenland *et al.,* 2018). Manufacturing workers may be exposed to multiple chemicals in addition to PFAS, making it difficult to isolate PFAS-specific health effects. Selection effects related to employment and retention in hazardous industries may bias health outcome assessment.

Community-based studies may be affected by exposure-related migration patterns, with health-conscious individuals potentially moving away from contaminated areas (Bartell *et al.,* 2010). This selective migration could bias study populations and affect the generalizability of findings to broader populations.

Table 5: Critical Research Gaps Summary

Research Area	Current Status	Priority Gaps	Required Investment	Timeline for Progress
Toxicology	<1% compounds studied	Short-chain, precursors, mixtures	High ($50-100M annually)	5-10 years
Exposure Assessment	Limited pathway integration	Multi-pathway modeling, biomarkers	Moderate ($20-50M annually)	3-5 years
Epidemiology	Small cohorts, short follow-up	Large birth cohorts, long-term follow-up	High ($100-200M initial)	10-20 years
Analytical Methods	Limited compound coverage	Non-target screening, standards	Moderate ($10-30M annually)	2-5 years
Treatment Technology	Limited destruction options	Advanced oxidation, waste management	Moderate ($30-50M annually)	5-10 years

CONCLUSION

The scientific evidence documenting public health risks associated with PFAS in drinking water has grown substantially over the past two decades, establishing these "forever chemicals" as a priority environmental health concern requiring urgent and sustained response. The weight of evidence demonstrates clear associations between PFAS exposure and multiple adverse health outcomes, with the strongest evidence for cancer (kidney, testicular), cardiovascular effects (elevated cholesterol, hypertension), immune system dysfunction (reduced vaccine efficacy), and developmental impacts (reduced birth weight, growth effects).

The consistency of findings across diverse study populations and geographic regions strengthens the evidence base, with effects observed in highly exposed occupational cohorts, contaminated communities, and general population studies. The biological plausibility of observed associations is supported by mechanistic studies demonstrating PFAS interactions with critical biological pathways, including peroxisome proliferator-activated receptors, immune system function, and endocrine signaling.

Population-level risk estimates suggest significant public health impacts, with millions of people worldwide exposed to PFAS levels associated with adverse health outcomes in epidemiological studies. The global distribution of contamination, combined with the persistence and bioaccumulation characteristics of PFAS, indicates that exposure will continue for decades even with immediate cessation of all PFAS releases. The most vulnerable populations—children, pregnant women, and occupationally exposed groups—face disproportionate risks that require targeted protection strategies.

Global Cooperation and Knowledge Sharing

The global nature of PFAS contamination requires international cooperation in research, regulation, and remediation efforts (Glüge *et al.,* 2020). Harmonization of analytical methods, sharing of toxicological data, and coordination of regulatory approaches can improve efficiency and effectiveness of PFAS management efforts

worldwide. International agreements on PFAS restrictions and elimination may be necessary to address the global scale of contamination.

Knowledge-sharing platforms that facilitate rapid dissemination of research findings, treatment technology developments, and regulatory innovations can accelerate progress in PFAS management. Professional networks, scientific societies, and international organizations play critical roles in facilitating information exchange and coordinating research priorities.

Capacity building in developing countries will be essential for addressing PFAS contamination in regions with limited analytical and treatment infrastructure. Technology transfer, training programs, and financial assistance may be necessary to ensure equitable access to PFAS monitoring and treatment capabilities globally.

The path forward for PFAS management requires acknowledgment that this challenge will persist for decades due to the environmental persistence of these compounds and the time required for comprehensive scientific characterization and regulatory response (Cousins *et al.,* 2019). Success will require sustained commitment to research investment, regulatory innovation, and international cooperation, along with interim protective measures based on current scientific understanding. The magnitude of this challenge demands immediate action to protect public health while building the scientific foundation for more comprehensive long-term solutions.

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