PFAS and Human Health

A State-of-the-Science Report to Assist in the Understanding of Human Exposures to PFAS and Related Health Concerns

Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large group of more than 4,000 compounds[1] that have gained increased attention in recent years. These man-made chemicals contain multiple fluorine atoms and have structures that give them unique chemical and physical properties, such as being oil and water repellent and temperature resistant, and reducing friction. Because of these attributes, PFAS have been widely used in numerous consumer and industrial products such as non-stick cookware, stain-resistant textiles, paint, metal plating, food packaging, and firefighting foams. The two PFAS that have been most extensively studied are perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS).

Though the unique properties of PFAS have made them useful in multiple applications, they have also made PFAS stable in the environment and food sources. For example, PFAS are resistant to conversion processes such as photooxidation, direct photolysis, and hydrolysis[2]. However, some PFAS precursors undergo biotransformation, resulting in persistent metabolites. Most PFAS are bioaccumulative, mobile, and persistent in soil and water. PFAS can also undergo long-range atmospheric and oceanic transport; they are globally distributed across the environment and have been found in biota in remote regions. They are found in all environmental media and are of particular concern in drinking water. Because of the pervasive use and persistent nature of PFAS, there is widespread human exposure. Most people in the United States have some form of PFAS in their blood, particularly PFOS and PFOA[2].

Concerns regarding the potential health and environmental effects from PFAS have led to political, industrial, and regulatory attention. Production of longer chain PFAS, including PFOS and PFOA, has ceased in the United States, Europe, and Japan, and both are listed as persistent organic pollutants (POPs) under the Stockholm Convention on POPs[3], reflecting international concern surrounding these chemicals. Despite these measures, numerous PFAS are still being produced and released into the environment, and new PFAS compounds such as GenX chemicals and perfluorobutanesulfonic acid (PFBS) are being manufactured to replace those that have been eliminated. Little is known about the potential human exposures to and toxicity of these new replacement PFAS, although early assessments suggest they may be similarly toxic[4,5]. While evidence indicates that exposure to certain PFAS compounds are associated with human health effects, the available information focuses primarily on a small subset of PFAS. Associations vary by compound, with inadequate detection and quantification of exposure or dose; therefore, more research is needed to further understand these effects across a wider range of PFAS variants.

Battelle's Expertise

Battelle has in-depth understanding of PFAS and extensive expertise in human exposure, risk assessment, and human health investigations—in adults and more vulnerable populations such as children and older adults—to help advance the science around PFAS and human health. For example, Battelle was a key partner in the seminal C8 Science Panel (www.c8sciencepanel.org), a large-scale, population-based study that sought to understand PFOA contamination of drinking water and numerous epidemiologic outcomes, resulting in more than 30 publications.

This report provides a brief summary of the state of knowledge surrounding PFAS and human health, identifies the gaps in understanding we still face, and recommends steps needed to fill these gaps.

[1] Birnbaum, LS (National Institute of Environmental Health Sciences). 2018 Sep 26. Hearing on the federal role in the toxic PFAS chemical crisis. Testimony before the Senate Committee on Homeland Security and Governmental Affairs, Subcommittee on Federal Spending Oversight and Emergency Management. [accessed 2020 Feb 5]. https://www.niehs.nih.gov/about/assets/docs/hearing_on_the_federal_role_in_the_toxic_pfas_chemical_crisis_508.pdf.

[2] [ATSDR] Agency for Toxic Substances and Disease Registry. 2018 Jun. Toxicological profile for perfluoroalkyls: draft for public comment. Atlanta (GA): ATSDR, Division of Toxicology and Human Health Sciences. [accessed 2020 Feb 5]. https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf.

[3] [UNEP] United Nations Environment Programme. Forthcoming. Stockholm convention on persistent organic pollutants: texts and annexes. Stockholm (Sweden): Secretariat of the Stockholm Convention (SSC). [accessed 2020 Feb 5]. http://chm.pops.int/TheConvention/Overview/TextoftheConvention/tabid/2232/Default.aspx.

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PFAS Exposure

Research has begun to define and quantify the routes of PFAS exposure for children and adults; however, more work is needed to fully understand the various routes of PFAS exposure and their relative importance to human health. Populations are exposed to PFAS through numerous pathways, including ingestion, dermal contact, and inhalation as a result of exposures to a variety of substances containing PFAS, such as food, water, dust, soil, and consumer products[2]. Exposures can vary across populations, with occupational and point source exposures being higher than those of the general population[2]. Children and infants have additional sources of PFAS exposure, such as through breast milk and in utero through umbilical cord blood. Further, children may be at higher risk of exposure than adults due to activities such as crawling and from hand-to-mouth transfer, which can potentially lead to increased exposure to PFAS found in carpets and dust. In addition, the ongoing development of their biological systems and metabolism, along with more time spent indoors, may make children and infants more sensitive and susceptible to PFAS exposure than adults.

Water consumption can be a significant source of PFAS among exposed populations. To help protect human health, the U.S. Environmental Protection Agency (EPA) recommends PFOA and PFOS levels in drinking water should not exceed 70 parts per trillion (ppt)[6]. PFAS levels in drinking water have been found to vary significantly, depending on the geographic area and water treatment processes[7]. For example, drinking water samples (N = 36,149) across the United States contained PFOS and PFOA levels ranging from below detection to 101–349 ppt for PFOA and 201–1,800 ppt for PFOS, with detectable levels in 33 states[8].

In addition to water intake, food consumption is another main source of PFAS exposure, particularly for PFOS and PFOA[2,9]. Food can be contaminated with PFAS through contact with PFAS-treated food wrapping or packaging material, and plant uptake of PFAS through land applied biosolids or wastewater reuse for farming[10]. PFAS have been found in a variety of food types; in particular, fish and seafood are major contributors to dietary intake of PFAS9. The European Food Safety Authority has issued suggested total dietary intake guidelines for PFOS and PFOA; current data indicate that intake of these PFAS by general populations is usually below these limits[9].

Dust ingestion may be a significant contributor to PFAS exposure, particularly for infants and toddlers, among whom it may account for uptake similar to or higher than uptake from food and water ingestion[2,11].

Research on dermal absorption and inhalation of PFAS is limited. Dermal absorption of PFAS has not been reported as a main contributor of PFAS exposure; however, there is limited information regarding the uptake of PFAS through the skin[10,12].

Similarly, research on inhalation of PFAS is limited, particularly among the general population. For occupationally exposed workers, inhalation is an important exposure pathway[2].

[6][EPA] United States Environmental Protection Agency. c2019. Drinking water health advisories for PFOA and PFOS. [accessed 2020 Feb 5]. https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos.

[7]Boone JS, Vigo C, Boone T, Byrne C, Ferrario J, Benson R, Donohue J, Simmons JE, Kolpin DW, Furlong ET, Glassmeyer ST. 2019 Feb 25. Per-and polyfluoroalkyl substances in source and treated drinking waters of the United States. Sci Total Environ. 653:359–369. [accessed 2020 Feb 5]. https://doi.org/10.1016/j.scitotenv.2018.10.245.

[8]Hu XC, Andrews DQ, Lindstrom AB, Bruton TA, Schaider LA, Grandjean P, Lohmann R, Carignan CC, Blum A, Balan SA, Higgins CP. 2016 Aug 9. Detection of poly-and perfluoroalkyl substances (PFASs) in US drinking water linked to industrial sites, military fire training areas, and wastewater treatment plants. Environ Sci Tech Let. 3(10): 344–350. [accessed 2020 Feb 5]. https://pubs.acs.org/doi/10.1021/acs.estlett.6b00260.

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[10]Michigan PFAS Science Advisory Panel. 2018 Dec 7. Scientific evidence and recommendations for managing PFAS contamination in Michigan. Report developed for Michigan PFAS Action Response Team (MPART), Lansing, MI. [accessed 2020 Feb 5]. https://www.michigan.gov/documents/pfasresponse/Science_Advisory_Board_Report_641294_7.pdf.

[11]Winkens K, Vestergren R, Berger U, Cousins IT. 2017 Jun 1. Early life exposure to per-and polyfluoroalkyl substances (PFASs): a critical review. Emerging Contaminants. 3(2):55-68. [accessed 2020 Feb 5]. https://doi.org/10.1016/j.emcon.2017.05.001.

[12]Poothong S, Padilla-Sánchez JA, Papadopoulou E, Giovanoulis G, Thomsen C, Haug LS. 2019 Jan 21. Hand wipes: a useful tool for assessing human exposure to poly-and perfluoroalkyl substances (PFASs) through hand-to-mouth and dermal contacts. Environ Sci Tech. 53(4):1985–1993. [accessed 2020 Feb 5]. https://doi.org/10.1021/acs.est.8b05303.

Due to the ubiquitous nature of PFAS and the multiple routes of exposure, most people have PFAS in their blood. The U.S. population's average PFAS blood levels are 1.56 parts per billion (ppb) for PFOA, 4.72 ppb for PFOS, and 1.18 ppb for PFHxS[13]. These levels are lower than what was observed 20 years ago, likely related to production of these PFAS compounds ceasing in the United States[2,14]. Highly exposed populations such as PFAS manufacturing workers have been shown to have significantly higher blood PFAS levels related to concentrations of substances measured in facilities[15].

The half-life of PFAS compounds in humans varies widely, from several days to more than 15 years, depending on the PFAS chemical. Longer chain chemicals have been found to be the most persistent[2,10]. Longer half-lives can impact bioaccumulation and potentially related health effects.

Biomarkers of Exposure

Understanding exposures to harmful chemicals and relationships between exposures and health effects is often best accomplished using biomarkers. The most widely used biomarker of PFAS exposure in humans is serum or whole-blood PFAS concentration[2]. It is noteworthy that correlations may differ across moieties. Potential non-invasive biomonitoring samples such as urine, hair, and nails have shown varied reliability and validity across exposure levels and PFAS compounds[16].

Health Outcomes

Considerable epidemiological research has been conducted to understand the possible adverse health effects of PFAS in humans, ranging from adverse biological function to frank disease. These studies have focused on highly exposed communities, workers at PFAS production or use facilities, and the general population[2]. Most of these studies have focused on PFOS and PFOA, and a few other PFAS, investigating blood PFAS levels in the selected population in relation to adverse health endpoints. The health effects most commonly studied and reported are immunological, developmental or reproductive, hepatic, hormonal, and to a lesser extent, carcinogenic.

Immunological Effects

Investigations of immune system responses related to PFAS exposure have included asthma, allergic disorders, ulcerative colitis, infectious diseases, vaccine response, and autoimmune disorders. Of these outcomes, evidence suggests PFAS reduces vaccine efficacy in children, decreasing antibody production[17,18]. However, this association may vary based on vaccine type, and is less clearly understood among adults compared to children[17]. Other associations between PFAS exposure and immunosuppression are also evident, particularly for PFOA and PFOS[18]. A few studies suggest PFOA may be related to increased risk of ulcerative colitis, an autoimmune disease that causes inflammation in the colon, and asthma[2]. The evidence for other immunological health effects such as allergies is mixed, requiring further research[18,19].

Developmental and Reproductive Effects

Studies examining fetal exposure and health outcomes, including rate of growth, obesogenicity, and neurodevelopment, have had mixed results, while studies of birth weight suggest a small reduction in birth weight associated with elevated PFAS[10]. Decreased fertility has also been linked to elevated serum PFOA and PFOS levels[2].

[13]ATSDR. 2019 Dec 6. PFAS: An overview of the science and guidance for clinicians on per- and polyfluoroalkyl substances (PFAS). [accessed 2020 Feb 14]. https://www.atsdr.cdc.gov/pfas/docs/ATSDR_PFAS_ClinicalGuidance_12202019.pdf

[14][CDC] Centers for Disease Control and Prevention. 2018. Fourth national report on human exposure to environmental chemicals. Updated Tables, March 2018, Volume One. Atlanta (GA): Centers for Disease Control and Prevention. [accessed 2020 Feb 5]. https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2018.pdf.

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[16]Wang Y, Shi Y, Vestergren R, Zhou Z, Liang Y, Cai Y. 2018 Sep 15. Using hair, nail and urine samples for human exposure assessment of legacy and emerging per-and polyfluoroalkyl substances. Sci Total Environ. 636:383–391.

[17]Chang ET, Adami HO, Boffetta P, Wedner HJ, Mandel JS. 2016 Apr 20. A critical review of perfluorooctanoate and perfluorooctanesulfonate exposure and immunological health conditions in humans. Critical Reviews Toxicol. 46(4):279–331. [accessed 2020 Feb 5]. https://www.tandfonline.com/doi/pdf/10.3109/10408444.2015.1122573.

[18]Sunderland EM, Hu XC, Dassuncao C, Tokranov AK, Wagner CC, Allen JG. 2019 Mar. A review of the pathways of human exposure to poly-and perfluoroalkyl substances (PFASs) and present understanding of health effects. J Expo Sci Env Epid. 29(2):131–147. [accessed 2020 Feb 5]. https://www.nature.com/articles/s41370-018-0094-1.

Hepatic Effects

Multiple reports summarizing current PFAS knowledge indicate a possible relationship between PFOA, PFOS, perfluorononanoic acid (PFNA), and perfluorodecanoic acid (PFDeA), and increased total and LDL cholesterol[2,10,19]. There may be a biphasic dose-response-curve for PFAS and total cholesterol. Specifically, lower levels of PFOA were associated with higher increases in total cholesterol levels, suggesting changes in effect based on dose/serum level[2]. Research also suggests an inverse relationship between elevated serum PFAS and reduced HDL[18]. Similarly, while there is conflicting evidence for an association between PFOS and triglyceride levels[2,19], an overall pattern of positive association is emerging[18,19].

Endocrine Disruption

Recent research has increasingly identified PFAS compounds as endocrine disruptors. Increased PFOA serum levels have been linked to an increased risk of thyroid disease, but this association was not found when examining perfluorohexanesulfonic acid (PFHxS), PFNA, or PFDeA2. A few additional studies have explored perfluorodecanoic acid (PFDA) and perfluoroundecanoic acid (PFUnDA) and found positive associations with thyroid disease[18]. Thyroid stimulating hormones, when disrupted, may result in frank disease outcomes such as Graves' disease or benign pituitary tumors. In addition to disease, there are other reproducible adverse health effects associated with pre-clinical changes in thyroid function. For example, serum PFAS is likely associated with altered thyroid hormones[20,21,22].

Research has also examined relationships between PFAS and metabolic function, uric acid levels or hypertension, and insulin function. However, this research is limited, and additional studies are needed to understand the impact of PFAS on these endocrine and metabolic endpoints[2,19].

Cancer

Studies have explored the association between PFAS blood levels and increased risk for numerous types of cancer, including colorectal, prostate, ovarian, melanoma, pancreatic, bladder, kidney, lung, testicular, breast, colon, and liver cancer. While many of these studies have been inconclusive, and results rely on non-standardized exposure assessments, studies evaluating populations with increased exposure to PFOS and PFOA have found a greater risk for testicular and kidney cancer[2]. However, research on cancer outcomes remains limited. The International Agency for Research on Cancer concluded that PFOA is possibly carcinogenic[23], and the U.S. EPA determined that there is suggestive evidence of carcinogenic potential of PFOA and PFOS in humans[24,25]. Despite these findings, the Michigan Panel noted that "cancer may not be the most sensitive health outcome to guide regulations for the protection of public health"[10].

[19]New Jersey Drinking Water Quality Institute, Health Effects Subcommittee. 2018 Jun 5. Health-based maximum contaminant level support document: perfluorooctane sulfonate (PFOS), Appendix A. [accessed 2020 Feb 5]. https://www.state.nj.us/dep/watersupply/pdf/pfos-recommendation-appendix-a.pdf.

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[25]EPA. 2016 May. Health effects support document for perfluorooctane sulfonate (PFOS). Washington (DC): U.S. Environmental Protection Agency, Office of Water, Health and Ecological Criteria Division. [accessed 2020 Feb 5]. https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf.

The Next Frontiers of Research on PFAS and Health

Although considerable research has been conducted to understand the potential health effects associated with exposures to PFOA, PFOS, and limited other PFAS, there are still significant gaps and limitations in scientific knowledge, particularly across PFAS as a class.

- Epidemiological studies have established associations between PFAS exposures and adverse health effects in humans; however, reliance primarily on cross-sectional studies limits the ability to demonstrate causality. Many study designs have been inadequate, with some lacking proper controls for confounding effects19.
- Results from epidemiological studies are often inconsistent and inconclusive due to a variety of factors, including limitations in exposure assessment methods, outcome measures, and study designs.
- Only a small number of PFAS compounds have been investigated. Exposures are not limited to these select PFAS, and new PFAS compounds continue to be developed. The associations between compounds and health endpoints for select PFAS analytes may not be applicable to other PFAS.
- Chronic exposure studies are lacking, leaving important gaps in understanding the long-term effects of PFAS exposure in various populations, especially children.
- Limited research has been conducted to understand and quantify the routes of exposure and the relative importance of individual exposure pathways, particularly as related to bioaccumulation of PFAS in humans. Differences may exist for populations based on age and proximity to PFAS sources.
- Limited research has been conducted to map exposures in high use agricultural areas used for food and milk production, which impacts vulnerable consumer populations.
- Understanding of chemical mixture exposures and possible synergistic or additive effects associated with potential health effects have not been studied, although exposures are likely to include a range of PFAS along with other known toxic pollutants.
- Evidence is limited and inconclusive for a variety of health outcomes, including hepatic effects, reproductive effects, various types of cancer, and some immune responses.

There is still progress to be made in the scientific community to fully understand the exposures to and health effects from PFAS. Closing these gaps in our understanding of these issues is paramount to helping to protect human health. Some of the critical next frontiers of PFAS research to begin to address these gaps include:

- Longitudinal (prospective) epidemiology studies, particularly of children, that address clinical health outcomes.
- Exposure assessment studies that map environmental exposures in water, soil, and air against human agricultural practices and consumer products.
- Exposure assessment studies investigating all pathways of exposure across multiple cohorts in differently exposed populations. There is a particular need to investigate and understand the importance of different exposure pathways for infants and children.
- Inclusion of additional PFAS and their new alternatives such as GenX chemicals and PFBS.
- Consideration of exposure to multiple PFAS and resulting toxicity effects.
- Identification of cost-effective, reliable, and non-invasive biomarkers of exposure for more and newer PFAS compounds.
- Metabolomic studies to expand understanding of metabolic disruptions caused by PFAS compounds.

Battelle's Capabilities and Expertise

Battelle can address these critical gaps in the science surrounding PFAS and human health. From premier analytical laboratory capabilities to health-related data collection and expert analysis, Battelle offers a suite of services and scientific staff to better understand human exposure to PFAS and their impacts on human health. Battelle is on the leading edge of PFAS research and is spearheading development of technologies and methods to deepen the scientific community's understanding of PFAS. We can assist you with:

- Designing scientifically defensible studies
- Assessing appropriate exposure and health impacts
  - Collecting biospecimens, including blood, urine, hair, nails, saliva, breast milk, and cord blood
  - Collecting indoor/outdoor environmental samples, including water, air, dust, wipes, soil, and biota
  - Collecting and assessing food and duplicate diet samples and behaviors
  - Abstracting and analyzing medical record data
  - Conducting central and peripheral neurobehavioral assessments
  - Conducting anthropometric measurements
  - Developing and gathering questionnaire data
  - Conducting data analysis based on defensible exposure-effect or dose-response curves
- Convening focus groups and expert panels
- Conducting cognitive interviews
- Recruiting, retaining, tracing, and locating cohort members
- Analyzing complex data
- Developing reports, data visualization, and dissemination plans
- Analyzing samples in our analytical laboratory, which is accredited for detection of dozens of PFAS in soil, sediment, tissues, and water
- Using cutting-edge technologies and expertise to develop methods for measuring PFAS in different exposure matrices.

In addition, Battelle provides environmental services to reduce exposure, including:

- Risk assessment
- Field sampling for site assessment, characterization, and monitoring
- Remediation and treatment
- Remedy selection and optimization
- Environmental and computational toxicology
- New technology and method development.

At Battelle, we offer all of the expertise you need under one roof. Battelle's world-class scientists can help solve your most difficult PFAS problems.

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