PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS) REPORT

A Report by the

JOINT SUBCOMMITTEE ON ENVIRONMENT, INNOVATION, AND PUBLIC HEALTH

PER- AND POLYFLUOROALKYL SUBSTANCES STRATEGY TEAM

of the

NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

About the National Science and Technology Council

The National Science and Technology Council (NSTC) is the principal means by which the Executive Branch coordinates science and technology policy across the diverse entities that make up the Federal research and development enterprise. A primary objective of the NSTC is to ensure science and technology policy decisions and programs are consistent with the President's stated goals. The NSTC prepares research and development strategies that are coordinated across Federal agencies aimed at accomplishing multiple national goals. The work of the NSTC is organized under committees that oversee subcommittees and working groups focused on different aspects of science and technology. More information is available at https://www.whitehouse.gov/ostp/nstc/.

About the Office of Science and Technology Policy

The Office of Science and Technology Policy (OSTP) was established by the National Science and Technology Policy, Organization, and Priorities Act of 1976 to provide the President and others within the Executive Office of the President (EOP) with advice on the scientific, engineering, and technological aspects of the economy, national security, homeland security, health, foreign relations, the environment, and the technological recovery and use of resources, among other topics. OSTP leads interagency science and technology policy coordination efforts, assists the Office of Management and Budget (OMB) with an annual review and analysis of Federal research and development in budgets, and serves as a source of scientific and technological analysis and judgment for the President with respect to major policies, plans, and programs of the Federal Government. More information is available at http://www.whitehouse.gov/ostp.

About the Per- and Polyfluoroalkyl Substances Strategy Team

Congress directed an Interagency Working Group (IWG) to coordinate Federal research on Per- and Polyfluoroalkyl Substances (PFAS) through the National Defense Authorization Act (NDAA) for Fiscal Year (FY) 2021.[1] In response, OSTP developed the PFAS Strategy Team (ST) under the Joint Subcommittee on Environment, Innovation, and Public Health (JSC EIPH or “the JEEP”) in late 2021. The ST coordinates interagency PFAS research and development activities and supports the development and implementation of the PFAS strategic research plan. The ST is co-chaired by OSTP, OMB, and Department of Defense (DoD).

About this Document

The NDAA for FY 2021 directs the PFAS ST to identify all currently Federally-funded PFAS research and development; to identify scientific and technological challenges that must be addressed to understand and to significantly reduce the environmental and human health impacts of PFAS; to identify cost-effective (1) alternatives to PFAS that are designed to be safer and more environmentally friendly, (2)

1

methods for removal of PFAS from the environment, and (3) methods to safely destroy or degrade PFAS; and to establish goals and priorities for Federally-funded PFAS research and development that take into account the current state of research and development. The PFAS ST solicited input from eight PFAS technical writing teams on critical research gaps and needs for PFAS. OSTP also issued a Request for Information (RFI) to receive public comment. The PFAS Report provides a high-level overview of research on PFAS as a chemical class by addressing the following strategic areas: removal and destruction, safer alternatives, sources and pathways of exposure, and toxicity. **This document is a state of the science report that includes gaps and opportunities for the Federal Government.**

Following this report, the PFAS ST will develop a Federal strategic plan to address identified data gaps. This report focuses on the consensus science of PFAS as a chemical class. An appendix of references that informed the report is included in this document.

Copyright Information

2

NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

Chair

Arati Prabhakar, Assistant to the President for Science and Technology, Director, OSTP

Executive Director

Kei Koizumi, Acting Executive Director, National Science and Technology Council, Principal Deputy Director for Policy, OSTP

COMMITTEE ON ENVIRONMENT

Co-Chairs

Jane Lubchenco, Deputy Director for Climate and Environment, OSTP

Rick Spinrad, Administrator, NOAA

Chris Frey, Assistant Administrator, Office of Research and Development, EPA

JOINT SUBCOMMITTEE ON ENVIRONMENT, INNOVATION, AND PUBLIC HEALTH

Co-Chairs

Melanie Buser, Assistant Director for Environmental Health, OSTP

Annette Guiseppi-Elie, National Program Director, Chemical Safety for Sustainability, EPA

David Balshaw, Acting Director, Division of Extramural Research and Training, NIH/NIEHS

Executive Secretary

Brooke Holmes, Program Analyst, Office of Research and Development, EPA

PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS) STRATEGY TEAM

Co-Chairs

Melanie Buser, Assistant Director for Environmental Health, OSTP

April Kluever, Senior Toxicologist, OMB

Natalia Vinas, Deputy Director, Chemical and Material Risk Management, DoD

Executive Secretary

Sharon Elyashiv-Barad, Lead Chemist, HHS/FDA

Strategy Team Members

Linda Abbott, USDA
Jonathan Alter, SBA
Timothy Appleman, NASA
Betsy Behl, EPA
Patrick Breysse, HHS/CDC/ATSDR
Susan Burden, EPA
Margaret Thompson, DOE
Gerald Collert, DHS
Marie DeLorenzo, NOAA
Brendan Deyo, NASA
Mamadou Diallo, NSF
Chris Diaz, VA
Elizabeth Ditto, DOT
Alexander Domesle, USDA
Emilio Esteban, USDA
Bill Flynn, HHS/FDA
Chris Gamache, EOP/OMB
Carlos Gonzalez, DOC/NIST
Rachel Gooding, DHS
Robert Gordon, DOE
Kristina Hatlelid, CPSC
Heather Henry, HHS/NIH/NIEHS
Eric Hooker, CPSC
Lloyd Hough, DHS
Natalie Karouna-Renier, USGS
Andrea Leeson, DoD
Carmine Leggett, EOP/OMB
Alex Long, DoD
Scott Masten, HHS/NIH/NIEHS
Jeff McCoy, USGS
Anita Meyer, DoD
Pete Siebach, DOE
David Morton, DHS
Herb Nelson, DoD
Mitchell Otey, DOT
Benjamin Place, DOC/NIST
Lisa Quiveors, DHS
Kathleen Raffaele, EPA
Christopher Reh, HHS/ATSDR
Jessica Reiner, DOC/NIST
Debbie Rosano, DOE
Ashley Ruocco, DOE
Irvin Schultz, NOAA
Robert Seifert, DOE
Jennifer Shieh, SBA
James Smith, DoD
Paul South, HHS/FDA
Andrea Tokranov, USGS
Marc Tonnacliff, DOT
James Tyree, DOE
Patricia Underwood, DoD
Terra Vincent-Hall, VA
Clinton Williams, USDA
Jody Wireman, DoD
Ed Wirth, NOAA
Tayyaba Zeb, SBA Advocacy
Christopher Zevitas, DOT

Technical Writing Team Members

I.
Susan Burden, EPA
Eileen Abt, HHS/FDA
Ryan Matsuda, USDA
Moiz Mumtaz, HHS/ATSDR
David Morton, DHS
Ben Place, NIST

II.
Mamadou Diallo, NSF
Chris Zevitas, DOT
Heather Henry, HHS/NIH/NIEHS
Marc Mills, EPA
Tom Speth, EPA
Phillip Potter, EPA

III.

Jessica Kratchman, OMB
Herb Nelson, DoD
Mary Bedner, NIST
Beth Ditto, DOT
Sharon Koh-Fallet, HHS/FDA
Ravi Subramamiam, EPA
Natalia Vinas, DoD
Chris Zevitas, DOT

IV.

Karen Scruton, HHS/ATSDR
Elaine Cohen-Hubal, EPA
Dan Hautman, EPA
Barry Hooberman, HHS/FDA
John Offenberg, EPA
Andrea Tokranov, USGS
James Tyree, DOE

Analytical Methods

Janice L. Willey, DoD
Sara Burket, EPA
Antonia Calafat, HHS/CDC
Lowri Dejager, HHS/FDA
Susan Genauldi, HHS/FDA
Ivan Lenov, USDA
Ryan Matsuda, USDA
Jeff McCoy, USGS
Benjamin Place, DOC/NIST
Jessica Reiner, DOC/NIST
Debbie Rosano, DOE
Robert Seifert, DOE
Troy Strock, EPA

V.

Epidemiological

Andrea Winquist, HHS/CDC
Jessica Kratchman, OMB
Moiz Mumtaz, HHS/ATSDR
Rachel Rogers, HHS/CDC/ATSDR
Terra Vincent-Hall, VA

Animal Toxicology

Sue Fenton, HHS/NIH/NIEHS
Laura Carlson, EPA
Brittany Jacobs, EPA
Shruti Kabadi, HHS/FDA
Allison Narizzano, DoD
Lynn Post, HHS/FDA
Penelope Rice, HHS/FDA
Avanti Shirke, EPA
Ravi Subramanian, EPA
Brittany Szafran, HHS/ATSDR

Ecotoxicology

Natalia Vinas, DoD
Brett Blackwell, EPA
Marie DeLorenzo, NOAA
Mike Elias, EPA
Andrea Kirk, EPA

VI.

Carmine Leggett, OMB
Athena Gemella, HHS/ATSDR
Timothy McLeod, HHS/ATSDR
Lisa Quiveors, DHS
Pamela Protzel Berman, HHS/CDC/ATSDR
Rachel Rogers, HHS/CDC/ATSDR
Kimberly Spencer, HHS/ATSDR

Acknowledgments

This document was prepared by over 60 subject matter experts from departments and agencies across the Executive Branch. This truly was a whole-of-government endeavor and represents a dedicated effort to provide an overview of a complex scientific challenges facing the Federal government. The ST Chairs thank all the contributors of this document: authors, reviewers, editors, and advisors.

OSTP and the ST sincerely appreciate the valuable comments provided by respondents to the RFI from the Public on Identifying Critical Data Gaps and Needs to Inform Federal Strategic Plan for PFAS Research and Development; this input provided information and perspectives from a wide range of stakeholders.

OSTP and the ST thank Brian Berridge, Scientific Director, Division of Translational Toxicology, NIH/NIEHS for his leadership on the Joint Subcommittee and the expert scientific guidance he provided until he retired in January 2023.

March 2023

Dear Members of Congress,

It is my pleasure to transmit the *Per- and Polyfluoroalkyl (PFAS) Report* pursuant to Section 332 of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021. This document was prepared by over 60 subject matter experts from 15 Federal departments and agencies, a truly all-of-government effort. This report enables Federal agencies and the nation to better understand and use cutting-edge science and innovation to make informed decisions about our environment and our drinking water. The interagency PFAS Strategy Team solicited input on critical research gaps and needs when developing the report from eight technical writing teams, as well as from the American public through a public comment process.

The PFAS Report is being released at a critical time. Historical investments through the Bipartisan Infrastructure Law and the Inflation Reduction Act provide an unprecedented opportunity to combat dangerous chemicals in our environment and our drinking water. Due to their heat- and stain-resistant properties, PFAS are used in a wide range of commercial and consumer products, from carpets to food packaging, nonstick cookware, and waterproof clothing. They are used at manufacturing and processing facilities, as well as at airports and military installations. PFAS may be in firefighting foam and clothing and are therefore a source of exposure for firefighters.

The PFAS Report provides a high-level overview of research on PFAS as a chemical class by addressing the following strategic areas: removal and destruction, safer alternatives, sources and pathways of exposure, and toxicity. The report also describes the state of Federal PFAS research and development, including relevant Federal funding and activities.

This report focuses on the consensus science of PFAS as a chemical class. This report outlines current PFAS research and identifies data gaps that serve as a roadmap to advance the science in those specific areas. The report emphasizes the importance of collaboration among governments at every level and the private sector to build a strong foundation for future research. Following this report, the PFAS interagency working group will develop a Federal strategic plan to address identified data gaps. On behalf of the PFAS Strategy Team, I am pleased to transmit this Report. I look forward to working closely with Congress to ensure that this interagency PFAS collaboration is successful in developing and implementing a strategic plan to fill the data gaps and research needs identified to deliver information on PFAS that the Nation and the world urgently need.

Sincerely,

Arati Prabhakar

Assistant to the President for Science and Technology

Director, White House Office of Science and Technology Policy

Table of Contents

GC-TOF-MS Gas Chromatography-Time-of-Flight Mass Spectrometry

GHG Greenhouse Gas

GWP Global Warming Potential

H Hydrogen

HDPE High Density Polyethylene

HF Hydrogen Fluoride

HFPO-DA Hexafluoropropylene Oxide Dimer Acid, GenX Chemicals

HHS Department of Health & Human Services

HOME Health Outcomes Military Exposures

IARC International Agency for Research on Cancer

IX Anion Exchange resins

LASD Laboratory and Analytical Services Division

LC-MS/MS Liquid Chromatography-Tandem Mass Spectrometer

MilCo Millennium Cohort Study

ML Machine Learning

NAFLD Non-Alcoholic Fatty Liver Disease

NAMs New Approach Methodologies

NASA National Aeronautics and Space Administration

NASEM National Academies of Science, Engineering and Medicine

NCCOS National Centers for Coastal Ocean Science

NCEH National Center for Environmental Health

NDAA National Defense Authorization Act

NHANES National Health and Nutrition Examination Survey

NIEHS National Institute of Environmental Health Sciences

NIOSH National Institute for Occupational Safety and Health

NIST National Institute of Standards and Technology

NOAA National Oceanic and Atmospheric Administration

NPDES National Pollutant Discharge Elimination System

NSF National Science Foundation

NSTC National Science and Technology Council

NTA Non-targeted Analysis

NTP National Toxicology Program

NWQL National Water Quality Laboratory

OCRSO Office of the Chief Readiness Support Officer

OSTP Office of Science and Technology Policy

OST-R Office of the Assistant Secretary for Research and Technology

OMB Office of Management and Budget

PAC Powdered Activated Carbon

PAG Photoacid Generator

PFAS Per- and Polyfluoroalkyl Substances

PFBA Perfluorobutanoic Acid

PFBS Perfluorobutanesulfonic Acid

PFCA Perfluoroalkyl Carboxylic Acids

PFDA Perfluorodecanoic acid

PFDoDA Perfluorododecanoic Acid

PFHpA Perfluoroheptanoic Acid

PFHxA Perfluorohexanoic Acid

PFHxS Perfluorohexane Sulfonic Acid

PFNA Perfluorononanoic Acid

PFOA Perfluorooctanoic Acid

PFOS Perfluorooctane Sulfonic Acid

PFPeA Perfluoropentanoic Acid

PFSA Perfluoroalkyl Sulfonic Acids

PFUnA Perfluoroundecanoic Acid

PIC Products of incomplete combustion

PID Products of incomplete destruction

PK Pharmacokinetic

PNNL Pacific Northwest National Laboratory

PPT Parts Per trillion

PTFE Polytetrafluoroethylene

PVDF Polyvinylidene Fluoride

PWS Public Water System

R-125 Pentafluoroethane

R&D Research and Development

RCRA Resource Conservation and Recovery Act

RFI Request for Information

S&T Science and Technology

S/S Solidification and Stabilization

SC DOE Office of Science

SEMS Superfund Enterprise Management System

SERDP Strategic Environmental Research and Development Program

SRP Superfund Research Program

ST Strategy Team

TDS Total Diet Study

TJNAF Thomas Jefferson National Accelerator Facility

TK Toxicokinetic

TOF Total Organic Fluorine

TRB Transportation Research Board

TRI Toxic Release Inventory

TSCA Toxic Substances Control Act

UCMR Unregulated Contaminant Monitoring Rule

US United States

USDA United States Department of Agriculture

USGS United States Geological Survey

UV Ultraviolet

VA Veterans Affairs

WQP Water Quality Portal

WMA Water Mission Area

WWTP Waste Water Treatment Plant

Executive Summary

The Biden-Harris Administration is committed to delivering clean drinking water, clean air, and safe food to all Americans and particularly to people in underserved communities. To advance that commitment, the Administration has accelerated efforts to protect Americans from harmful effects due to Per- and Polyfluoroalkyl Substances (PFAS) exposure. Section 332 of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021 (NDAA for FY 2021) directed an Interagency Working Group to coordinate Federal research on PFAS. In response, the White House Office of Science and Technology Policy (OSTP) established the PFAS Strategy Team (ST). The PFAS ST created and solicited input from eight technical teams of agency subject matter experts on critical gaps and needs for PFAS removal and destruction, safer alternatives, sources and pathways of exposure, and toxicity. OSTP also issued a Request for Information (RFI) to receive public comments that would inform this report. This document is an analysis of the state of the science of PFAS and provides information that will be used to direct the development of a Federal strategic plan, harnessing coordination and collaboration across agencies to accelerate progress and innovation. This report focuses on the current science of PFAS as a chemical class, identifies scientific consensus, and portrays uncertainties in the scientific information where consensus is still sought. An appendix of references that informed this report is included in the document.

This report provides an overview of PFAS in the introduction that includes information on PFAS life cycle, key definitions related to PFAS, PFAS as a class of chemicals, and PFAS research and development. Additionally, this Report aligns with Administration priorities around environmental justice, climate change, equitable access to data and technological developments, and broad engagement across stakeholders. This Report identifies four key strategic areas that, when addressed, will generate actionable information to address PFAS:

Removal, destruction, or degradation of PFAS. This section details technologies used for removal, safe destruction, and degradation of PFAS in various environmental media (e.g., air, water) including benefits and limitations of existing technologies. The safe removal and destruction of PFAS depends on many factors such as the type of PFAS present, PFAS concentrations, the background constituents, the volume or mass of material to treat, the removal or destruction goals, energy use, the cost of treatment, the intended use of the final cleaned material, the ability to manage residual materials, and the technical expertise of the treatment staff. Advancement towards mitigating adverse effects of PFAS necessitates a holistic approach to removal, destruction, and degradation, with emphasis on the complex interplay of treatment technologies.

Safer and Environmentally-Friendlier Alternatives. An inherent complexity to PFAS is the limited understanding of where PFAS is present in products, including where PFAS is intentionally added and where it is present as a byproduct of other processes. This section highlights ongoing activities around the development of safer and more environmentally friendly alternatives that are functionally similar to those made with PFAS. Specific challenges highlighted include firefighting foams, industrial uses, food packaging and contact materials, pesticides, textiles, recreation products, cosmetics and personal care products, pharmaceuticals, and medical devices. An important consideration to advancing this area of research and development is identifying critical uses of PFAS.

Sources and Pathways of Exposure. Understanding the sources and pathways of exposure is critical to mitigation of PFAS. PFAS sources, releases, fate and transport considerations, and potential pathways of exposure such as exposure media and routes are detailed. Inherent to these considerations is a need for sensitive analytical methods to detect PFAS. Mitigation efforts and health-protective measures cannot be implemented without the ability to detect PFAS at levels of concern. Addressing the challenge of developing additional analytical methods with higher sensitivity to detect both single and mixtures of PFAS is a critical opportunity to accelerate advancement across all other areas.

Toxicity. As with many topics, PFAS presents a unique challenge to our traditional understanding of toxicity. PFAS toxicity information is informed by laboratory animal data, ecological data, human health data, and predictive modeling information. However, the limitations of each of these evidence streams is distinctive for PFAS compared to other environmental exposures. To fully leverage our understanding of PFAS toxicity, a weight-of-evidence approach that takes into account the different evidence streams is needed. Because of the large number of PFAS currently identified in commerce, one goal of future research is to determine whether all PFAS, or specific groups, might pose a similar hazard to human and ecological receptors. Such PFAS groupings may provide a means by which agencies might regulate PFAS for the protection of humans and ecological receptors.

In this report, the data gaps identified within each strategic area provide a roadmap for R&D activities that, when addressed, will generate actionable information to guide Federal agencies and PFAS collaborators and partners. The capabilities and approaches developed in response to this report should lead to a holistic approach to PFAS. Over the next year, the PFAS ST will operationalize a strategic plan and implementation framework that organizes and coordinates activities in these strategic areas by harnessing existing research and accelerating transformative advancements. The information generated will inform PFAS advisories, disposal approaches, development of PFAS alternatives, and fuel other innovative public health actions and help our Nation realize its vision of clean drinking water, clean air, and safe food for all Americans.

I. Introduction

Introduction to PFAS

PFAS are a class of organofluorine chemicals that have been manufactured and used for decades. Because PFAS can confer resistance to oil and water and withstand high temperatures, they are used in a variety of applications, including firefighting foams, food packaging and contact materials, textiles, and various industrial uses (see Section III for additional uses of PFAS).

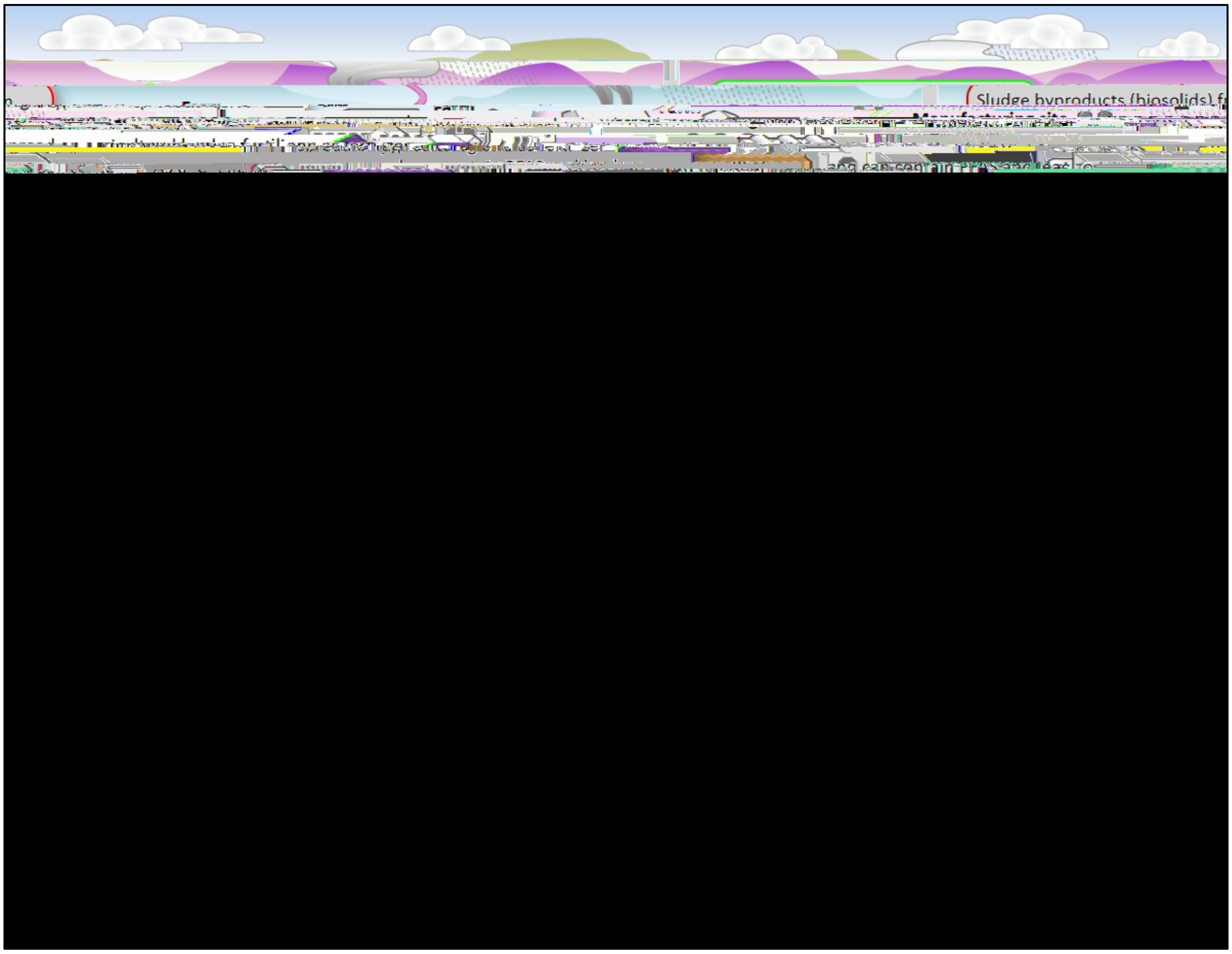

Figure 1: Possible routes for PFAS release into the environment (https://www.gao.gov/assets/gao-22-105088.pdf). This figure does not include all potential sources of PFAS releases, such as air emission and transport, uptake into plants, and permitted industrial discharges. (Source: Government Accountability Office.)

Figure 1 describes possible sources of PFAS to the environment throughout their lifecycle from manufacturing, to processing, to distribution in commerce, use, and disposal. PFAS are generally resistant to natural degradation processes due to their strong carbon-fluorine bonds and therefore pose a potential threat to human and environmental health because of their persistence in the environment and bioaccumulation in organisms. Due to their widespread use and environmental persistence, most people in the United States have been exposed to certain PFAS[3].

PFAS as a Class of Chemicals

There is no consensus definition of PFAS as a class of chemicals. Commonly-cited, chemical structure-based definitions of the PFAS class are summarized in Table 1. Estimates of the number of substances within a PFAS class depend on the definition used and the database of chemical substances to which the definition is applied. The definitions listed in Table 1 are generally ordered from broadest (i.e., largest number of substances) to narrowest (i.e., small number of substances).

Table 1. Chemical Structure-Based Definitions of the PFAS Class[*]

Broadest Definition

Narrowest Definition

Source	Definition
NDAA for FY 2021	A man-made chemical in which all of the carbon atoms are fully fluorinated carbon atoms, and man-made chemicals containing a mix of fully fluorinated carbon atoms, partially fluorinated carbon atoms, and non-fluorinated carbon atoms.
Organisations for Economic Co-operation and Development 2021[4]	Fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any hydrogen (H)/chlorine/bromine/iodine atom attached to it), i.e., with a few noted exceptions, any chemical with at least a perfluorinated methyl group ($–CF_3$) or a perfluorinated methylene group ($–CF_2–$) is a PFAS.
Buck et al. 2011[5]	Highly fluorinated aliphatic substances that contain one or more carbon (C) atoms on which all the H substituents (present in the nonfluorinated analogues from which they are notionally derived) have been replaced by fluorine (F) atoms, in such a manner that they contain the perfluoroalkyl moiety C_nF_{2n+1}.
EPA's Office of Pollution Prevention and Toxics [6]	A structure that contains the unit $R–CF_2–CF(R')(R'')$, where R, R', and R'' do not equal H and the carbon-carbon bond is saturated (note: branching, heteroatoms, and cyclic structures are included).

[3] https://www.gao.gov/assets/gao-21-37.pdf.

[4] https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/terminology-per-and-polyfluoroalkyl-substances.pdf

[5] https://setac.onlinelibrary.wiley.com/doi/10.1002/ieam.258.

[6] Although EPA does not have a consensus definition of PFAS, some offices, such as EPA's Office of Pollution Prevention and Toxics, have applied certain criteria or definitions to advance program-specific efforts under different statutory authorities. OPPT's definition, for example, has been used for purposes of carrying out certain actions under the Toxic Substances Control Act (TSCA), such as identifying already-commercial PFAS on the TSCA inventory, searching in-house databases for possible chemical analogues, etc. The definition has evolved, and continues to evolve, with our improved understanding of the science. Further, EPA's efforts under TSCA are not constrained by this definition; the Agency may choose to apply a broader or narrower set of criteria as deemed appropriate for a particular action.

*The order of definitions above reflects the information contained in Table 1 of William et al. (2022).

II. Removal, Safe Destruction, or Degradation of PFAS From the Environment

The removal and destruction of PFAS can be challenging because of the large number of PFAS, their functional groups, and the strength of the carbon-fluorine bond, which particularly impacts the ability to destroy the PFAS. The selection of technology (or combination of technologies in treatment trains) depends on a number of factors, including the type of contaminated media (water, solid, air), contaminant concentrations, specific PFAS targeted for removal, treatment goals, ability to manage residual waste stream discharges or disposal, and operating costs of treatment[7].

Many treatment technologies have shown potential for PFAS removal and destruction; however, uncertainties remain regarding the effectiveness of available destruction techniques. Conventional water-treatment technologies, which are primarily designed for pathogen removal and control, are not generally effective in removing PFAS. In addition, in instances where water facilities are designed for removing dissolved contaminants, the systems may not be optimized for removing a large number of PFAS. This is compounded for systems treating more contaminated waste streams from industrial sites, landfill leachates, and groundwaters that received large inputs of Aqueous Film Forming Foam (AFFF) from incident response and fire training.

There are also performance challenges associated with the treatment of solid matrices such as contaminated soils, industrial wastes, spent adsorption media, and municipal wastes – especially biosolids. Due to the unique characteristics of many PFAS, typical treatment systems for solids, such as soil washing or thermal treatment systems, need to be optimized for PFAS removal or destruction. Soils, spent media, and other solids that need to be returned to the environment or reused should not contain PFAS levels (including degradation products) that may cause a significant public health or environmental risk. For certain other contaminants, natural attenuation is effective in mitigating a subsurface soil contamination event. However, natural processes have been shown to break down PFAS that are precursor compounds (e.g., fluorotelomer alcohols) into other PFAS that may be more stable (i.e., more resistant to degradation; more persistent) and deleterious to human health and the environment. In some cases, volatile PFAS are subject to long-range atmospheric transport and can degrade into stable and bioaccumulative end products.

To date, thermal technologies, namely hazardous waste combustion technologies[8], are the most promising among the many PFAS destruction processes that have been evaluated at the bench and pilot scale. However, these processes and other non-thermal treatment and disposal management techniques generate off-gas streams, which may contain products of incomplete combustion (PICs) and require further treatment, representing an active area of ongoing research. Off-gas treatment systems include adsorption, scrubber, and thermal processes. Since the discharge of these systems are often released to the environment, there is a great need to evaluate the extent of destruction of various PFAS compounds and the formation of products of incomplete destruction (PIDs). Also, some of these

[7] ITRC. 2021. Per- and Polyfluoroalkyl Substances Technical and Regulatory Guidance. https://pfas-1.itrcweb.org/.

[8] This refers to permitted hazardous waste facilities, which have stringent regulatory controls, subject to the considerations outlined in EPA's Interim Guidance on Destruction and Disposal. 2020. https://www.epa.gov/pfas/interim-guidance-destroying-and-disposing-certain-pfas-and-pfas-containing-materials-are-not.

processes will produce residual streams that will need to be treated or disposed of in a sequestered state to minimize their release into the environment.

Due to the incredibly strong nature of the C-F bond, disposal of PFAS-containing wastes can create additional releases, if not properly controlled. Consumer products and industrial waste (i.e., from chrome plating, manufacturing, application) are introduced into landfills where they can leach PFAS into the environment without proper control. Various sludge products from wastewater treatment plants or other sources can be used in application on agricultural fields and leach PFAS over time.

Incomplete thermal degradation via incineration of PFAS wastes can release toxic air pollutants, such as 1,4 dioxane, and greenhouse gases like shorter-chained tetrafluoromethane and hexafluoroethane, potent greenhouse gases with long atmospheric half-lives known to contribute to global warming.

Below an overview is provided of the different treatment processes and technologies applicable to the removal and destruction of PFAS from water, solids, and air media, including a discussion of the readiness level, challenges, and research needs; further details are provided in Appendix E, Tables E-1a through E-1e.

Treatment technologies for the removal and safe destruction or degradation of PFAS

Water Treatment Technologies

Water treatment plants are typically designed and built around an integrated set of unit operations and processes to achieve a target water quality outcome. For instance, in a typical drinking-water treatment plant, these unit operations/processes are integrated into treatment trains that, depending on source water quality, can include: 1) conventional treatment to remove suspended materials; 2) additional treatment to remove dissolved inorganic or organic solutes (e.g., PFAS or other contaminants); 3) post-treatment to prepare the water for distribution (e.g., final disinfectant addition or corrosion control approaches); and, 4) residuals management to treat, reuse, or dispose of the residuals that were generated. Variations of this approach allow the possibility to combine and integrate these operations depending on the target PFAS and efficiency of removal. One example of a variation is which removal technology is selected for the process. PFAS can be removed using powdered activated carbon (PAC) within the conventional treatment process where the spent PAC is removed with the naturally-occurring particulates. In this case, however, the PFAS removal is not as efficient as using other treatment approaches, such as deep-bed granular activated carbon (GAC), anion exchange resins (IX), or high-pressure membranes, which are specifically designed for PFAS removal. Due to the relatively high source water quality in the U.S., these advanced technologies are not typically used in drinking water plants because of increased costs compared to conventional treatment alone. If used, these technologies require significant pretreatment efforts due to their inability to handle high turbidities, organic loadings, and inorganic precipitation. They also generate residuals such as spent media or high-concentration waste streams that need to be managed subsequently. Smaller, household-scale point-of-use or point-of-entry systems also require residuals management and may be limited in their ability to achieve treatment objectives for many of the same reasons mentioned above.

These operational challenges also hold true for the treatment of other waters containing PFAS (e.g., industrial waste streams, wastewater, landfill leachate, and liquid residual streams from the primary treatment of PFAS). While treating large volumes of such media will be costly due to higher PFAS concentrations or background matrices, treating the higher contaminant levels at the source before they get diluted is advantageous, as most treatment systems exhibit greater efficiency at higher contaminant concentrations due to kinetic or capacity factors.

The GAC, IX, and high-pressure membrane systems (reverse osmosis and nanofiltration) are generally effective at full-scale removal of PFAS. GAC is the most studied and utilized, and is considered the baseline technology for comparing the performance and cost of other alternatives. For instance, IX treatment generally has higher capacities, but is also more expensive per media weight; and high-pressure membranes are more expensive and energy-intensive than GAC and can also make water more corrosive, which may result in metals leaching from pipes into water. Each technology, or combination, may have its niche as the most cost-effective depending on the choice of media or membranes, the PFAS compounds to be removed and their concentrations, the treatment goals, background water characteristics, system size (ranging from point-of-use to large full-scale facilities), and the ability to manage the residual streams. The exact trade-offs have not been fully discerned across all waters and technologies (including combinations of technologies), and pilot testing is needed for accurate full-scale designs where the ultimate capital and operating costs can be evaluated.

Beyond the field-demonstrated technologies above, a number of other water-treatment technologies continue to be studied for the removal of various PFAS with different characteristics (e.g., chain length) (Appendix E, Table E-1a through E-1e). The first two categories (sorbents and separation technologies) require additional processes to deal with the residual streams, such as spent media or concentrated liquid waste streams. The most promising technologies have either lower costs than GAC or IX or they have higher capacities. Work is needed to find an adsorbent that combines lower cost with higher capacities. Another challenge is maximizing the kinetics of adsorption for a particle size that can be used in a fixed bed, like GAC or IX.

For separation technologies, membrane systems can typically produce very high-quality water; however, costs and energy uses are high. Foam fractionation and electrocoagulation can be useful in pretreatment scenarios at high PFAS concentrations where the final water product can be further treated with another technology. There are separation technologies such as evaporation ponds and brine concentrators that focus on managing PFAS-laden brines or waste streams. This approach can provide very concentrated PFAS waste for final disposal.

Non-thermal destruction technologies such as oxidative or reductive chemical and photocatalytic systems are generally energy-intensive and may require high PFAS concentrations to be cost-effective. Exceptions include biological, nature-based, or solvent-assisted low-temperature chemical degradation. However, these technologies have not been demonstrated at scales large enough to support pump-and-treat or *in situ* treatment applications. In addition, there are still unresolved challenges and critical knowledge gaps about the ability, robustness, and reliability of biological systems to achieve efficient PFAS degradation in complex environmental media. Other non-thermal processes have largely been evaluated at the bench or pilot scale without clear results showing destruction of broad ranges of PFAS in multiple water matrices. Variables, such as different background water quality, can limit the effectiveness of these technologies. Also, some processes are not practicable in a real-world water treatment scenario because, for example, some of the processes are only effective at very high or low pH levels or the process requires a long contact time in water.

Solids Treatment Technologies

Solid-phase treatment systems are used for many types of materials, such as manufacturing wastes, contaminated soils, municipal solid wastes, and spent adsorption media. Many of these technologies are also used to treat slurries such as wastewater sludges and concentrated liquids including AFFF formulations.

The technologies used to treat solid matrices can be broken into three categories: solidification and stabilization (S/S), separation technologies, and thermal destruction/desorption. S/S technologies for PFAS include the addition of binders, sorbents, and other amendments that sequester contamination by physically encapsulating or chemically altering the soil matrix to reduce the solubility, mobility, and toxicity of contaminants. Separation technologies include

Additional PFAS-destruction technologies used to treat solid matrices include kinetic systems, supercritical water oxidation, e-beam, and advanced oxidation processes. However, these technologies are generally not commercially available and may be limited to certain waste streams.

Residual streams coming from the systems discussed here will need to be further managed. These residual streams may include spent adsorptive media, scrubbing water, filters, and fly ash. The optimal management strategy for these residual streams is an area of active research in the federal government.

Air Treatment Technologies

Gas-phase treatment devices are used to treat releases from manufacturing facilities. They are also used to treat the gas coming off from disposal or destruction technologies ("off gas"), such as landfill gas, or for treatment control techniques, such as commercial incinerators, soil desorbers, pyrolyzers, and spent GAC reactivation facilities.

Air or gaseous matrices containing PFAS are generally treated through destruction and separation. Currently, gas-phase PFAS destruction centers around high-temperature chemical breakdown or incineration to destroy PFAS. Other destructive approaches are being investigated; however, these approaches are not considered commercially available and remain a research need (e.g., supercritical water oxidation, bioremediation).

Problems encountered when treating other media also occur when treating air, including formation of HF and partial PFAS destruction products.

Adsorption systems such as GAC or scrubbing systems are separation technologies that treat the primary air stream and can be used as an air pollution control device on a thermal process. The choice of technology may be dictated by volumetric flowrate, temperature, PFAS concentrations, PFAS to be removed, and the treatment goal.

Residual streams need to be managed for both thermal and separation techniques. Spent media are either incinerated or reactivated for further application using thermal treatment[10]. Aqueous residuals, such as scrubber water, are directed to appropriate wastewater treatment or management. Solid residuals, such as bottom ash or fly ash from air pollution control systems, can be used for other applications or be landfilled, but both choices may potentially result in contaminant leaching back to the environment. Optimal management strategies for these residual streams are an area of active research. Similar to the primary waste stream, residuals can be directed toward further treatment or concentration techniques, which present the need for additional treatment, disposal, or destruction to minimize releases to the environment.

Gas-phase interactions between PFAS and particulates can lead to adsorption of PFAS onto particles. Particle-bound PFAS can then be transported in the atmosphere. To avoid this, combustion-generated particulate matter can be captured from thermal treatment systems using a variety of air pollution control systems, including wet scrubbers and electrostatic precipitators.

[10] EPA. Interim Guidance on Destruction and Disposal. 2020. https://www.epa.gov/pfas/interim-guidance-destroying-and-disposing-certain-pfas-and-pfas-containing-materials-are-not.

Summary and Research Gaps

The safe removal and destruction of PFAS from contaminated environmental media/matrices is a complex and challenging undertaking that depends on many factors such as the type of PFAS present, PFAS concentrations, the background constituents, the volume or mass of material to treat, the PFAS needed to be removed and destroyed, the removal or destruction goals, energy use, the cost of treatment, the intended use of the final cleaned effluent stream, the ability to manage residual streams, and the technical expertise of the treatment staff. This is the case regardless of whether the PFAS are in water, solid, and gas matrices. Adding to the complexity is that additional treatment trains may be needed to enable the safe management, disposal, or reuse of the residual streams (e.g., biosolids for land applications, agriculture, and farming) that will be generated by most PFAS treatment and remediation technologies. At this time, mineralization of PFAS is an ideal situation given the many unknowns; however, this increases the number of treatment processes, the cost, and the complexity.

Several recent reports identified critical R&D needs to advance removal and destruction technologies for PFAS: The Government Accountability Office treatment-related findings/recommendations[11]; Strategic Environmental Research and Development Program (SERDP) and Environmental Security Technology Certification Program (ESTCP) "2022 Workshop Report"[12]; and the Interstate Technology and Regulatory Council's report on "Improving Evaluation of PFAS Treatment Technologies"[13]. These recommendations include:

1. Calling for advancing the basic science and engineering knowledge required to overcome limitations in current PFAS remediation/treatment technologies;
2. Opportunities to combine machine learning (ML), artificial intelligence (AI), multiscale computational chemistry and materials design, and multiscale and multiphysics process modeling;
3. Designing, developing, and demonstrating the next generation of high-performance separation and catalytic media and systems for safe and cost-effective removal and destruction of PFAS; and,
4. Accelerating field testing and pilot testing to advance promising technologies and their optimization and integration into treatment trains to safely remove and destroy contaminated environmental media and matrices.

III. Safer and Environmentally Friendlier PFAS Alternatives

PFAS alternatives largely fall into two categories: functional alternatives, which involve technical or engineering solutions (non-chemical methods), and chemical alternatives, which involve the replacement of fluorinated compounds (short-chain PFAS up to large fluoropolymers) with non-fluorinated alternatives that impart a similar function in the manufacturing process or finished product[14]. The long-term goal is to eliminate PFAS in all sectors to the maximum extent possible by

[11] https://www.gao.gov/products/gao-22-105088
[12] https://www.serdp-estcp.org/focusareas/e18ec5da-d0de-47da-99f9-a07328558149
[13] https://pfas-1.itrcweb.org/wp-content/uploads/2022/09/PFAS-Guidance-Document-9-2022.pdf
[14] https://doi.org/10.1039/C9EM00163H

applying sustainable chemistry principles and embracing an essential use concept[15] as a rapid pathway towards effective management or phase out of PFAS-containing products. This section highlights the development and deployment of safer and more environmentally friendly alternatives, including non-fluorine-based alternatives, that are functionally similar to those made with PFAS. Both the development of alternative processes, as well as the understanding of the performance and risk trade-offs of PFAS alternatives, have been identified as critical research needs.

Firefighting Foams

From their introduction in the 1970s, most formulations of so-called "legacy" AFFF were PFAS-based. Starting in 2016, AFFF formulations were modified to contain shorter chain (C6) fluorosurfactants. In the past two years, Department of Defense (DoD) has tested a number of commercially-available and under-development PFAS-free AFFF alternatives. These alternatives provide acceptable fire suppression performance when used against kerosene-based fuel (e.g., Jet A) fires with fresh water as the diluent. Additional development is required to improve the performance of these alternatives for gasoline fires and in the presence of sea water, and to further evaluate trade-offs concerning performance, human health, safety, and environmental impacts.

Selected Industrial Uses

Coatings, paints, and varnishes (CPVs). Coatings on wires, cables, solar panels, indoor and outdoor paints, and other surfaces use fluoropolymers, such as polytetrafluoroethylene (PTFE), which provide durability and resistance to weathering, corrosion, flames, heat, chemicals, abrasion and scratching, and ultraviolet (UV) light. Other polymers (e.g., polyolefins and polyurethanes) are suitable, cost-effective alternatives to fluoropolymers, but only for applications that do not require high-performance coatings. For bridge coatings, fluoropolymer-based paints cost more initially but have superior durability and save cost in the long run over polyurethane coatings that need to be reapplied more often. For solar panels, alternate chemicals and materials, such as glass and polyester, do not perform as well. More R&D is needed to find alternatives that meet the performance requirements. Household paints and varnishes often use short-chain PFAS surfactants, which act as levelling, wetting, and stain-blocking agents. Alternatives to PFAS in floor varnishes include soft waxes and sulfosuccinate chemicals[16]. Overall, more understanding is needed on the health and environmental risks of PFAS and non-PFAS alternatives used in CPVs.

Chemical Industry/Fluoropolymer Production. Fluorinated surfactants are used as aids in the production of chemicals, such as chlorine and solvents, and in the emulsification process commonly used to produce fluoropolymers. One option is using alternative polymers (e.g., acrylate, siloxane and polymeric glycol-based chemistries) as fluorine-free emulsifiers for making polyvinylidene fluoride (PVDF). Some manufacturers have patented fluorine-free emulsifiers for producing PVDF, but it is

---

[15] Essential use is defined as a use of PFAS for which use of a replacement substance is impossible or impractical. H.R.7900 - National Defense Authorization Act for Fiscal Year 2023. https://www.congress.gov/bill/117th-congress/house-bill/7900.

[16] https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/per-and-polyfluoroalkyl-substances-alternatives-in-coatings-paints-varnishes.pdf

unclear if they are in use. The alternative emulsifiers for producing PVDF represent a wide range of individual substances with different chemistries and hence vary in their health and safety hazards, but many are expected to be less hazardous than the fluorinated surfactants they are replacing[17]. Research to identify alternative emulsifiers for producing other types of fluoropolymers is still needed.

Electroplating. PFAS surfactants are used in chrome electroplating for reducing aerosol formation and inhalation exposure to hexavalent chromium [Cr(VI)], which is recognized as a known human carcinogen[18,19,20]. A closed system with controlled pressure to prevent aerosol formation may be a functional alternative for processes using Cr (VI). An alternative being investigated includes switching the process from Cr(VI) to trivalent chromium [Cr(III)], which is less toxic and does not require PFAS to suppress aerosol formation. Because Cr(III) is not currently suitable for all chrome plating applications, additional research is needed on the implementation and development of non-chrome alternatives.

Electronics. PFAS are used in electronic devices (e.g., flat panel displays) and as cooling fluids, cleaning solutions, and in lubricants and etching solutions. The most widely-used PFAS in the electronics industry is the hydrofluorocarbon pentafluoroethane (aka R-125), which is a concern due to its persistence and potent global warming potential (GWP)[21]. While efforts are underway to reduce the production and use of R-125, fluorine-free alternatives are strongly needed.

Semiconductor industry. Perfluorooctane sulfonic acid (PFOS) was traditionally used in the photolithography process as a strong photoacid generator (PAG) in lithographic patterning for producing semiconductors. PFOS was replaced with the shorter alkyl chain perfluorobutanesulfonic acid (PFBS), but there is still a need for fluorine-free alternatives. Aromatic sulfonates and aromatic anions can generate strong acids and may be less hazardous than PFAS; however, these processes have technical performance limitations. More R&D is needed for fluorine-free PAGs[22]. PFAS are also used in immersion lithography as surfactants in developer and chemical rinse solutions. In addition to the extensive use of PFAS in semiconductor manufacturing, fluoropolymer-coated cables (previously described under CPVs) are frequently used in electronics products.

Machinery and equipment manufacturing. Hydrofluorocarbon R-125 is widely used as a "functional fluid" in manufacturing, for example as a refrigerant. More information about PFAS use in this category is needed, along with more environmentally-friendly alternatives.

Production of plastic and rubber. Fluoropolymer PFAS are also used as mold release agents, polymer processing aids, anti-blocking agents for rubber, and as curatives in the production of plastic and

---

[17] Gluge et al. (2022) Information Requirements under the Essential-Use Concept: PFAS Case Studies, ES&T, 56, 6232-6242.

[18] EPA Integrated Risk Information System. https://iris.epa.gov/ChemicalLanding/&substance_nmbr=144.

[19] IARC Monograph. Chromium (IV) Compounds. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono100C-9.pdf.

[20] NTP 15th Report on Carcinogens. 2021. https://ntp.niehs.nih.gov/ntp/roc/content/profiles/chromiumhexavalentcompounds.pdf.

[21] The GWP was developed to allow comparisons of the global warming impacts of different gases. Specifically, it is a measure of how much energy the emissions of 1 ton of a gas will absorb over a given period of time, relative to the emissions of 1 ton of carbon dioxide.

[22] Gluge et al. (2022) Information Requirements under the Essential-Use Concept: PFAS Case Studies, ES&T, 56, 6232-6242.

rubber. This industry is targeted for PFAS replacement due to its high use of fluoropolymers, but no information could be found regarding alternatives.

Cleaning products. PFAS are used as surfactants in a variety of industrial and household cleaning products. Alternative surfactants are available and used in household cleaning products such as dish soap, laundry detergent, floor polish, car wash/coating products, and carpet spot cleaner. In most cases these alternative surfactants are more biodegradable and have reduced human health and environmental risks than PFAS, indicating that PFAS should not be used in most household cleaning products. For industrial cleaning products, the performance requirement for each use needs to be evaluated individually to determine if suitable alternatives are available.

Food Packaging and Contact Materials

PFAS may be found in four main areas of food contact: (1) coatings in non-stick cookware and other non-stick uses, (2) O-rings and gaskets used in food processing equipment, (3) processing aids in the manufacture of conventional non-fluorinated polymers, and (4) grease-proofing agents used on food contact paper and paperboard. The use in non-stick cookware can result in minimal dietary exposure due to the high processing temperatures of the PTFE polymerization process, resulting in minimal low molecular weight PFAS available to migrate to food. Alternatives to PTFE nonstick coatings include ceramics and other nonstick materials. Uses #2 and #3 have also shown to result in negligible dietary exposure, but may still have environmental impacts from a life-cycle perspective.

PFAS used in paper/paperboard functions as a water/oil barrier during time of use or intended duration of the packaging in contact with food. Most of the PFAS used as grease-proofing agents in the U.S. are polymeric. They are coated onto the paper or cellulose fibers and used in applications such as take-out containers, fast food wrappers, and other food containers (e.g., molded fiber bowls). Alternatives may be considered in two categories, physical and chemical barriers. Physical barriers are where the structure inhibits the penetration of liquid. Paper typically gets wet when the cellulose fibers soak up the liquid through capillary pores. Physically, pores that are narrow or refined result in a barrier impervious to water and oil as seen in microfibrillated cellulose. Alternatively, a physical barrier is formed by placing a thin layer of plastic or aluminum on top of the cellulose fibers. Such layers could be made from either polyl(actic acid), silicone polymers, or aluminum foil. Chemical barriers are chemical treatments on the cellulose fiber itself or used as a coating on top of the paper. Examples include internal sizing agents such as alkyl ketene dimers, alkenyl succinic anhydride, and rosin that are added to the molded pulp fiber articles at the wet-end as well as external chemical treatments of the formed paper such as biowaxes (which are safe for direct dietary consumption), clays, starches, and plant and animal-based proteins. Currently, there are three acrylate-based polymers authorized through effective food contact substance notifications for use as water and grease resistant agents. Drawbacks to the known alternatives is the cost and processing time. Chemical alternatives typically cost double that of current short-chain PFAS treatments to paper and paperboard; physical barriers are four times the cost of current PFAS treatments[23].

[23] https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/PFASs-and-alternatives-in-food-packaging-paper-and-paperboard.pdf.

Alternatives to traditional cellulose for use in paper that are being explored include elephant grass, palm leaves, bamboo, clay and wheat straw. However, these may present their own concerns; for example, the use of palm leaves may present safety concerns due to the presence of alkaloids and their potential to migrate to food.

FDA published a letter[24] to manufacturers, distributors, and users of fluorinated polyethylene food contact articles that only containers manufactured in accordance with FDA regulations (21 CFR 177.1615) are authorized for food contact use. FDA has also issued a Request for Information on the use of fluorinated polyethylene food contact containers seeking scientific data and information on the current food contact uses of fluorinated polyethylene, consumer dietary exposure that may result from those uses, and safety information on substances that may migrate from fluorinated polyethylene food containers.

Pesticides

PFAS are used as anti-foaming agents, insecticidal agents, dispersing agents, and inert additives in pesticides. Registrations for many PFAS-containing insecticides have been withdrawn in the U.S. but are still permitted in other countries. Regarding pesticide packaging, diluted fluorine gas is used to fluorinate high density polyethylene (HDPE) plastic packaging to improve container stability, and to make containers less permeable, reactive and dissolvable. PFAS may migrate from these containers and contaminate the pesticide formulation itself. Steel drums and non-PFAS coated HDPE containers are alternatives to PFAS-containing packaging. There are also alternative fluorination processes that reduce the potential for unintentional manufacture of PFAS, which the EPA and United States Department of Agriculture (USDA) have communicated to manufacturers.

Textiles

PFAS are often applied to converted fabrics and textiles such as carpets, rugs, clothing and protective apparel, shoes, and upholstery to create materials that eliminate or repel stains, dirt, oil, or water and to increase durability and performance. Research is needed to identify suitable replacements that achieve equivalent performance standards without leading to substitution regret.

Recreation Products

Use of PFAS in recreation, other than the clothing discussed above, include ski wax and bike chain lubricants. PFAS-free alternatives have been developed, and their use is mandated by a number of sport and governmental regulatory bodies.

[24] https://www.fda.gov/media/151326/download.

Cosmetics and Personal Care Products

PFAS can be found in a broad range of cosmetics[25] and personal care products[26]. Examples include moisturizers, body lotions, nail polish and enamel, cleansers, hair products, and make-up products like foundations, lipsticks, ms2 (TJ0s)8C0.06Cn Tw -35d4 17.541/Att2.2 (n)2.5.003 Tw 9BDCTw290 Tc 0 Tw 3 (dul (9 Tt(r/M

3. The possibility that certain non-fluorinated alternatives may not be less harmful, which could lead to substitution regret; and,
4. Technical challenges in identifying and implementing alternative products and processes.

IV. Sources of PFAS and Pathways to Human Exposure

The presence of some PFAS in 98% of CDC's National Health and Nutrition Examination Survey (NHANES) serum samples collected in a representative U.S. population (approximately 2,000 individuals per each 2-year survey cycle) suggests that there are many sources of PFAS contributing to exposure in the general U.S. population[30]. Sources include, but are not limited to, PFAS manufacturing, the use of PFAS-containing AFFF, sludge generation, and the use of biosolids as a soil amendment.

Other exposure media to PFAS include indoor air, ambient air, dust, and soil, as well as occupational exposure (e.g., during firefighting duties), and the manufacture, processing, distribution, and use of PFAS or PFAS-containing products. PFAS may be present in, and released from, building materials, textiles, and consumer products in residential environments. In certain cases, diet was identified as a significant source of human exposure. PFAS may enter food through multiple sources and pathways including from biosolid/treated effluent applications, composting, growth of food in soil containing PFAS, and/or irrigations with PFAS-containing water, food packaging and food preparation. PFAS may also percolate through the soil to impact the underlying groundwater, resulting in PFAS in drinking water.

Methodologies for analysis of serum and water are routinely used either by CDC's Environmental Health Laboratory for NHANES serum analysis or by municipalities for the analysis of PFAS in public water systems. Methods for collection and analysis of PFAS in other media are not as well developed.

Available national (and some state level) data on PFAS sources and environmental occurrence are collated and updated, and a tool for mapping these data is also available to Federal and State Agencies[31]. Recently, the EPA Enforcement and Compliance History Online program updated their website to include location-specific information related to PFAS manufacture, release, and occurrence in the environment as well as facilities potentially handling PFAS (Figure 2)[32].

Three categories of PFAS were considered in the ECHO initiative and include 1) perfluoroalkyl carboxylic acids/perfluoroalkyl sulfonic acids (**PFCA/PFSA**) (PFAS classes that include perfluorooctanoic acid [PFOA] and PFOS, respectively), 2) **PFAS Precursors** (chemicals with fluorocarbon structures that can transform into intermediate and terminal PFAS and their degradation products such as PFCA/PFSA), and 3) **Other/Emerging PFAS**, including PFAS such as hexafluoropropylene oxide dimer acid (HFPO-DA or GenX chemicals).

[30] CDC National Report on Human Exposure to Environmental Chemicals. https://www.cdc.gov/exposurereport/
[31] https://echo.epa.gov/tools/data-downloads/national-pfas-datasets
[32] https://www.epa.gov/newsreleases/epa-releases-new-pfas-analytic-tools

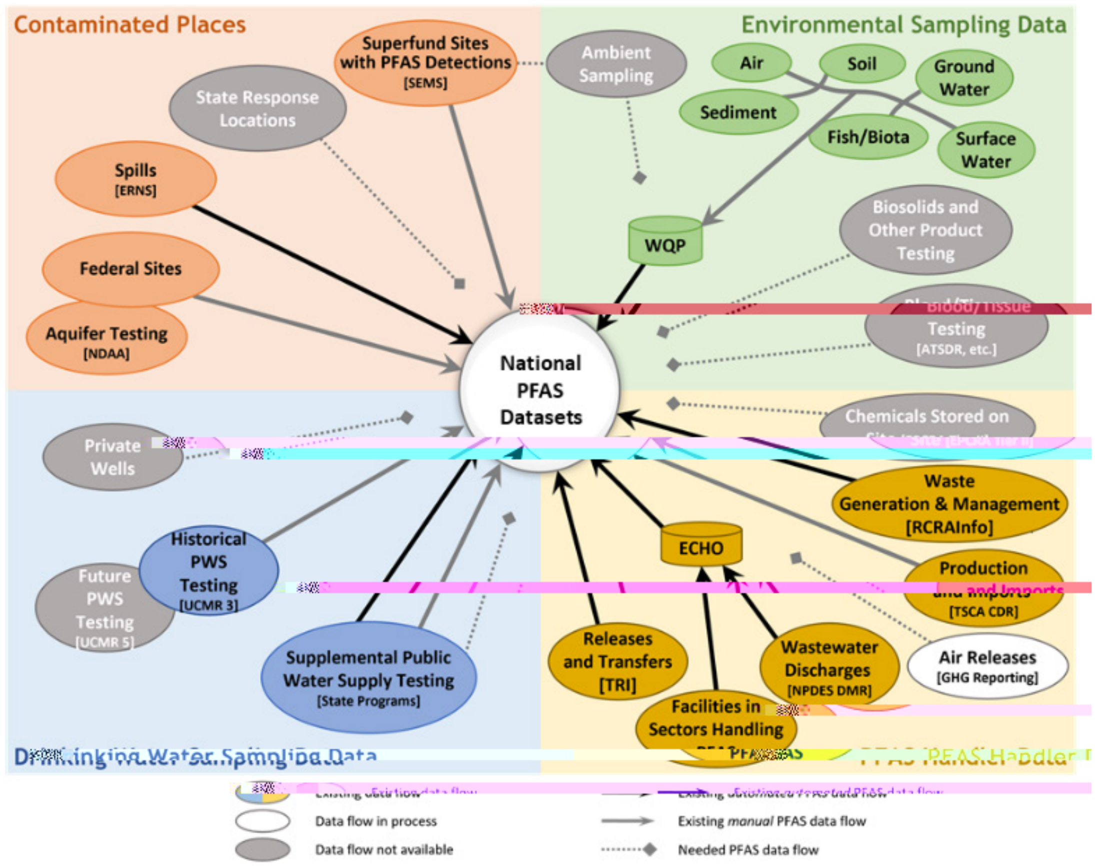

Figure 2: Available National (and Some State Level) Data on PFAS Sources and Environmental Occurrence[33]. WQP = Water Quality Portal; PWS = Public water system; ERNS = Emergency Response Notification System, UCMR = Unregulated Contaminant Monitoring Rule, NPDES = National Pollutant Discharge Elimination System, DMR = Discharge Monitoring Reports, RCRA = Resource Conservation and Recovery Act, SEMS = Superfund Enterprise Management System, TSCA = Toxic Substances Control Act, CDR = Chemical Data Reporting, NDAA = National Defense Authorization Act, GHG = Greenhouse Gas, TRI = Toxic Release Inventory, ECHO = Enforcement and Compliance History Online (source:

Table 2. Current Availability and Quality of Information on Sources of Environmental PFAS Contamination and Pathways of Exposure to the Public.*

	PFCA/PFSA	PFAS Precursors	Other/Emerging PFAS
Sources (location, volume, chemicals)			
PFAS manufacturing	L	L	M
PFAS processing	L	L	L
Product use			
o Industrial	M	L/M	L

[33] https://echo.epa.gov/tools/data-downloads/national-pfas-datasets

o Medical	L	L	L
o Pharmaceutical	L	L	L
o Cosmetics and personal care	M	L	L
o Textiles	M	L	L
o Food packaging	M	L	L
o Agricultural (includes pesticides)	M	M	M
o Fire suppression (AFFF)	H	M	N/A
o Recreational (e.g., ski wax, waterproofing)	M	L	L
Product Recycle	L	L	L 0t .8 (0er 104 1
Product Disposal/Destruction			

[redacted]

o Air	L	L	L
o Dust	M	L	L
o Surfaces	L	L	L
o Drinking water	H	L	L
o Food	M	L	L
Exposure Routes			
Inhalation	L	L	L
Ingestion	M	L	L
Dermal Contact	L	L	L

* L: limited or no information, M: some information available, H: information available and actionable.

Sources

Table 2 provides a summary of current knowledge of PFAS sources by their location, volume, and PFAS category. Data gaps are evident in Table 2, except for some specific uses of certain PFAS of the first category (PFCAs and PFSAs, of which PFOA and PFOS are the primary data sources, respectively). Certain product uses of PFAS are being phased out (such as in food packaging[34]), and in others, alternative PFAS are being adopted in response to toxicity concerns. Significant data gaps remain in our knowledge of these alternatives, as detailed above. We have limited knowledge about PFAS manufacturing and processing as sources of PFAS at the beginning of the supply chain and similarly lack knowledge of product disposal and destruction.

Release

PFAS enter the environment through a variety of release mechanisms as detailed above in Table 2. PFAS are released to air, water and soil and are also re-released from landfill leachate; dissolution from soil amendments (biosolids, waste-water treatment plant [WWTP] effluent) after land application; volatilization of some PFAS and transformation to other PFAS (e.g., PICs) during low temperature combustion/incineration. To adequately control the impacts of these sources on human and ecosystem health, the extent of source characterization, reporting of source strengths and compound identities, and confirmatory measurements need to be improved.

Fate and Transport

Transport is the movement of PFAS through the environment, typically by water or air. Fate is the ultimate destiny of PFAS, and is related to degradation of PFAS to other, often more persistent intermediate and terminal PFAS degradation products, including PFSAs and PFCAs. Across all media (air, water, soil, and biota), there is limited information available regarding fate, transport, and transfer for PFAS and precursor compounds. For example, although some PFAS are mobile in soils and easily

[34] https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-agreement-manufacturers-phase-out-certain-short-chain-pfas-used-food.

transported to groundwater, some PFAS are more readily adsorbed to air-water and solid-water interfaces than others[35].

The impact of water chemistry on PFAS transport is poorly understood. For example, it is unclear whether low oxygen levels and subsequent dissolution of iron oxides in groundwater result in enhanced PFAS transport. Parameters, such as partition coefficients and acid dissociation constants, are needed for models to predict PFAS concentrations in environmental media. Further, PFAS sorption at the air-water interface is an important process affecting retention of PFAS. Quantifying this effect across a range of different PFAS, soil types, climate conditions, and subsurface conditions remains a knowledge gap. Similarly, transport depends on preferential flow paths, variable soil characteristics, nonlinear sorption, competitive sorption, and non-equilibrium conditions, among other factors. Zones with complex biogeochemistry and heterogeneity, such as at groundwater/surface water interfaces, and across salinity gradients (e.g., saltwater intrusion zones) may also have significant impacts on PFAS mobility.

The transfer of PFAS from soils into crops and animal feed

Exposure Media

Elevated levels of PFAS in blood serum are associated with occupational exposure to PFAS (e.g., manufacturing, fire-fighting, etc.; see Table 2). Available information on populations in the U.S., Canada, and Western Europe provide evidence that drinking water, diet, and house dust contribute to levels of PFAS measured in human serum samples in the general population; less information is available on whether air is an important exposure media. Moreover, the contribution to total exposure from different media is not well-understood. The approaches and assumptions used in these studies vary widely. Many of the data are obtained from individual studies conducted at single locations and are not nationally representative. The most studied compounds are PFOS and PFOA; the most studied media are water, certain foods, soil and dust. Media concentrations range widely. The air, soil and dust measurements are limited, regional, and variable. Only a handful of studies looked for PFAS in products and food packaging.

A recent systematic review[37] investigated PFAS exposure pathways for eight PFAS from the indoor environment including consumer products, household articles, cleaning products, personal care products, and indoor air and dust. Of the over 7,000 papers searched, screened, and reviewed, only 9 reported consistent exposure data on PFAS occurrence in indoor media (7 dust and 2 air) and PFAS concentrations in serum. Ongoing work focuses on very small cohorts mostly in impacted communities. Future work should consider a broader range of PFAS (e.g., fluorotelomer alcohols, perfluoroalkane sulfonamides, and perfluoroalkane sulfonamidoethanols), as the small subset of the PFAS evaluated to date are not likely representative of the diverse spectrum of environmentally-abundant PFAS in the indoor environment.

Exposure Routes

Information on exposure routes other than ingestion is either being developed or is lacking. Estimates of PFAS transfer to the fetus during gestation and the infant during breastfeeding are being studied, and inhalation and dermal exposure to contaminated water during indoor water use, including showering and bathing, are currently being estimated using an exposure model developed by ATSDR[38], although studies of human exposure are lacking. Estimates of dermal exposure to treated fabrics are not available, but recent studies suggest that certain PFAS are readily absorbed through skin at levels much greater than previously thought.

Estimated human exposure to PFAS in drinking water applies only to direct ingestion of tap water and beverages or soups prepared locally. These estimates do not generally include PFAS in water that becomes incorporated into solid foods during processing, preparation and cooking. Exposure to PFAS precursors is rarely evaluated, yet these may contribute to total exposure. Studies estimating uptake of PFAS through the inhalation and dermal routes are generally lacking, but recent studies suggest that

---

[37] DeLuca, N. M.; Minucci, J. M.; Mullikin, A.; Slover, R.; Cohen Hubal, E. A., Human exposure pathways to poly- and perfluoroalkyl substances (PFAS) from indoor media: A systematic review. Environ. Int. 2022, 162, 107149; DOI https://doi.org/10.1016/j.envint.2022.107149

[38] https://www.atsdr.cdc.gov/pha-guidance/conducting_scientific_evaluations/epcs_and_exposure_calculations/estimating_inhalation_exposures.html

these exposure routes may prove to be a significant source of exposure to some occupational populations. Furthermore, the contribution to total PFAS exposure from different exposure routes is not well-understood.

Analytical Methods

To date, numerous analytical methods have been developed to quantify a small number of PFAS in various media. For example, Federal agencies have published and made publicly available a number of methods as well as developed additional methods for internal use only (Appendix E, Table E-2). Existing methods include those developed for various environmental media (e.g., drinking water, groundwater, Methods that are under development to quantitate a total PFAS concentration currently appear to, in general, be unable to quantify in the low parts per trillion (ppt) quantitation range. There are multiple reasons for this lack of sensitivity, such as the presence of significant background PFAS concentrations due to the PFAS content in laboratory supplies used and PFAS-containing components of analytical instrumentation. These methods typically also lack in selectivity due to the method's inability to distinguish between PFAS and other fluorine-containing compounds. Determinations below this range (e.g., low ppt range AFFF and AFFF replacements) need alternative preparation and analytical techniques to be developed; it is possible that such relatively low levels may not be achievable in some matrices.

For example, beyond the treatment aspects of gas-phase treatment raised in Section II above, sampling and analysis for PFAS in ambient air and stack emissions remains an active area of research. Volatile, short-alkyl chain PFAS are sampled by collecting a whole air sample using an evacuated canister. Semi-volatile PFAS are sampled from stack emissions using an impinger train.

Analyses of PFAS collected from the gas-phase typically involve either solvent extraction from the impinger trains, direct GC injection from the whole air canisters, or thermal desorption of sorbent tubes. While targeted species analysis is the most common analytical method used to screen common PFAS, there is a critical need for NTA and total organic fluorine (TOF) analysis to assess emerging commercial PFAS, degradation products, and destruction efficacy[40].

Summary and Research Gaps

Existing research demonstrates a need to fill data gaps through the following information:

1. Inventory of documented PFAS exposure sources that is complete and regularly updated.
2. Increased real-time monitoring of PFAS releases across the chemical and product lifecycle.
3. Laboratory-measured Fate & Transport parameters for representative PFAS from each chemical class to build out domain of applicability for current Quantitative Structure–Activity Relationship models.
4. Research to understand, and models to predict, fate and transport of PFAS in environmental (air, waters, soil) and biological (food web) media for existing and new PFAS.
5. Elucidation of the PFAS degradation process and accompanying degradation products in the environment.
6. Monitoring of existing and emerging PFAS in outdoor and indoor environmental media, including increased monitoring of PFAS in drinking water sources.
7. Surveillance of both targeted PFAS and TOF in human biospecimens for both impacted communities and for the general population.
8. Develop pharmacokinetic (PK) models to determine Absorption, Distribution, Metabolism, and Excretion for use in estimating route-specific exposures, estimating the relative target organ specific toxicity, and the understanding of contributions of exposure sources to body burden.
9. Increased source, fate, and exposure research on PFAS of emerging concern.

[40] NSTC. National Emerging Contaminants Research Initiative. 2022. https://www.whitehouse.gov/wp-content/uploads/2022/08/08-2022-National-Emerging-Contaminants-Research-Initiative.pdf.

10. Studies on cumulative exposures and associated health risks (e.g., exposure to more than one PFAS, exposure from multiple sources through multiple media, consideration of exposure to other toxic chemicals)

Agencies are conducting numerous ongoing R&D efforts relative to current analytical method data gaps (Appendix A). These efforts include, but are not limited to, expanding the scope of existing methods through the expansion of the analytes and/or sample matrix types they encompass, field screening techniques, field sensors such as passive samplers, and the determination of organofluorine content or total oxidizable precursors content as "proxies" for total PFAS content. If these efforts are unsuccessful or prove to be impractical due to limitations such as cost, ease of use, or applicability, other techniques will need to be explored. Additional research data gaps for analytical methods include:

1. High-throughput methods for co-occurring compounds, sensors for PFAS or co-occurring compounds, and proxy models may prove valuable for nationwide water quality monitoring.
2. Additional research and validation of methods for defining total PFAS burden to better understand what fraction of the total body burden can be analytically identified.
3. Validated, consistent sampling protocols for all environmental matrices to ensure samples are representative of the environmental matrix being sampled, free from contamination, and reproducible.
4. Standardized protocols to ensure adequate recoveries would ensure consistency across sampling campaigns.
5. Further development and standardization of methods for volatile PFAS precursors and PICs and for non-targeted analysis that could be used to assess inhalation exposure risk.
6. Facilitate development of a wider range of certified PFAS reference materials for use in expanding analytical method development (e.g., for quantitative analysis) and validation efforts in various media and related exposure assessments; development efforts include Federal agencies and collaborations with commercial reference material manufacturers.
7. Standardize aqueous leaching methods to evaluate *in situ* treatment technologies and to improve fate and transport modeling.

V. Understanding the Toxicity of PFAS to Humans and Animals

PFAS toxicity information is found in different data "streams," for example, laboratory animal data, ecological data, human health data, and predictive modeling information. A systems approach to understanding PFAS toxicity is needed to integrate and read across these streams. Current efforts to elucidate PFAS toxicity are largely focused on human health effects, but adverse outcomes at the ecosystem level are also of great concern, including potential effects on wildlife following PFAS exposure. Studies in laboratory animal species to understand the possible health hazards of PFAS are complemented by *in vitro* studies that provide mechanistic information. Epidemiological studies provide additional evidence that potential harms identified in the laboratory are actually occurring in human populations. Ecotoxicological studies, including studies in laboratory animals, observational studies in ecosystems, and predictive approaches can assess PFAS effects on organisms and their habitats.

Each of these evidence streams provides a unique contribution to understanding the toxicity of PFAS. Traditional toxicology studies in animals allow for controlled exposures, broad assessment of health effects, dose-response assessments, insights into life stage susceptibilities and even characterization of the pathogenesis of the health effects. As is often the case, non-human modeling systems are not perfect surrogates for humans increasing the importance of taking a more integrated and multi-modal approach to assessment. Epidemiological studies assess the association of PFAS exposure to health effects in real world human contexts. In addition, epidemiological studies typically assess exposure using biomarkers (such as serum PFAS concentrations), modeled exposure, or other types of proxies, which may lead to some uncertainty in understanding actual exposure to PFAS in environmental media. Ecotoxicological studies help elucidate potential hazards to ecological species and can address both controlled laboratory exposures and less controlled but more realistic scenarios (e.g., *in situ* field exposures or sampling). However, the broad range of species, life strategies, scenarios, and confounding factors challenge our ability to truly understand adverse effects at the ecosystem level.

Because of the large number of PFAS currently identified in commerce, one goal of future research is to determine whether all PFAS, or specific groups and their combined mixture effects, might pose a similar hazard to human and ecological receptors. Such PFAS groupings may provide a means by which agencies might regulate PFAS for the protection of humans and ecological receptors.

Overall, in order to understand and thus address PFAS-related hazards, a systematic review and weight-of-evidence approach that takes into account the different evidence streams is needed. The knowledge gleaned from all of these studies allows for an understanding of PFAS-related human health effects. This comprehensive approach can inform risk assessment and future regulations. This section summarizes what is known about these three streams of evidence along with current data gaps.

Epidemiological Studies of PFAS

Epidemiological studies have the advantage of assessing associations between PFAS exposures and real health effects in humans though the complexity and variability of the human context can sometimes undermine the strength of those associations. They seek to identify health effects associated with environmentally relevant exposures and environmentally relevant mixtures, which vary by population, space, and time. These studies examine the human health effects of exposures as they occur during the course of life. This necessitates the use of study designs and analytic methods that address potential confounding factors, sources of bias, and the possibility of different effects in different populations, life stages, and settings.

There is now a growing body of epidemiological literature on the human health effects from exposure to some PFAS. PFAS exposure is ubiquitous; essentially everyone in the United States has PFAS in their blood. Occupationally exposed populations typically have the highest exposures. Communities with PFAS-contaminated drinking water can also have exposures that are much higher than the general population, but usually lower than occupationally exposed populations. Studies of PFAS health effects must be interpreted and compared with consideration of the different extents and sources of exposure. In addition, some studies include populations that might be uniquely susceptible to effects of particular health outcomes, such as children, pregnant women, and people with certain underlying health conditions (such as diabetes). The composition of PFAS mixtures have also varied across studies, as have exposures to other environmental factors. The approach to exposure measurement or estimation has also varied across studies. The most studied types of PFAS are PFOA, PFOS, and to a somewhat lesser extent perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA). Other types of PFAS have been considered in far fewer studies. Epidemiological studies have examined a very wide range of health outcomes including reproductive, birth, developmental, behavioral, neurologic, endocrine, immunologic, metabolic, cardiovascular and cancer outcomes. For some health effects (such as pediatric cancer, hepatocellular carcinomas, and birth defects); there have been very few studies, and existing studies have been conducted on small sample of cases.

Summarizing the current state of knowledge about PFAS health effects from epidemiological studies is challenging because of the wide range of potential health effects, the wide range of PFAS, and the potential for health effects to differ in populations with different extents of exposure, co-occurring exposures, or characteristics that influence susceptibility (e.g., exposure at life stages of greatest vulnerability). Conflicting results from different studies must be interpreted with consideration of differences in the populations and extents of exposure studied, as well as careful consideration of the strengths and weaknesses of each study. Substantial evidence from epidemiological studies contributes to the overall weight-of-evidence that PFAS exposure is associated with a range of human health effects.

The evidence for PFAS health effects has been reviewed by several organizations that have made determinations relating to the degree to which the available evidence indicates an association between PFAS exposure and various human health effects. These determinations generally use a weight-of-evidence approach that considers various evidence streams (e.g., epidemiology, animal or *in vitro* toxicology) to make conclusions about the association between PFAS exposure and human health effects. These determinations are summarized in Table 3. One of the earliest consensus statements about PFAS health effects was from the C8 Science Panel, a panel of three environmental epidemiologists charged with determining which health effects were probably linked to PFOA exposure, as part of a class-action lawsuit settlement in Mid-Ohio Valley communities exposed to PFOA releases from a chemical plant. ATSDR published the Toxicological Profile for Perfluoroalkyls, which summarizes and interprets available information from animal and epidemiological studies to identify adverse health effects relevant to human PFAS exposure. The US EPA published documents summarizing evidence from epidemiological and animal studies relating to health effects of selected PFAS (PFBS, GenX Chemicals, PFOA and PFOS), and uses that information to help guide its actions. The European Food Safety Authority (EFSA) has reviewed health effects of several PFAS to inform a risk assessment for PFAS in food. In addition, the National Academies of Science, Engineering and Medicine (NASEM) recently reviewed PFAS health effects in a report that provides considerations for PFAS testing, clinical care and follow up of PFAS exposed patients. The International Agency for Research on Cancer (IARC) has reviewed evidence for the carcinogenicity of PFOA, and the National Toxicology Program (NTP) has reviewed evidence relating to immunologic effects of PFAS.

There has been general agreement between these organizations relating to specific health effects for which there is evidence of an association with certain PFAS exposure (see Table 3). Human health effects for which at least three of these groups determined that there was evidence of an association with exposure to at least one PFAS include:

- increased cholesterol levels (specifically total cholesterol and LDL cholesterol),
- increase in circulating liver enzymes,
- decreased infant birth weights,

- decreased immune response to vaccination,
- thyroid disorders and decreased thyroid hormones (including diagnosed thyroid disease),
- pregnancy-induced hypertension and preeclampsia, and
- some cancers (testicular and kidney cancer).

However, there are several other health effects for which only one or two of these groups determined that there was some evidence of an association with a specific PFAS exposure, demonstrating that there is still some uncertainty relating to these other PFAS health effects. The reader is referred to these consensus reports for additional details on evidence from epidemiological studies.

Table 3. Human health effects for which organizations have concluded there is evidence for an association with PFAS. Outcomes where organizations have made a conclusion that the epidemiological evidence indicates there is an association are indicated by an "X" followed by the specific PFAS that conculsion applies to. A cell with "(-)" indicates that the organization determined that the epidemiological evidence was not sufficient to make a conclusion on the association between any specific PFAS or PFAS as a class and the outcome.

Category	Outcome	ATSDR[41],[42]	US EPA[43]	EFSA[44]	C8 Science Panel (considered PFOA only)[45]	NASEM[46] (considered PFAS as a group)	Other Statements
Areas of Consensus							
Carcino-genicity		**X**	**X** (PFOA)	(-)	**X** (PFOA)	**X** (sufficient evidence)	The International Agency for Research on Cancer (IARC) has classified PFOA as possibly carcinogenic to humans (Group 2B). They concluded, "There is limited evidence in humans for the carcinogenicity of perfluorooctanoic acid (PFOA). A positive association was observed for cancers of the testis and kidney."[47] EPA concluded that there is suggestive evidence of carcinogenic potential of PFOA and PFOS in humans.[23,24]
		X	**X** (PFOA)	(-)	**X** (PFOA)	**X** (limited or suggestive evidence)	
Metabolic Disease		**X**	**X**	**X**	(-)	**X** (limited or suggestive evidence)	
		X	**X**	**X**	**X** (PFOA)	**X** (sufficient evidence)	

[41] ATSDR. Toxicological Profile for Perfluoroalkyls. Available at: https://www.atsdr.cdc.gov/ToxProfiles/tp200.pdf. Accessed 6/2/2022.
[42] ATSDR. What are the health effects of PFAS? Available at: https://www.atsdr.cdc.gov/pfas/health-effects/index.html. Accessed 6/2/2022.
[43] Science Advisory Board 2022. Review of EPA's Analysis to Support EPA's National Primary Drinking Water Rulemaking for PFAS. https://sab.epa.gov/ords/sab/f?p=100:18:16490947993:::RP,18:P18_ID:2601#report. The SAB report supports epidemiological evidence for major effects described in footnotes 28 and 29. Please note that footnotes 28 and 29 were submitted for external peer review in December 2021.
[44] EFSA Panel on Contaminants in the Food Chain. Risk to human health related to the presence of perfluoroalkyl substances in food (2020). EFSA J. 2020 Sep 17;18(9):e06223. doi: 10.2903/j.efsa.2020.6223.
[45] C8 Science Panel. Probable Link Reports. Available at: http://www.c8sciencepanel.org/prob_link.html. Accessed 6/2/2022.
[46] National Academies of Sciences, Engineering and Medicine 2022. Guidance on PFAS Exposure, Testing, and Clinical Follow-Up. Washington, DC: The National Academies Press. https://doi.org/10.17226/26156. Accessed 9/9/2022.
[47] IARC. IARC Monographs Volume 110: Perfluorooctanoic Acid, Tetrafluoroethylene, Dichloromethane, 1,2-Dichloropropane, and 1,3-Propane Sultone. Available at: https://publications.iarc.fr/547. Accessed 6/2/2022.

Immune		**X**	**X**	**X**	(-)	**X** (sufficient evidence)	The National Toxicology Program (NTP) concluded that PFOA and PFOS are presumed to be an immune hazard to humans based on a high level of evidence that PFOA and PFOS suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans[48]
Endocrine		(-)	**X**	(-)	**X** (PFOA)	**X** (limited or suggestive evidence)	
Reproductive and Birth Outcomes		**X**	**X**	**X**	(-)	**X** (sufficient evidence)	
		X	**X**	(-)	**X** (PFOA)	**X** (limited or suggestive evidence)	
Areas without Consensus							
Carcino-genicity	Breast cancer	(-)	(-)	(-)	(-)	**X** (limited or suggestive evidence)	
Immune		(-)	(-)	(-)	(-)	(-)	
		(-)	(-)	(-)	(-)	(-)	
		(-)	(-)	(-)	**X** (PFOA)	**X** (limited or suggestive evidence)	

[48] NTP. NTP Monograph: Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate. Available at: https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf. Accessed 6/2/2022.

Metabolic Disease		(-)	(-)	(-)	(-)	(-)	
		(-)	(-)	(-)	(-)	(-)	
		(-)	(-)	(-)	(-)	(-)	
		(-)	(-)	(-)	(-)	(-)	
Develop-mental	Multiple outcomes have been considered, such as neurodevelopmental outcomes and growth	(-)	(-)	(-)	(-)	(-)	
Repro-ductive and Birth Outcomes		(-)	(-)	(-)	(-)	(-)	
		(-)		(-)	(-)	(-)	
Cardio-vascular		(-)	(-)	(-)	(-)	(-)	
Skeletal		(-)	(-)	(-)	(-)	(-)	

*While the Toxicologic Profile for Perfluoroalkyls does not make cancer conclusions, ATSDR lists kidney and testicular cancer as health effects on its web site.

PFOA=Perfluorooctanoic acid, PFOS=Perfluorooctane sulfonic acid, PFHxS=Perfluorohexane sulfonic acid, PFNA=Perfluorononanoic acid, PFDA=Perfluorodecanoic acid

Summary and Research Gaps

To advance knowledge about PFAS health effects, additional epidemiological studies could contribute to filling data gaps for the following:

1. PFAS (or groups of PFAS) most likely to be associated with which health effects;
2. Understanding of the relative effects of varying levels of exposure for those associations;
3. How the health effects vary by route of exposure;
4. What factors (such as age and underlying health conditions) increase susceptibility to the effects of PFAS on various health outcomes;
5. What measurable intermediate biomarkers of effect in exposed humans can lead to better understanding of biological mechanisms leading to disease;
6. What public health and medical interventions are most effective in alleviating health effects following PFAS exposure; and,
7. The influence of different PFAS mixtures and co-occurring exposures (chemical and non-chemical) on PFAS-associated health effects.

Epidemiological studies with strong designs that help minimize bias, such as longitudinal cohort studies, nested case-control, and case-cohort studies, should take priority in the future. Studies that use newer approaches to assessing PFAS health effects, such as studies that incorporate causal-inference-based analytic approaches and studies using advanced computational techniques for addressing specific questions about effects of mixtures may offer additional insight about human health effects. Development of new epidemiological methods and analytic approaches might also help advance knowledge about PFAS health effects. This might include measuring biomarkers of effect early in the progression of disease to provide an opportunity for early intervention. Epidemiological studies are needed that have good characterization of both PFAS exposures (e.g., exposure routes, duration and intensity, changes over time, mixtures, reconstruction of past exposures when appropriate) and other co-occurring exposures. There is also a need for studies that examine exposure at stages of life during which people might be particularly vulnerable to development of particular health effects as a result of PFAS exposure (sometimes called, “windows of susceptibility”). In addition, studies are needed that minimize important sources of bias, such as potential biases that can result from associations between measured PFAS serum concentrations and factors that influence PFAS elimination (e.g., decreased renal function, menstruation, other sources of blood loss). There is a particular need for studies of the health effects of novel PFAS and for studies of less-studied health outcomes. Engagement with impacted communities is important when designing epidemiological studies, to ensure that studies appropriately address issues of concern. Finally, there is a need for efficient use of existing resources, such as making use of existing cohort studies, sharing exposure data between research teams and public health agencies, encouraging collaboration, and streamlining access to health outcome data sources while still protecting confidentiality.

PFAS Toxicity in Laboratory Animal Models

Toxicity studies in animals evaluate health effects following controlled exposures in laboratory settings, which can help avoid issues of confounding. However, these studies must consider differences between species and differences between exposures and mixtures in lab settings vs real-life settings. Toxicity studies have focused most intensely on PFOA and PFOS, using laboratory rodents and zebrafish as primary models. Other perfluoroalkyl acids of varied carbon-alkyl chain lengths and a few replacement PFAS (such as GenX chemicals, 4,8-dioxa-3H-perfluorononanoic acid [ADONA], and Nafion by-products) have also been examined in these models. Some PFAS (e.g., PFHxS, PFOA, and PFNA) have longer half-lives in mice than rats and typically much longer half-lives in humans. Bioaccumulation of these PFAS in pregnant mice and humans has led to exposure concerns for breastfed offspring[49]. Differences in elimination kinetics should be considered in cross-species extrapolation of health effects. Some PFAS (e.g., PFOA and PFNA) exhibit gender-related differences in the rate of chemical elimination and bioaccumulation in the rat where females eliminate them faster than males. Although limited studies have been conducted, sex differences in half-lives for those PFAS studied are reported to be minimal in humans. Mice may have more limited sex-based PFAS elimination differences making them potentially useful for assessing PK extrapolation to humans. Mice also have consistency in reported health findings with humans for PFOA, with lower no adverse effect levels than those reported in rats, so mouse data have been used in formulating state-based PFOA reference doses[50].

Animal toxicity studies generally test a wide range of exposures often extending beyond what may be measured in humans to account for differences in susceptibility, sensitivity and kinetics across the species. Studies in which tested PFAS demonstrated adverse pregnancy/birth outcomes, and health effects at lower doses in gestationally exposed offspring compared to exposed adults, have been essential in 1) initiating investigation in human cohorts and/or 2) providing causal evidence in test models for health effects that have been observed in humans. In general, health effects associated with PFOA and PFOS exposure in animal models agree with the epidemiological human literature including: altered lipid metabolism (dyslipidemia), liver disease, obesity, developmental and reproductive toxicity, immune suppression, cancer, and endocrine disruption[51,52,53,54,55,56]. These findings in animals were derived from well-controlled experiments, with coherence across species in many cases, and dose ranges that considered differences in half-life across species. Biological targets demonstrating statistically significant health effects in laboratory animal models following exposure to select PFAS and their common replacements are shown in Table 4. Our understanding of the toxicologic properties of PFAS other than PFOA and PFOS is notably less advanced and, in the case of emerging replacements and by-products (see Table 4), incompletely explored.

---

[49] https://pubmed.ncbi.nlm.nih.gov/35195447/
[50] https://setac.onlinelibrary.wiley.com/doi/full/10.1002/etc.4863
[51] https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=1117&tid=237
[52] https://setac.onlinelibrary.wiley.com/doi/full/10.1002/etc.4890
[53] https://pubmed.ncbi.nlm.nih.gov/35475652/
[54] https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf
[55] https://ntp.niehs.nih.gov/publications/reports/tox/000s/tox096/index.html?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tox096abs
[56] https://ntp.niehs.nih.gov/publications/reports/tox/000s/tox097/index.html?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=tox097abs

Table 4. Significantly affected health endpoints in animal toxicity studies for selected PFAS and their common replacements.*

Health Effect Endpoint	PFBA (4)	PFBS (4)	PFPeA (5)	PFHxA (6)	PFHxS (6)	HFPO-DA (6)	ADONA (7)	PFHpA (7)	FOSA (8)	PFOA (8)	PFOS (8)	PFNA (9)	PFDA (10)	PFUnA (11)	PFDoDA (12)
Body weight	•	•		•	•	•	•		•		•	•	•	•	•

*Table was updated from original published in: Agency for Toxic Substances and Disease Registry (ATSDR). 2021. Toxicological profile for Perfluoroalkyls. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Released May 2021 (Table 2.2). It now includes data in PubMed (with the exception of PFPeA) up to June 10, 2022. The (#) after each PFAS in the header denotes the carbon number.

The common acronyms for the PFAS in Table 4 and their unique CASRN: PFBA (Perfluorobutanoic acid) 45048-62-2; PFBS 375-73-5; PFPeA (perfluoropentanoic acid) 2706-90-3; PFHxA (Perfluorohexanoic acid) 92612-52-7; PFHxS 82382-12-5; HFPO-DA 13252-13-6; ADONA 958445-44-8; PFHpA (Perfluoroheptanoic acid) 375-85-9; FOSA (perfluorooctane sulfonamide) 754-91-6; PFOA 335-67-1; PFOS 1763-23-1; PFNA 375-95-1; PFDA 73829-36-4; PFUnA (Perfluoroundecanoic acid) 2058-94-8; PFDoDA (Perfluorododecanoic acid) 307-55-1.

Cardiometabolic and liver diseases. The liver is a definitive target organ for toxicity from oral or *in utero*/lactational exposure to PFAS in rodents and other animal models. Recent systematic assessments of the rodent model literature concluded that exposures to several long-chain PFAS are associated with increases in serum liver enzymes (human-relevant biomarkers of hepatotoxicity), and hepatic steatosis (or fatty liver) or non-alcoholic fatty liver disease (NAFLD). Developmental exposure to GenX chemicals in mice results in sex-dependent liver toxicity, excess fat mass accumulation, and elevated fasting insulin levels like that seen following PFOA exposures. Liver cancer has been shown in animal models with PFAS exposure, and only recently in one study in humans[57].

Mice developmentally exposed to PFOA and GenX chemicals also exhibit obesity as young adults, altered blood lipids (dyslipidemia), increased body fat mass and blood insulin levels, and other endpoints consistent with metabolic disease and diabetic outcomes. In *in vivo* and *in vitro* models, activation of nuclear receptor genes that regulate lipid, bile acid, and glucose metabolism and transport have been reported with PFAS exposure. However, the relative effects of these receptors may differ between rodents and humans. *In vitro* studies with human and mouse pre-adipocytes or liver cell

[57] https://pubmed.ncbi.nlm.nih.gov/35475652/

cultures, as well as some animal studies with or without high-fat diets, implicate PFAS in increasing cholesterol.

Immune system. Toxicity studies in rodents and nonhuman primates identified the immune system as a sensitive target of exposure to some PFAS. Studies with numerous individual long-chain PFAS have reported alterations in organ weight and/or immune cells of the spleen and thymus. Overall, PFOA and PFOS effects in animals are immunosuppressive; the most predominant effect being impaired antibody response or, to a lesser extent, impaired responses to infectious diseases. A 2016 NTP systematic review of immunotoxicity data concluded that PFOA and PFOS were immune hazards to humans based on a high level of evidence that they suppressed the antibody response in animals and a moderate level of evidence from studies in humans[58]. Since 2016, several additional good quality immunotoxicity studies in humans, including in children, have reported an association between PFOA or PFOS exposure levels and suppressed response to vaccines. Studies in rodents after sub-chronic exposure to GenX chemicals reported some immune effects, particularly lymphoid organ lesions, but was less potent to functional immune alterations than other PFAS. Only a few animal studies have evaluated the mechanisms of PFAS effects on the developing immune system.

Adverse pregnancy and birth outcomes. Animal models have shown that some PFAS transfer to the developing offspring through nursing and the placenta. PFAS developmental effects have included low birth weight, other growth deficits, and developmental delays at low dose exposures, and neonatal morbidity and mortality at the highest doses tested. Other adverse outcomes with some evidence in animal models include lactation impairment, gestational hypertension (pre-eclampsia), and decreased weight gain during pregnancy. Multiple developmental outcomes for several long- and short-chain PFAS have been reported in multiple laboratory species, including fish, rats, mice, and non-human primates following gestational and lactational exposures.

Thyroid and other endocrine related outcomes*.* The thyroid is the control center for multiple critical functions in the body ranging from early life IQ to puberty timing to metabolic function. Considerable evidence exists for endocrine-related effects in animals exposed to PFAS. Multiple studies on diverse species (developing rodents and fish) suggest that some PFAS (e.g., PFOS, PFOA, PFNA, GenX chemicals, PFHxS, PFDA, PFBA, PFBS, PFHxA) interfere with thyroid hormone signaling pathways and thyroid homeostasis through various mechanisms, including regulation of hepatic glucuronidation enzymes and deiodinases in the thyroid gland. Maternal transfer of thyroid hormones is critical for fetal brain development and assists in regulating metabolism in offspring. Further, there is interplay between the thyroid axis and the reproductive/steroid axis. In rats, PFAS exposures lead to hypothyroxinemia and reduction of serum testosterone. Mouse model and *in vitro* studies have shown some PFAS to have estrogenic effects. However, the evidence for PFAS activating steroid receptor signaling is mixed and varies across species.

Some rodent models provide support for testicular damage, possibly due to endocrine disruption. Before much of the current body of evidence for PFAS was available, the US EPA Science Advisory

---

[58] NTP. 2016. Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf

Board[59] recommended classifying PFOA as a "likely human carcinogen," based on findings of multi-site carcinogenicity in two rodent (mouse and rat) studies which included testicular cancer findings (Leydig cell tumors).

The results of studies evaluating the impact of PFAS on pubertal timing in rodents appear to be compound, dose, and strain dependent. Some studies reported delayed phenotypic puberty timing in male or female mice and others reported no effects. Deficits in mammary gland development were observed in several studies of mice exposed to PFOA during gestation with the effects persisting into adulthood. Little data exists on female cyclicity in PFAS-exposed rodents. Reproductive/fertility effects such as ovulation failure and male sperm deficits have been reported in mice exposed to PFOA.

Kidney disease/cancer. Despite the large number of rodent studies investigating associations between PFAS exposure and kidney function, the effects are not completely understood. Studies in rodents with some long-chain PFAS reported increased kidney weights but lacked corresponding changes in renal function or histopathological alterations. Rat studies using 6:2 fluorotelomer alcohol reported significant renal pathology, leading to mortality, and changes in clinical pathology endpoints reflective of kidney function have been reported. Likewise, chronic exposure to PFHxA caused mild renal tubular degeneration, mild to severe papillary necrosis, and increased mean urine volume and reduced specific gravity in female rats. Adverse renal lesions were observed in adult female rats given the highest doses of GenX chemicals in sub-chronic and chronic studies. The IARC has classified PFOA as "possibly carcinogenic to humans" (Group 2B), based on limited evidence in humans that it can cause testicular and kidney cancer, and limited evidence that it can cause cancer in lab animals (pancreatic, liver, testicular).

Evidence in domestic species. Health effects and accumulation of PFAS are largely unstudied in agricultural animals (e.g., cattle, pigs, and poultry) and companion animals (e.g., horses, dogs, cats). Household pets can serve as sentinels for indoor exposures. Indoor cats have been surveyed, and those containing the highest levels of PFAS were found to have associated health outcomes (thyroid disease and adverse respiratory, liver kidney effects). Farm animals can demonstrate the movement of PFAS through the food chain, which may lead to the accumulation of PFAS in food animal tissues or products.

Summary and Research Gaps

It is impractical to assess the health effects of the large number of structurally distinct PFAS in commerce and the environment in a traditional animal study-based approach. Additionally, experimental studies of PFAS are limited by the availability of analytical standards, test chemicals, and compound-specific details that are often considered confidential business information. Work is also confounded by the prevalence of background PFAS levels in laboratory materials and challenged by physicochemical properties that can complicate *in vitro* studies and analytical measurement. Consequently, sufficient information to conduct quantitative risk assessment is currently available for a relatively few PFAS and predominately by the oral route of exposure.

[59] EPA. 2022.

Higher throughput methods for prioritizing PFAS needing laboratory animal testing. Most PFAS are "data poor" (see Appendix E-3), and studies are critically needed to fully capture the range of potential hazards represented by the diverse chemical structures. Screening PFAS with limited data for biological activities in inexpensive, high throughput assays, focused on the targeted cell types involved in human and rodent/aquatic PFAS-associated disease is an immediate need. Development of PFAS-specific high throughput assays would more efficiently and effectively screen emerging PFAS. Strategically identifying those emerging PFAS that are the most potent or bioaccumulative would prioritize them for further study in more resource intensive assays with more complex model systems. Animal studies that define mechanistic pathways correlated with biological outcomes (liver and birth outcomes, tissue accumulation data, etc.) hold potential for predictive toxicology screening assays in human liver, placental, breast, kidney and other cells or short fit-for-purpose animal studies.

Biological Targets and Biomarkers of PFAS-induced health effects. There is cross-species consensus on some health effects of PFAS, and although that information has been generated on relatively few chemicals, several of the effects are seen across the tested PFAS. There is an on-going need for well-designed rodent studies to understand the developmental origins of these disease states more completely and identify the various cellular or receptor-based (biological) targets within the organs (e.g., kidney, testes, breast) to futuristically:

1. Identify clinical biomarkers in exposed rodents for use in early detection of human disease, especially for those disease states where there are multiple potential targets or long disease latency (e.g., adverse pregnancy outcomes, cancers, metabolic disease, and thyroid, liver, and kidney disease).
2. Characterize biological targets in exposed animal models for which interventions may be integrated/tested in affected human populations (e.g., fertility, decreased birth weight, lactation duration, advanced liver disease, childhood obesity/diabetes/fatty liver, immune-based diseases such as colon, thyroid, immunosuppression).
3. Develop a list of health effects which should be tested for required rodent studies as emerging PFAS are introduced into commerce. Chemicals inducing these disease endpoints should be avoided in the future.

Endocrine basis for health effects. Endocrine-based health effects may be at the level of a target tissue, but typically involve more than one part of an endocrine axis and multiple targets, with hormonal feedback loops, complicating the ability to study them *in vitro*. Evidence from laboratory and domestic animal studies (e.g., rabbit, rodent, non-human primate, and cats) suggest PFAS interactions with thyroid hormone-binding proteins result in perturbed feedback relationships between the free thyroid hormone available to cells (free T_4) and the hypothalamic–pituitary axis. Alterations in thyroid deiodinases or metabolizing enzymes (UDPGTs) can also impact local T_3 availability in the placenta, breast, and other tissues. However, many times the decrease in T_3 and T_4 in animals following PFAS exposure is not accompanied by the compensatory increase in thyroid stimulating hormone. Thyroid homeostasis has critical roles in fertility, fetal growth, infant cognition, metabolic disease, obesity, breast development, and other reported health effects for PFAS. Further, there may be important endocrine interactions (e.g., thyroid, androgen, and estrogen pathways) following PFAS exposures. The role of the thyroid and interacting steroid pathways in these disease states is not well-studied (a research gap) and deserves future investigation. This may be a rich area for biomarker development.

PFAS mixtures and biologically relevant accumulation data. Historically, rodent toxicology studies have investigated single PFAS for health effects, yet it is clear from epidemiological evidence that communities are exposed to mixtures of PFAS. The additive or synergistic effects of exposures to co-occurring PFAS are uncharacterized in animal or *in vitro* models, creating further challenges in extrapolation of animal to human health effects. This major research gap needs prioritization to provide actionable data for future PFAS mixtures risk evaluations.

Due to challenges associated with performing inter-species and route-to-route extrapolations (e.g., oral-to-inhalation extrapolation and vice versa) for PFAS, it is difficult to draw conclusions about their potential to accumulate in humans based on animal studies. The potential to accumulate in blood has been characterized for only a handful of PFAS, and the TK profiles for most PFAS have not been elucidated. Some recently published studies focus on assessing accumulation of PFAS from the perspective of steady state; however, achieving steady state in the blood may not be equivalent to reaching steady state in tissues, such as liver, kidney, and fat. Not all PFAS are substrates of renal transporters, but they may have a potential to accumulate in the body because of other mechanisms such as enterohepatic circulation. Accumulation data would help in determining margins of exposure and potentially identify those PFAS most apt to remain in the environment/body and affect human health. Identifying biomarkers of exposure or outcomes to characterize the potential for data-poor PFAS to accumulate is needed.

Last, accumulation and depletion studies are needed in domestic food sources (beef, dairy, poultry, eggs, pork, fish) to identify sentinel PFAS molecules and tissues that may be recoverable after point, short -term, or chronic exposures, and for modeling purposes. Resulting data would improve TK models to estimate the concentration of PFAS in edible animal food products based on the PFAS concentrations in the animal diets. However, methodological advances in these more complex matrices would be needed.

Inhalation and dermal toxicity studies. Few toxicological studies evaluated inhalation or dermal exposure routes. ATSDR has reviewed the literature on several PFAS (see Table 4) and concluded the "database was not considered adequate" for derivation of toxicity values for inhalation; and "Though inhalation data are available for PFOA and PFNA, these studies examined a limited number of endpoints and the data are not adequate for identifying the most sensitive targets of toxicity or establishing dose-response relationships[60]. No inhalation data are available for other perfluoroalkyls." There is a demonstrated need to understand potential risks from inhaled PFAS (especially for volatile species) to inform risk management decisions due to PFAS emissions commonly found in indoor and outdoor air. Although largely unexplored, there is some evidence in animals for skin damage from dermal PFAS exposure. There is a lack of TK data from inhalation and dermal exposure. Additional TK and toxicological data are needed to inform potential oral-to-inhalation (and vice versa) dosing extrapolations for PFAS and bridge this data gap.

[60] ATSDR. 2021. Toxicological profile for Perfluoroalkyls. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Released May 2021

Health effects in aged populations. Physiological and pathophysiological changes occur during normal aging including alterations in blood flow and brain chemistry, metabolism, cessation of menstruation, decreased bone density, and a decline in immune function. The combination of an increased susceptibility of disease in aging populations (due to immune senescence) and concerns regarding the increased body burden of PFAS in these populations warrants urgent investigation. Although it is possible to conduct chronic lifetime exposure studies in animal models, the long-term health effects of PFAS exposure, such as cancer in an aging population, may require study in epidemiological cohorts, given practical concerns with utilizing chronically exposed animal models.

Ecotoxicology Data

Ecotoxicology is the study of the effects of chemicals and other stressors on organisms and their habitats. Understanding exposure to PFAS and potential subsequent adverse effects across the diversity of ecological species is critical to determining risk to the environment, including commercially and recreationally important environmental resources. Exposure scenarios vary across taxa (e.g., aquatic vs. terrestrial), requiring an in-depth understanding of PFAS sources, fate, and transport to predict exposure to ecological species. Following exposure to PFAS, the uptake and subsequent adverse effect is dependent on the specific attributes of each PFAS and organism. Ecotoxicity testing provides data to inform regulatory agencies tasked with setting chemical thresholds that will be protective of environmental health. Efforts are ongoing to develop acute and chronic water quality criteria for PFOS and PFOA. Ongoing testing will help to refine those values, determine additional thresholds for chronic exposures, and set criteria for other PFAS.

Exposure and Bioaccumulation

Decades of widespread use, along with mobility and persistence, have resulted in ubiquitous PFAS contamination worldwide. The persistence of PFAS is concerning as some chemicals can accumulate in tissues, resulting in high chemical burdens in some organisms. The potential to bioaccumulate or magnify through the food web varies with the physicochemical properties (i.e., mobility, persistence) of a specific PFAS; however, bioaccumulation models previously developed based on chemical partitioning into lipids (fats) are not applicable to most PFAS, in part due to their affinity for proteins, thus making traditional lipid partitioning models inaccurate. The presence of PFAS in tissues of aquatic and terrestrial species has been documented in studies conducted across every continent, including remote regions far from direct sources, such as the high arctic, Antarctica, and oceanic islands. Air breathing animals have been found to exhibit greater PFAS bioaccumulation than aquatic animals with gills, and higher trophic level predators, including human consumers of fish, shellfish, birds and other game, accumulate some PFAS at greater concentrations than lower-level consumers. PFAS accumulation within any organism may cause adverse health effects directly or indirectly.

Effects

Ecotoxicity data has increased significantly over the past several years; however, the depth and breadth of information for the wide range of aquatic and terrestrial species remains limited. The majority of available data are for PFOA and PFOS related to aquatic species in freshwater environments. Aquatic toxicity data remains limited for the universe of other PFAS individually and in mixtures, degradation products, and for estuarine and marine environments. Data currently available indicate that PFAS have the potential to cause both acute (short-term higher-level exposures) and chronic (long-term lower-level exposures) effects to freshwater and marine vertebrates (e.g., fish, amphibians), invertebrates (e.g., insects, shellfish), and aquatic plants, all of which represent important components of an aquatic community. Documented effects of PFAS in aquatic organisms include mortality, cellular membrane damage, impaired growth and development, reproductive failure, hormone disruption, nervous and immune system disruption, and liver and kidney damage. For terrestrial organisms, similar effects have been observed. In birds and mammals, effects have been reported on development, reproductive success, and oxidative stress. As with other species, most data exist for PFOS, PFOA, and some shorter-chain sulfonates and carboxylic acids. While laboratory studies provide cause-effect thresholds, effects in wild populations may be less predictable, due to differences in route of exposure, increased genetic variability and the presence of other environmental stressors. In order to assess the long-term risks of PFAS to plant and animal populations, it will be necessary to conduct continuous exposures to examine effects across multiple generations. PFAS may cause reduced reproductive fitness, potentially impacting subsequent generations. Additionally, abiotic factors such as temperature, salinity, UV light, and pH can alter their fate, transport, and toxicity. Ultimately, data and models are needed to predict the effects of PFAS, especially for threatened and endangered species, which may be more susceptible to PFAS exposure given their vulnerable population status.

Summary and Research Gaps

1. Predicting bioaccumulation: There is a need to characterize PFAS exposure (water, sediment, diet) in aquatic and terrestrial environments to generate data to predict bioaccumulation for a diversity of PFAS structures. These data can be used to develop models (i.e., uptake, depuration, biotransformation), given that existing bioaccumulation models for most organic contaminants are not applicable to PFAS. The characterization of bioaccumulation and biomagnification potentials is critical to predicting risk to environmental food webs and to human consumers.
2. Toxicity data: There is a need to generate additional toxicity data on diverse PFAS structures using assays representing multiple taxa, including those underrepresented in the existing literature, such as volatile PFAS precursors and PICs. The use of tiered screening approaches using computational, in vitro, and in vivo assays (including population-relevant endpoints) will allow for generation of data across a larger diversity of PFAS and provide the basis for identifying the most common biological pathway interactions for PFAS. Partial life cycle testing can also be used to provide data on the most sensitive life stages in a shorter time frame. Grouping by mechanism of action and/or structure will facilitate development of mechanistically and/or empirically based prediction models to estimate toxicity thresholds for additional PFAS.

VI. Equity and Environmental Justice Considerations

Studies on disparate impacts on human health and the environment from PFAS exposure are severely lacking, and better understanding of PFAS exposure and health outcomes in marginalized and overburdened communities will assist in more comprehensive and effective risk management and policy decisions to better protect people from PFAS pollution. PFAS contamination in historically marginalized and overburdened communities may result in disproportionate economic and biological burden of PFAS environmental harms and risks. In addition, systemic racism in medical care has been shown to exacerbate poor health for disadvantaged groups[61]. Such historical inequities have persisted; therefore, the Biden-Harris Administration announced in January 2021 that the policy of the Administration is that the Federal Government should pursue a comprehensive approach to advancing equity for all[62,63] In addition, the Biden-Harris Administration has committed to advance environmental justice through a whole-of-government effort.[64] Reports from 2017[65] and 2019[66] revealed that when considering the number of low-income households and people of color living within a five-mile radius of a reported PFAS-exposed area, 38,962 more low-income households (15% more than expected based on US census data) and 294,591 more people of color (22% more than expected) were living within five miles of a site containing PFAS than expected based on U.S. census data. These data and similar studies underscore the urgent need to identify methods to redress inequities in policies and programs that serve as barriers to equal opportunity, and address environmental injustice related to exposures to PFAS, and ensure policies and programs moving forward that advance the Administration's ambitious agenda on equity and its whole-of-government approach on environmental justice.

A critical element of this comprehensive approach is effective community engagement. Creating an inclusive and participatory decision framework necessitates understanding the breadth and diversity of all communities. Engaging communities from the initiation of a decision-making process, including the identification of research priorities and problem formulation, through mitigation and evaluation of results is a mechanism to build public trust. This could also increase equity in decision making and mitigate outcomes by ensuring engagement with underrepresented and disproportionately impacted groups. Additionally, Indigenous Knowledge should inform PFAS research. The Administration has formally recognized the importance of this body of knowledge, emphasizing the important contributions Indigenous Knowledge has to advancing our understanding of the natural world[67,68].

Any strategic plan for PFAS R&D should start with engagement of stakeholders, collaborators, and partners that ranges from researchers and citizen scientists, to public health experts, industries, governments (Federal, State, local, and Tribal), non-governmental organizations, academic institutions, and civil society. For example, there are many insights that can be gleaned from the NASEM

[61] https://www.healthaffairs.org/doi/10.1377/hlthaff.2021.01466.

[62] EO 13985. Executive Order On Advancing Racial Equity and Support for Underserved Communities Through the Federal Government | The White House

[63] Executive Order on Further Advancing Racial Equity and Support for Underserved Communities Through The Federal Government | The White House

[64] *See, e.g.*, EO 14008. Executive Order on Tackling the Climate Crisis at Home and Abroad. https://www.whitehouse.gov/briefing-room/presidential-actions/2021/01/27/executive-order-on-tackling-the-climate-crisis-at-home-and-abroad/

[65] American Chemical Society 2017

[66] SSEHRI 2019

[67] OSTP and CEQ. 2022. Guidance for Federal Departments and Agencies on Indigenous Knowledge. https://www.whitehouse.gov/wp-content/uploads/2022/12/OSTP-CEQ-IK-Guidance.pdf.

[68] OSTP and CEQ. 2022. Implementation of Guidance for Federal Departments and Agencies on Indigenous Knowledge. https://www.whitehouse.gov/wp-content/uploads/2022/12/IK-Guidance-Implementation-Memo.pdf.

PFAS report on guidance development and their community listening sessions[69]. Building these relationships will provide the opportunity for researchers to understand the concerns, values, and perspectives of collaborators and partners, as well as allow for transparency, openness, and clear communication.

For PFAS, environmental justice considerations are relevant for all topics discussed in this report. Any research to better understand PFAS should also consider equitable access to data, principles of scientific integrity, and public transparency on research results[70,71].Members of underserved and historically marginalized communities should have input into Federal agency decision-making processes. There are several issues of underrepresentation in he(t)-0.8 (in)0.3sy cvt- inpt he(t8/MC

7. Transparency and data availability to ensure affected communities are aware of potential exposure sources and information about Federal actions to address this exposure, including potential treatment or disposal, so they can meaningfully engage in public participation opportunities regarding such actions.
8. Community engagement in all stages of research to ensure that communities, including those that are overburdened or historically marginalized, have decision-making power and can choose to participate in a more complete characterization of exposures to individual and mixtures of PFAS.

VII. Shared Challenges

There are many places identified in this report that demonstrate numerous challenges facing the Federal government to continue and accelerate PFAS R&D. At a high level, these shared challenges include:

Analytical Technology

Health-protective measures cannot be implemented without the ability to detect PFAS with sensitive and reliable methods. Therefore, it is not surprising that many shared challenges relate to analytical methods. Current challenges include a lack of intra- and interlaboratory-validated methods for a wider range of PFAS, particularly at very low concentration levels. Recent estimates suggest that there are hundreds to thousands of PFAS already in the market that have entered the environment and may be present in environmental media. Available methods have been validated for drinking water, ground water, some agricultural products, and some foods; however, currently the limit of detection of these methods cannot accurately measure extremely low levels of PFAS. There is a need for more methods with demonstrated reliability and sensitivity for a wider range of food and environmental media, as well as human biomonitoring, including rapid and sensitive methods to measure mixtures of PFAS, to truly grasp the magnitude of human exposure to PFAS. To enhance reliability and sensitivity, additional analytical standards will need to be developed. This will guide targeted cleanup actions, community-specific health-protective measures, and research and development efforts to advance understanding the human health effects of PFAS mixtures. Furthermore, there is a need to identify the priority PFAS, both at the conceptual and the analytical level. An important consideration is access to and cost of PFAS analytical methods influenced by the currently limited number of labs capable of performing such analyses and the length of time needed to develop and validate methods.

Communication

Communicating about chemical exposures in general is challenging but remains a particular challenge for PFAS due to the differences in state and Federal government approaches to treating and preventing future PFAS exposure as well as the sheer number of PFAS that may need to be evaluated. Further, poor risk communication has a particular impact on communities with higher exposures to PFAS, including underserved communities. Additionally, people who have concerns about PFAS exposure level need effective communication from their primary care physicians. NASEM[72] recommends that there is a need for better doctor-patient communication, including greater emphasis on training in medical programs related to environmental health and chemical exposures.

It is important to develop harmonized outreach materials that can be used across the Federal agencies. These should integrate communications around uncertainty, potential risks, and mitigation measures, so the public's overall literacy related to these chemicals is improved.

Alternatives

Many challenges remain to identifying cost-effective, safer, and environmentally-friendly alternatives, while still avoiding substitution regret. There is also a need to use a common definition of a PFAS 'alternative' that can be adopted by all agencies. Identifying critical or essential uses of PFAS (e.g., infrastructure, energy, defense, and technology) is needed in order to drive scientific, technological, and engineering innovations towards safer alternatives.

Mixtures

Understanding mixtures remains a challenge in all strategic areas. PFAS treatments need to be designed to address single compounds and co-occurring mixtures. The large number of PFAS compounds and their almost limitless potential combinations (e.g., occurrence-based, potency-based, etc.) makes hazard prediction and the development of analytical methods extremely challenging.

PFAS Reporting

Being able to address PFAS hazard, potential exposure, and mediation efforts requires understanding where PFAS are. The uncertainty of which PFAS are where makes addressing exposure extremely challenging. Standardized reporting requirements (e.g., PFAS concentrations in drinking water) would help address the uncertainties related to understanding and prioritizing mitigation efforts. Additionally, the development of a centralized, widely-accessible database containing PFAS exposure information (e.g., state-level data, Federal data, etc.) would allow for easier and more effective data sharing, as well as reducing potential duplication of efforts.

New Approach Methodologies

The very large amount of PFAS and the even greater potential mixture combinations necessitates a better understanding and development of New Approach Methodologies (NAMs). Moreover, PFAS-specific chemical and physical characteristics might make the use of existing NAMs challenging. Understanding which NAMs can be employed and when and how they can be applied, both at the *in vitro* and *in silico* levels, would help advance our predictive capabilities and at the minimum provide information at the screening level. Inclusion of AI and other advanced computational techniques can also help move the PFAS R&D activities forward. Higher throughput hazard assessment approaches (e.g., physiologically-based pharmacokinetic and toxicokinetic [PBPK/PBTK], *in vitro* to *in vivo*

[72] https://www.nationalacademies.org/our-work/guidance-on-pfas-testing-and-health-outcomes.

extrapolation [IVIVE], read across, structural activity alerts, etc.) are being researched/developed and may play an essential role in understanding effects particularly for PFAS with very little empirical data.

Ambient Levels

PFAS have been found to be ubiquitous in the environment, present from the far Arctic reaches of the planet to urban rainwater. An improved scientific understanding of background, or ambient, levels of PFAS in the environment will help agencies moving forward to identify "additional" localized environmental releases that should be addressed to manage and minimize risk to public health.

VIII. Priority Areas for Opportunity

The areas for opportunity directly correlate with the shared challenges. Addressing the challenge of developing additional analytical methods with higher sensitivity to detect both single and mixtures of PFAS is a critical opportunity, as it is needed to accelerate advancement across all other areas. Development of additional and more sensitive methods may be accelerated by continued and expanded collaborations across the government, partnership with states, Tribal governments, industry scientists, and academia. In particular, where entities are focused on developing methodologies to address the same issue, for example, sensitive and reliable TOF measurements, harnessing collaborative efforts will reduce personnel and monetary resourcing and will accelerate the ability to develop and validate the methods.

Second, a comprehensive approach to understanding human and ecological health effects of PFAS is critical to further risk characterization and assessment of PFAS exposure. Filling these data gaps will allow for progressive policy decisions that better protect the health of all Americans. This can be accelerated in a number of ways:

- Developing shared data systems across the Federal government, with contributions from Tribal governments, the states, industry, and academia. Harnessing data combined across all these sources will lead to more robust modeling of PFAS physicochemical properties, potential health effects, and efforts to categorize PFAS.
- PFAS-specific high throughput assays could decrease the need for traditional toxicity testing and improve hazard prediction at early stages of development. These inputs will allow greater confidence in estimating the health effects of PFAS for which there are no available empirical data. Testing each chemical is not only impractical, it is extremely costly in monetary and personnel resources, time, as well as animal lives. Given the number of PFAS and the goal of reducing, refining, and replacing animal testing (the 3 Rs), these models will push innovative health-based assessments while also generating data that may allow progress towards the 3 Rs.
- Working collaboratively to harmonize approaches to the safety and risk assessment of PFAS. This includes development of a mixtures approach that can be used across governmental programs, a standard approach to systematic reviews, and a standard approach to weight of evidence evaluation. Differences in these areas across local, state, Federal, and international organizations contribute to divergent interpretations of the same body of evidence. Working together with state, Tribal, Federal, and international partners to advance harmonized methods will ultimately reduce some of the uncertainty in health-based analyses across

entities, although differences in interpretation may remain due to programmatic needs and approaches to address specific challenges.

Finally, detecting PFAS and understanding human and environmental effects of PFAS exposure is only part of mitigation. Mitigation efforts for PFAS should include a broad range of strategies including removal and reduction of PFAS in environmental media; disposal of PFAS wastes using environmentally sustainable methods; and development of PFAS alternatives. Development of alternatives necessarily depends on identifying where PFAS is used in products and identifying critical uses. In cases of critical uses, other institutional controls (e.g., regulatory and administrative measures) may be employed.

IX. Summary and Next Steps

Appendix A: Inventory of Federally-funded PFAS research and development

Agency representatives from the PFAS strategy team compiled PFAS research and development highlights, including collaborative efforts across the Executive Branch. Below is a high-level overview of agency activities followed by a comprehensive overview of all activities.

The Department of Commerce (DOC)

National Institute of Standards and Technology (NIST)

NIST research activities focus on three major areas: 1) measurement Science - the development, validation, and application of targeted and non-targeted analytical methods for the identification, quantitation, and physicochemical characterization of PFAS; 2) data analytics and dissemination - the development of reference data and smart libraries for PFAS identification; and 3) measurement services- the development of reference materials for the measurement of PFAS in a wide variety of environmental, food, and human tissue materials as well as the archive and analysis of frozen specimens collected over time to establish PFAS temporal trends.

National Oceanic and Atmospheric Administration (NOAA)

NOAA's role is to assess the risk of PFAS to coastal, marine, and Great Lakes environments. NOAA is conducting laboratory studies to determine PFAS toxicity thresholds for marine and estuarine species, including for PFAS-free firefighting formulations, establishing bioaccumulation levels in shellfish, and monitoring for PFAS in coastal waters, sediments, fish, shellfish, and marine mammal tissues. We work closely with Federal and state agencies to translate our data into technological solutions and management actions that mitigate pollution impacts and protect sustainable use of coastal resources.

The Department of Defense (DoD)

DoD is conducting extensive research on PFAS including development of fluorine-free firefighting formulations as well as development of new treatment and detection technologies, including PFAS forensics. DoD's research addressing the characterization and treatment of PFAS will assist in the acceleration of DoD's investigation and cleanup of PFAS releases. DoD is interested in working with other agencies, particularly on occupational related PFAS exposures and health effects as well as personal protective equipment.

The Department of Energy (DOE)

DOE's research and development activities are primarily focused on evaluating promising technological approaches for PFAS detection, separation, destruction, treatment and disposal. Many DOE sites are characterizing whether, or to what extent, they have PFAS concerns. DOE has also suspended use of AFFF except in emergencies.

The Department of Health and Human Services (HHS)

Center for Disease Control (CDC); National Center for Environmental Health and the Agency for Toxic Substances and Disease Registry (NCEH/ATSDR)

The NCEH/ATSDR are conducting activities to expand the scientific knowledge base regarding the relationship between exposure to PFAS and human health outcomes. CDC's Environmental Health Laboratory measures a suite of PFAS in blood samples collected through the NHANES program and provides national reference values for PFAS exposure. High priority activities include 10 PFAS exposure assessments investigating drinking water exposures in communities near current or former military installations, a PFAS Multi-site Health Study to provide information about the health effects of PFAS exposure, and biomonitoring studies for PFAS. CDC/ATSDR are also partnering with EPA to expand on the environmental measurements gathered as part of the exposure assessments in order to identify significant non-drinking water sources of exposure. Other research includes a study on the impact of PFAS exposure on susceptibility to viral infection, including COVID-19; examining the rates of selected cancers, overall mortality, and birth outcomes in communities exposed to PFAS-contaminated drinking water; the development of additional laboratory methods to detect PFAS in blood and urine; and the development of models to estimate PFAS serum concentrations in community members.

CDC/National Institute for Occupational Safety and Health (NIOSH)

CDC's NIOSH is conducting a study that will address PFAS exposures among career firefighters and includes measurement of PFAS levels in gear. NIOSH is also studying the potential for PFAS toxicity resulting from dermal exposures.

Food and Drug Administration (FDA)

The FDA is continuing to expand its testing of the food supply to significantly advance its work to estimate dietary exposure to PFAS from food. FDA is working to expand its analytical capabilities to include additional PFAS analytes of health concern as well as expand the method to include additional foods. FDA has been analyzing foods collected under FDA's Total Diet Study (TDS), which represents foods in the average U.S. diet, and also conducting surveys of commodities to gather data on PFAS levels in specific foods. FDA is conducting research to assess the biopersistence potential and health effects of certain PFAS. Specifically, FDA is further characterizing the biopersistence of a PFAS impurity that may be found in some food contact substances.

National Institute of Environmental Health Sciences (NIEHS)

NIEHS is funding over 70 active academic research projects investigating the impacts of PFAS including mechanistic and epidemiology studies, fate and transport, detection approaches, novel remediation technologies and risk communication approaches. NIEHS scientists are conducting research in coordination with other Federal agencies to understand more about the potential adverse effects associated with PFAS exposure and to identify safer alternatives. In collaboration with CDC/ATSDR, NIEHS supported a study by the National Academies of Science, Engineering, and Medicine that examines PFAS human health effects and sources of exposure to inform potential changes to PFAS clinical guidance.

The Department of Homeland Security (DHS)

The DHS Office of the Chief Readiness Support Officer (OCRSO) has established an Integrated Project Team which provides strategic governance and oversight of the Department's emergent contaminants programs, operations, investment and decision-making processes. High priority activities include review of AFFF as a mission-critical tool and exploring methodologies for the safe destruction and/or degradation of PFAS contamination.

The Department of Transportation (DOT)

Federal Aviation Administration (FAA)

The FAA is testing and evaluating currently-available fluorine-free foams and funding the Transportation Research Board Airport Cooperative Research Program (TRB ACRP) to update existing guidance on PFAS management and create new guidance on PFAS source differentiation at airports. The FAA is working with the DOD to find AFFF alternatives. Additionally, the FAA has issued a Broad Agency Announcement (BAA) in search of new fluorine-free foam formulations.

Office of the Assistant Secretary for Research and Technology (OST-R)

Through the University Transportation Centers Program, OST-R is performing research on remedial strategies to address PFAS contaminated sediment and to assess the performance of nonstructural approaches, including enhanced street cleaning, to reduce sediment and a range of pollutants (including PFAS) in runoff from transportation infrastructure in urbanized areas.

The Department of Veterans Affairs (VA)

VA's Health Outcomes Military Exposures (HOME) is partnering with the Central Arkansas Veterans Healthcare System and the Naval Health Research Center to investigate PFAS exposure in military firefighters. The primary objective of this study is to conduct a comprehensive analysis of PFAS measured in existing serum collected from service members enrolled in the Millennium Cohort Study. Secondary objectives will examine whether observed PFAS concentrations and military firefighter occupation are associated with certain cardiometabolic health outcomes and biomarkers. Given the potential contribution of PFAS exposure to long-term health consequences for service members and veterans, this study will be critical for establishing historical baselines for body burden among military firefighters, as well as improving our understanding of their health care needs.

The Environmental Protection Agency (EPA)

EPA's PFAS Strategic Roadmap, released in October 2021, lays out EPA's whole-of-agency approach to protect public health and the environment from the impacts of PFAS. Research is a key component of the Roadmap, helping EPA to expand the scientific foundation for understanding and managing risk from PFAS. EPA's PFAS research and development activities fall under three key actions in the Roadmap: (1) developing and validating methods to detect and measure PFAS in the environment, (2) advancing the science to assess human health and environmental risks from PFAS, and (3) evaluating and developing technologies for reducing PFAS in the environment. EPA routinely collaborates with other Federal agencies, states, utilities, and academic institutions on PFAS research and development activities

The National Aeronautics and Space Administration (NASA)

NASA is closely monitoring the R&D from other Federal agencies as well as the Federal PFAS regulatory status and the regulatory status in states where the agency has facilities to continue to be protective of human health and the environment. NASA provides technical and scientific input to EPA on a range of draft PFAS assessments, guidance and policy through the EPA-led interagency review effort.

The National Science Foundation (NSF)

Fundamental research to understand, detect, and treat PFAS and other contaminants of emerging concern has been funded through multiple directorates, divisions, and programs at NSF. While significant advances in our understanding of the environmental fate of PFAS have been made, there remains a critical national need, hence continued NSF investment, to provide better understanding and prediction of the fate and transport of PFAS and to develop cost effective, feasible, and sustainable technologies/solutions to detect, degrade, destroy, and/or permanently sequester PFAS in soils, sediments, aquatic systems, and waste streams.

The United States Department of Agriculture (USDA)

Agricultural Research Service (ARS)

USDA ARS conducts scientific research and develops data and information to solve problems related to agriculture. ARS is currently conducting research to understand the fate and transport of PFAS in the environment, plants, animals and food packaging materials. The scientific data and information developed through these investigations can be used by government agencies, industry, and the community to develop and implement approaches for addressing PFAS in these matrices.

Food Safety and Inspection Service (FSIS)

FSIS makes decisions based on sound scientific data and evidence, which includes data gathered from localized PFAS contamination events and national-level surveillance. These data provide a better understanding of PFAS levels across the food supply and allow FSIS to take further action to protect public health when necessary.

National Institute of Food & Agriculture (NIFA)

The National Institute of Food & Agriculture (NIFA), USDA’s extramural research funding agency, invested approximately $3 million in the last two years to support several projects aimed at better understanding PFAS in agricultural systems. These projects have supported investigations in the occurrence, transport, and transformation of PFAS in soil, water, and plant systems, and to develop strategies for minimizing environmental and human health risks. NIFA is also supporting 32 active projects focused on PFAS at land-grant universities through Hatch Act funding. Examples of these include projects for: (i) characterizing the potential of PFAS to affect the actions of hormones during development, reproduction, and metabolism, with relevance to livestock, wildlife, and humans, (ii) development of new water treatment methods that will destroy and convert PFAS from waste streams and water treatment plants into nontoxic chemicals, and (iii) exploring human dietary interventions that may disrupt diseases (e.g., liver, and cardiovascular diseases) that may be initiated by exposure to PFAS.

United States Geological Survey (USGS)

The USGS has partnered with EPA, NIEHS, DOD, Fish and Wildlife Service (FWS) and academia for over a decade on PFAS research to ensure consistency of research results and avoid duplication of efforts. The USGS brings together a range of scientific disciplines and laboratory capabilities to fill data gaps on complex environmental contaminant issues such as PFAS. PFAS research is ongoing in two of its Mission Areas: Water (WMA) and Ecosystems (EMA). WMA research has developed and validated world-class PFAS field sampling protocols and laboratory analytical methodology to support national scale program studies that assess water quality and is developing methods to identify new or unknown PFAS contaminants in the environment. Within EMA, the Environmental Health Program (EHP) research in the Toxics Substances Hydrology and Contaminant Biology Programs work to assess and differentiate the environmental contaminant and pathogen exposures that cause actual health risks. EHP research has led the development of PFAS science at the USGS by addressing specific watershed issues while incorporating world-class analytical capabilities.

Appendix B: Summary of financial resources allocated to PFAS activities by each agency

The Office of Management and Budget (OMB) issued a Budget Data Request to collect information about PFAS R&D expenditures from 2019-2021, as well as estimated expenditures for 2022. It is the first snapshot of PFAS R&D spending for fiscal years 2019-2022. Responding departments included DHS, DOC, DoD, DOE, Department of the Interior, DOT, EPA, HHS, USDA, and VA. Responding independent agencies included NASA and NSF. The total estimated PFAS R&D expenditures were $725 million dollars with HHS reporting the greatest R&D expenditures ($200 million), followed by DoD ($187 million) and EPA ($116 million) for all included fiscal years.

Summary information for each responding department and agency are provided below. These data are the first such data collected by OMB. There may be some aspects that impact the accuracy of the results. Some agencies reported difficulty in parsing which of their R&D money was specifically spent on PFAS. In many cases, agencies estimated their reported expenditures in part because many budget data systems do not track R&D funding down to specific projects or contaminants. One example of this may be the expenditures reported by VA. In this case, VA could only estimate their PFAS-specific expenditures for FY 2021; however, the categories for Military and Environmental Exposure as well as Gulf War Illness may have included funding for PFAS-related research.

Overall, the summary information should be treated as a general indication of spending and distribution of funding within departments and agencies for PFAS; however, it may not represent spending with full accuracy.

Table B-1. PFAS Research and Development ($ in millions)

		Category	R&D Title	FY 2019 Actual	FY 2020 Actual	FY 2021 Actual	FY 2022 Estimated
Department of Homeland Security	Department of Homeland Security	Alternative Development/Deployment	EMW-2020-FP-00078 Incentives and Barriers to Adopting PFAS-free firefighter foams in fire training facilities	0.00	0.00	0.86	0.00
	Department of Homeland Security	Toxicity	EMW-2018-FP-00086 PFAS: Firefighter Exposure and Toxicity	1.43	0.00	0.00	0.00
	Department of Homeland Security	Toxicity	EMW-2018-FP-00562 Cancer among Indiana Firefighters: Case-Control Studies	1.43	0.00	0.00	0.00
	Department of Homeland Security	Toxicity	EMW-2019-FP-00526 Women Fire Fighters Study: Stress, Cancer Risk and Reproductive Toxicity	0.00	1.50	0.00	0.00
	Department of Homeland Security	Toxicity	EMW-2019-FP-00517 Cancer Risk and Risk Factors in Volunteer Firefighters: The NJ Firefighters Cancer Prevention Study (CAPS)	0.00	1.50	0.00	0.00
	Department of Homeland Security	Toxicity	EMW-2019-FP-00392 Effectiveness of Exposure Mitigation Strategies for Fire Investigators	0.00	1.30	0.00	0.00
	Department of Homeland Security	Toxicity	EMW-2020-FP-01120 Development of Contamination Resistance as a Measure for Firefighter Protective Clothing	0.00	0.00	1.50	0.00

	Department of Homeland Security	Toxicity	EMW-2021-FP-00141 Women Fire Fighters Study: Evaluation of Exposures and Toxicity	0.00	0.00	0.00	1.50
	Department of Homeland Security	Toxicity	EMW-2021-FP-00088 Developing a systematic tool for contamination protection and reduced exposure to contaminated PPE	0.00	0.00	0.00	1.50
	Subtotal			2.86	4.29	2.36	3.00
Department of Commerce	National Institute of Standards and Technology	Alternative Development/Deployment	PFAS Guarantee Equipment Safety	0.00	2.00	2.00	3.00
	National Oceanic and Atmospheric Administration	Toxicity	NCCOS PFAS Ecotoxicology and Bioeffects	0.00	0.00	0.00	1.00
	Subtotal			0.00	0.00	0.00	1.00
Department of Defense	Department of Defense	Removal	SERDP & ESTCP	2.79	2.82	8.18	19.70
	Department of Defense	Destruction/Degradation	SERDP & ESTCP	2.01	5.25	12.78	41.14
	Department of Defense	Alternative Development/Deployment	SERDP & ESTCP	2.14	10.42	14.10	17.27
	Department of Defense	Source/Exposure	SERDP & ESTCP	5.70	3.94	9.71	11.00
	Department of Defense	Toxicity	SERDP & ESTCP	2.85	4.88	3.35	7.46
	Subtotal			15.49	27.31	48.12	96.57
Dep art me	Department of Energy	Source/Exposure	PFAS Assessment	0.00	0.28	0.00	0.00

	Department of Energy	Source/Exposure	PFAS Funding to Network of National Laboratories for EM and Stewardship (NNLEMS)	0.00	0.00	0.00	0.20
	Subtotal			0.00	0.28	0.00	0.20
Department of Transportation	Federal Aviation Administration	Alternative Development/Deployment	FAA AFFF Replacement Research	0.98	1.36	1.39	1.42
	Federal Aviation Administration	Alternative Development/Deployment	FAA AFFF Replacement Research	0.00	0.65	0.09	0.64
	Subtotal			0.98	2.01	1.48	2.06
Environmental Protection Agency	Environmental Protection Agency	Source/Exposure	Research: Air, Climate, and Energy (name changed in FY 2022, ORD)	0.40	1.20	1.10	1.30
	Environmental Protection Agency	Alternative Development/Deployment	Research: Safe and Sustainable Water Resources	2.40	4.50	4.40	4.50
	Environmental Protection Agency	Alternative Development/Deployment	Research: National Priorities	4.10	0.00	0.00	0.00
	Environmental Protection Agency	Source/Exposure	Research: Sustainable and Healthy Communities (S&T)	2.50	4.60	3.50	3.90
	Environmental Protection Agency	Source/Exposure	Research: Sustainable and Healthy Communities (SF Transfer)	0.00	5.00	4.90	4.80
	Environmental Protection Agency	Source/Exposure	Homeland Security	0.10	0.20	0.20	0.20

	Environmental Protection Agency	Toxicity	'Health And Environmental Assessment (name changed from Human Health Risk Assessment in FY 2021, ORD) (S&T)	3.50	3.50	3.40	3.80
	Environmental Protection Agency	Toxicity	'Health And Environmental Assessment (name changed from Human Health Risk Assessment in FY 2021, ORD) (SF Transfer))	0.00	10.00	10.00	9.70
	Environmental Protection Agency	Toxicity	Chemical Safety and Sustainability (S&T)	2.70	5.90	5.00	5.50
	Subtotal			15.70	34.90	32.50	33.70
Health and Human Services	Agency for Toxic Substances and Disease Registry	Source/Exposure	Exposure Assessments	0.27	0.22	0.44	0.63
	Agency for Toxic Substances and Disease Registry	Toxicity	Multi-site Health Study	7.90	8.77	12.11	14.17
	Subtotal			8.17	8.99	12.55	14.80
	Food and Drug Administration	Source/Exposure		2.42	3.07	2.75	4.20
	Food and Drug Administration	Toxicity		0.31	0.80	0.42	0.18
	Subtotal			2.72	3.87	3.16	4.38
	National Institutes of Health	Toxicity	Young Investigators- Opportunities and Infrastructure Fund Projects	0.20	0.25	0.00	0.25
	National Institutes of Health	Toxicity	Effects of PFAS and stress on birth outcomes	0.10	0.50	0.00	0.00

	National Institutes of Health	Toxicity	Environmental exposures in the ReCHARGE cohort	0.00	0.30	0.00	0.00
	National Institutes of Health	Toxicity	PFAS and child metabolic health	0.00	0.20	0.00	0.00
	National Institutes of Health	Source/Exposure	PFAS exposure in ECHO children	0.00	0.00	0.00	0.30
	National Institutes of Health	Toxicity	Prenatal PFAS and child behavior	0.00	0.00	0.25	0.00
	National Institutes of Health	Toxicity	Prenatal PFAS and early language development	0.00	0.00	0.10	0.10
	National Institutes of Health	Source/Exposure	Report back PFAS results to pregnant participants	0.00	0.10	0.10	0.00
	National Institutes of Health	Toxicity	Effects of PFBS exposure on adverse pregnancy outcomes and fetal development	0.10	0.10	0.10	0.00
	National Institutes of Health	Toxicity	Project 2: Effects of perfluoroalkyl substances on gestational weight gain, breastfeeding, and early life growth	0.16	0.17	0.13	2.14
	National Institutes of Health	Toxicity	COBRE Center for Molecular Epidemiology	0.00	0.25	0.00	0.00

	National Institutes of Health	Source/Exposure	Iterative Design to Engage All (IDEA) Learners: A teacher-scientist collaboration to feature biomedical research and engage diverse high school students	0.00	0.00	0.27	0.26
	National Institutes of Health	Toxicity	PFOS-induced dopaminergic neurodegeneration across nematode, amphibian, and rodent models	0.00	0.22	0.49	0.00
	National Institutes of Health	Toxicity	A nested case-control study of circulating PFAS and ovarian and endometrial cancers in the PLCO Cancer Screening Trial	0.00	0.08	0.00	0.00
	National Institutes of Health	Toxicity	Extended Follow-up of the C8 Cohort: PFOA and Cancer	0.00	0.00	0.155	0.193
	National Institutes of Health	Toxicity	DoDSR Study of Serum PFAS and Testicular Cancer	0.068	0.00	0.093	0.003
	National Institutes of Health	Toxicity	PFAS/PFOS and Prostate Cancer Risk	0.00	0.00	0.239	0.013
	National Institutes of Health	Toxicity	Serum PFAS Concentrations and Renal Cell Cancer risk in PLCO	0.002	0.006	0.000	0.00
	National Institutes of Health	Toxicity	Serum PFAS Concentrations and Renal Cell Cancer in the MEC Study	0.00	0.00	0.00	0.145

	National Institutes of Health	Toxicity	PFAS-related Kidney Cancer Tumor Mutational Signatures within the Mutographs of Cancer Project	0.00	0.221	0.376	0.038
	National Institutes of Health	Toxicity	Serum PFAS Concentrations and Breast Cancer risk	0.00	0.00	0.00	0.007
	National Institutes of Health	Toxicity	Serum PFAS Concentrations and NHL, Thyroid Cancer in PLCO	0.00	0.00	0.159	0.104
	National Institutes of Health	Toxicity	Serum PFAS Levels and Ovarian, Endometrial Cancer in PLCO	0.00	0.00	0.150	0.00
	National Institutes of Health	Toxicity	PFAS and childhood leukemia and adult thyroid cancer in the Finnish Maternity Cohort	0.00	0.051	0.182	0.011
	National Institutes of Health	Source/Exposure	DREAM: Discovering cancer Risks from Environmental contaminants And Maternal/child health	0.00	0.00	1.15	1.14
	National Institutes of Health	Removal	Linking environmental contamination to residential history for risk identification	0.21	0.17	0.00	0.00
	National Institutes of Health	Toxicity	MI-CARES: The Michigan Cancer and Research on the Environment Study	0.00	0.00	1.11	1.11
	National Institutes of Health	Source/Exposure	Southern Liver Health Cohort	0.00	0.00	1.14	1.10
	National Institutes of Health	Toxicity	The 10,000 Families Cohort: a new study to understand the environmental causes of cancer	0.00	0.00	1.07	1.06

	National Institutes of Health	Toxicity	Metabolomic profiling of retinoblastoma (MPR)	0.00	0.00	0.15	0.00
	National Institutes of Health	Toxicity	Perfluoroalkyl Substances (PFASs) and Liver Cancer Risk in the United States	0.00	0.00	0.00	0.96
	National Institutes of Health	Toxicity	Cancer Risk and Environmental Exposures	1.68	2.59	1.16	1.16
	National Institutes of Health	Toxicity	Early Life Exposures and Subsequent Cancer Risk	1.57	1.26	0.71	0.71
	National Institutes of Health	Toxicity	Environmental Toxicokinetics and Toxicology	0.00	2.56	1.78	1.78
	National Institutes of Health	Toxicity	Mammary Gland as a Sensitive End Point to Effects of Endocrine Disruptors	3.88	3.40	4.28	4.28
	National Institutes of Health	Toxicity	Toxicological Assessments for the National Toxicology Program	9.23	9.25	9.25	9.25
	National Institutes of Health	Toxicity	Scientific Information Management and Literature-Based Evaluations for the NTP – Support for Scoping Activities	1.51	0.00	0.00	0.00
	National Institutes of Health	Toxicity	Chemistry Services Supporting PFAS	0.15	0.31	0.14	0.10

	National Institutes of Health	Destruction/Degradation	Grants- Destruction/Degradation	0.00	0.00	0.86	0.92
	National Institutes of Health	Removal	Grants- Removal	1.05	1.59	0.93	0.69
	National Institutes of Health	Source/Exposure	Grants- Source/Exposure	2.24	4.96	6.00	2.76
	National Institutes of Health	Toxicity	Grants- Toxicity	3.67	6.22	8.17	4.44
	Subtotal			25.82	34.76	40.69	35.02
	National Institute for Occupational Safety & Health	Removal	Evaluation of Firefighter Textiles for PFAS	0.00	0.00	0.04	0.03
	National Institute for Occupational Safety & Health	Toxicity	Toxicity Following Dermal Exposure to PFAS	0.00	0.00	0.00	0.25
	National Institute for Occupational Safety & Health	Alternative Development/Deployment	HPLC-MS/MS method for simultaneous quantitation of 10 perfluoroalkyl substances (PFAS) in sera and urine of dermally exposed mice	0.00	0.00	0.00	0.01
	Subtotal			0.00	0.00	0.04	0.29
	HHS Subtotal			38.24	49.93	56.96	55.83
National	National Science Foundation	Removal	NSF-funded Basic Research	0.75	0.25	1.40	0.80

	National Science Foundation	Destruction/Degradation	NSF-funded Basic Research	1.13	1.46	3.84	2.14
	National Science Foundation	Alternative Development/Deployment	NSF-funded Basic Research	0.00	0.45	0.00	0.15
	National Science Foundation	Source/Exposure	NSF-funded Basic Research	0.67	1.36	2.77	1.42
	National Science Foundation	Toxicity	NSF-funded Basic Research	0.00	0.00	0.10	0.00
	Subtotal			2.55	3.52	8.11	4.51
U.S. Department of Agriculture	US Department of Agriculture	Destruction/Degradation	NIFA - Hatch	0.00	0.00	0.02	0.02
	US Department of Agriculture	Destruction/Degradation	[redacted]				

	US Department of Agriculture	Removal	ARS - PFAS research and development	0.10	0.10	0.10	0.10
	US Department of Agriculture	Alternative Development/Deployment	ARS - The development and deployment of safer and more environmentally friendly alternative substances that are functionally similar to those made with PFAS	0.80	0.80	0.80	0.80
	Subtotal			1.59	1.85	3.85	3.25

Appendix C: Stakeholder Engagement

On July 13, 2022, OSTP posted in the Federal Register a Request for Information (RFI) on "Identifying Critical Data Gaps and Needs to Inform Federal Strategic Plan for PFAS Research and Development"[73]. The RFI requested input from all interested parties to identify data gaps in R&D regarding several aspects of PFAS. The information received in response has informed this report and will further be used to inform a strategic plan for Federal coordination of PFAS research and development and, in compliance with Section 332 of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021 (FY21 NDAA), the interagency strategy team on PFAS will also develop an implementation plan for Federal agencies.

OSTP received 86 responses from 37 unique individuals and/or organizations. The full text of all comments received in response to this RFI are available at OSTP's website[74].

---

[73] https://www.federalregister.gov/documents/2022/07/13/2022-14862/request-for-information-identifying-critical-data-gaps-and-needs-to-inform-federal-strategic-plan.

[74] https://www.whitehouse.gov/ostp/legal/

Appendix D: References

This appendix includes references used to develop this report. There is an abundance of PFAS literature, with many studies focusing on a single PFAS or only a few. In order to provide a comprehensive overview of our understanding of PFAS as a chemical class, the technical writing teams reviewed and synthesized the available literature and provided a comprehensive picture of our understanding of PFAS in the text.

Specific citations are included in the text when appropriate; however, this list provides a more inclusive list of references that contributed to this work. This is not meant to be an exhaustive list of all relevant PFAS literature.

Introduction to PFAS

- Buck, R.C., Korzeniowski, S.H., Laganis, E. and Adamsky, F. (2021), Identification and classification of commercially relevant per- and poly-fluoroalkyl substances (PFAS). Integr Environ Assess Manag, 17: 1045-1055. https://doi.org/10.1002/ieam.4450.
- Buck, R.C., Franklin, J., Berger, U., Conder, J.M., Cousins, I.T., de Voogt, P., Jensen, A.A., Kannan, K., Mabury, S.A. and van Leeuwen, S.P. (2011), Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. Integr Environ Assess Manag, 7: 513-541. https://doi.org/10.1002/ieam.258.
- Genualdi, S., Jeong, N., deJager, L., Begley, T. Investigation into perfluoroalkyl substances (PFASs) in a cranberry bog: method development and sampling results. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2017 Dec;34(12):2181-2189. doi: 10.1080/19440049.2017.1361046.
- Hammel, E., Webster, T.F., Gurney, R., and Heiger-Bernays, W., Implications of PFAS definitions using fluorinated pharmaceuticals. iScience. 2022 Apr 15;25(4). https://doi.org/10.1016/j.isci.2022.10420.
- Lupton, S.J., Huwe, J.K., Smith, D.J., Dearfield, K.L., Johnston, J.J. Absorption and excretion of 14C-perfluorooctanoic acid (PFOA) in Angus cattle (Bos taurus). J Agric Food Chem. 2012 Feb 1;60(4):1128-34. doi: 10.1021/jf2042505.
- OECD (2021), Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance, OECD Series on Risk Management, No. 61, OECD Publishing, Paris.
- Williams, A.J., Gaines, L.G.T., Grulke, C.M., Lowe, C.N., Sinclair, G.F.B., Samano, V., Thillainadarajah, I., Meyer, B., Patlewicz, G., Richard, A. M., Assembly and Curation of Lists of Per- and Polyfluoroalkyl Substances (PFAS) to Support Environmental Science Research, Frontiers in Environmental Science, 10 (2022), https://doi.org/10.3389/fenvs.2022.850019.
- https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/cbc/mono(2022)1&doclanguage=en
- https://www.epa.gov/system/files/documents/2021-10/pfas-roadmap_final-508.pdf.
- https://www.congress.gov/bill/116th-congress/senate-bill/1790
- https://www.epa.gov/system/files/documents/2021-10/pfas-natl-test-strategy.pdf
- https://www.energy.gov/pfas/articles/pfas-strategic-roadmap-doe-commitments-action-2022-2025.

- https://pubs.er.usgs.gov/publication/cir1490

Removal, Safe Destruction, or Degradation of PFAS from the Environment

- ITRC. 2021. Per- and Polyfluoroalkyl Substances Technical and Regulatory Guidance. https://pfas-1.itrcweb.org/

Safer and Environmentally Friendlier PFAS Alternatives

- Begley, T.H., White, K., Honigfort, P., Twaroski, M.L., Neches, R., and Walker, R.A., Food Additives and Contaminants, 2005, 22(10), 1023-1031.
- EPA. “Basics of Green Chemistry.” 17 May 2022, https://www.epa.gov/greenchemistry/basics-green-chemistry. Accessed 10 June 2022.
- Chemical Watch, 2018. Cosmetics giant L’Oréal to eliminate PFASs in products. https://chemicalwatch.com/68795/cosmetics-giant-loreal-to-eliminate-pfass-in-products
- Cousins, I.T., Goldenman, G., Herzke, D., Lohmann, R., Miller, M. Ng, C.A., Patton, S., Scheringer, M. Trier, X., Vierke, L., Wang, Z., DeWitt, J.C. 2019. “The concept of essential use for determining when uses of PFASs can be phased out” *Environ. Sci.: Processes Impacts*, 21, 1803-1815 DOI https://doi.org/10.1039/C9EM00163H.
- Hammel, E., Webster, T.F., Gurney, R., Heifer-Bernays, W. 2002. Implications of PFAS definitions using fluorinated pharmaceuticals. IScience 25(4): 104020. doi: 10.1016/j.isci.2022.104020
- Glenn, G., Shogren, R., Jin, X., Orts, W., Hart-Cooper, W., and Olson, L. 2021. Compr. Rev. Food Sci. Food Safety, 20, 2596-2625.
- Glüge et al., “An Overview of the uses of per- and polyfluoroalkyl substances (PFAS)” DOI: 10.1039/D0EM00291G (Paper) *Environ. Sci.: Processes Impacts*, 2020, 22, 2345-2373
- Glüge et al., “Information requirements under the essential-use concept: PFAS case studies” https://doi.org/10.1021/acs.est.1c03732; *Ennviron. Sci. Technol.* 2022, 56, 10, 6232–6242
- Goldenman, G., Fernandes, M., Holland, M., Tugran, T., Nordin, A., Schoumacher, C., McNeill, A. 2019. The cost of inaction--A socioeconomic analysis of environmental and health impacts linked to exposure to PFAS; a publication by The Nordic Council of Ministers.
- Kwiatkowski, C.F., Andrews, D.Q., Birnbaum, L., et al.. 2020. Scientific Basis for Managing PFAS as a Chemical Class. Environ. Sci. Technol. L.
- OECD. 2020. PFASs and Alternatives in Food Packaging (Paper and Paperboard) Report on the Commercial Availability and Current Uses.
- OECD. 2022. Per- and Polyfluoroalkyl Substances and Alternatives in Coatings, Paints and Varnishes (CPVs), Report on the Commercial Availability and Current Uses, OECD Series on Risk Management, No. 70, Environment, Health and Safety, Environment Directorate, OECD.
- Rand, A., Mabury, S.A. 2011. “Perfluorinated Carboxylic Acids in Directly Fluorinated High-Density Polyethylene Material,” Environmental Science & Technology 45, 8053-8059.
- Sinclair, E., Kim, S.K., Akinleye, H.B., and Kannan, K., 2007. Environ. Sci. Technol 41, 1180-1185.

Sources of Environmental PFAS Contamination and Pathways to Exposure

Epidemiologic Studies of PFAS

- ATSDR. Toxicological Profile for Perfluoroalkyls. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service; 2021.
- ATSDR. What are the health effects on PFAS? https://www.atsdr.cdc.gov/pfas/health-effects/index.html
- EFSA Panel on Contaminants in the Food Chain. Risk to human health related to the presence of perfluoroalkyl substances in food (2020). EFSA J. 2020 Sep 17;18(9):e06223. doi: 10.2903/j.efsa.2020.6223.
- Hernan MA, Robins J. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC; 2020.
- IARC. IARC Monographs Volume 110: Perfluorooctanoic Acid, Tetrafluoroethylene, Dichloromethane, 1,2-Dichloropropane, and 1,3-Propane Sultone. Available at: https://publications.iarc.fr/547. Accessed 6/2/2022.
- Joubert BR, Kioumourtzoglou MA, Chamberlain T, Chen HY, Gennings C, Turyk ME, et al. Powering Research through Innovative Methods for Mixtures in Epidemiology (PRIME) Program: Novel and Expanded Statistical Methods. Int J Environ Res Public Health. 2022;19(3).
- National Academies of Sciences, Enginieering and Medicine 2022. Guidance on PFAS Exposure, Testing, and Clinical Follow-Up. Washington, DC: The National Academies Press. https://doi.org/10.17226/26156. Available at: https://nap.nationalacademies.org/catalog/26156/guidance-on-pfas-exposure-testing-and-clinical-follow-up. Accessed 9/9/2022.
- NTP. NTP Monograph: Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid or Perfluorooctane Sulfonate. Available at: https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf. Accessed 6/2/2022.
- Kato K, Wong LY, Jia LT, Kuklenyik Z, Calafat AM. Trends in exposure to polyfluoroalkyl chemicals in the U.S. Population: 1999-2008. Environ Sci Technol. 2011;45(19):8037-45.
- C8 Science Panel. Probable Link Reports. Available at: http://www.c8sciencepanel.org/prob_link.html. Accessed 6/2/2022.
- US EPA. EPA Human Health Toxicity Assessment for PFBS. https://www.epa.gov/chemical-research/learn-about-human-health-toxicity-assessment-pfbs.

- US EPA. EPA Human Health Toxicity Assessments for GenX Chemicals. https://www.epa.gov/chemical-research/human-health-toxicity-assessments-genx-chemicals.
- US EPA. Health Effects Support Document for Perfluorooctanoic Acid (PFOA). EPA Document Number: 822-R-16-003, May 2016. https://www.epa.gov/sites/default/files/2016-05/documents/pfoa_hesd_final_508.pdf
- US EPA. Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). EPA Document Number: 822-R-16-002, May 2016. https://www.epa.gov/sites/default/files/2016-05/documents/pfos_hesd_final_508.pdf

<u>PFAS Toxicity in Laboratory Animal Models</u>

- Agency for Toxic Substances and Disease Registry (ATSDR). 2021. Toxicological profile for Perfluoroalkyls. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Released May 2021
- Ballesteros V, Costa O, Iñiguez C, Fletcher T, Ballester F, Lopez-Espinosa MJ. Exposure to perfluoroalkyl substances and thyroid function in pregnant women and children: A systematic review of epidemiologic studies. Environ Int. 2017 Feb; 99:15-28. doi: 10.1016/j.envint.2016.10.015.
- Blake BE, Fenton SE. Early life exposure to per- and polyfluoroalkyl substances (PFAS) and latent health outcomes: A review including the placenta as a target tissue and possible driver of peri- and postnatal effects. Toxicology. 2020 Oct; 443:152565. doi: 10.1016/j.tox.2020.152565. Epub 2020 Aug 27. PMID: 32861749; PMCID: PMC7530144.
- Blake BE, Rickard BP, Fenton SE. A High-Throughput Toxicity Screen of 42 Per- and Polyfluoroalkyl Substances (PFAS) and Functional Assessment of Migration and Gene Expression in Human Placental Trophoblast Cells. Front Toxicol. 2022 Apr 25; 4:881347. doi: 10.3389/ftox.2022.881347.
- Bost PC, Strynar MJ, Reiner JL, Zweigenbaum JA, Secoura PL, Lindstrom AB, Dye JA. U.S. domestic cats as sentinels for perfluoroalkyl substances: Possible linkages with housing, obesity, and disease. Environ Res. 2016 Nov; 151:145-153. http://dx.doi.org/10.1016/j.envres.2016.07.027
- Carlson LM, Angrish M, Shirke AV, Radke EG, Schulz B, Kraft A, Judson R, Patlewicz G, Blain R, Lin C, Vetter N, Lemeris C, Hartman P, Hubbard H, Arzuaga X, Davis A, Dishaw LV, Druwe IL, Hollinger H, Jones R, Kaiser JP, Lizarraga L, Noyes PD, Taylor M, Shapiro AJ, Williams AJ, Thayer KA. Systematic Evidence Map for Over One Hundred and Fifty Per- and Polyfluoroalkyl Substances (PFAS). Environ Health Perspect. 2022 May; 130(5):56001. doi: 10.1289/EHP10343.
- Chang S, Thibodeaux JR, Eastvold ML, et al. 2008. Thyroid hormone status and pituitary function in adult rats given oral doses of perfluorooctanesulfonate (PFOS). Toxicology 243:330-339
- Cope HA, Blake BE, Love C, McCord J, Elmore SA, Harvey JB, Chappell VA, Fenton SE. Latent, sex-specific metabolic health effects in CD-1 mouse offspring exposed to PFOA or HFPO-DA (GenX) during gestation. Emerg Contam. 2021; 7:219-235. doi: 10.1016/j.emcon.2021.10.004.
-
- Drew, R., Hagen, T. G., Champness, D. & Sellier, A. Half-lives of several polyfluoroalkyl substances (PFAS) in cattle serum and tissues. Food Additives & Contaminants: Part A 1–21 (2021) doi:10.1080/19440049.2021.1991004.

-

- Effect of Enterohepatic Circulation on the Accumulation of Per- and Polyfluoroalkyl Substances: Evidence from Experimental and Computational Studies. Environmental Science and Technology. 56: 3214-3224 (2022)
- Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, Ng C, Smith JS, Roberts SM. Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. Environ Toxicol Chem. 2021 Mar;40(3):606-630. doi: 10.1002/etc.4890.
- Foguth R, Sepúlveda MS, Cannon J. Per- and Polyfluoroalkyl Substances (PFAS) Neurotoxicity in Sentinel and Non-Traditional Laboratory Model Systems: Potential Utility in Predicting Adverse Outcomes in Human Health. Toxics. 2020 Jun 15; 8(2):42. https://pubmed.ncbi.nlm.nih.gov/32549216/
- Göckener, B., Eichhorn, M., Lämmer,R., Kotthoff, M., Kowalczyk, J., Numata, J., Schafft, H., Lahrssen-Wiederholt, M., Bücking, M. J. Agric. Food Chem 2020 68 (45), 12527-12538 DOI: 10.1021/acs.jafc.0c04456
- Goeritz, I., Falk, S., Stahl, T., Schafer, C., Schlechtriem, C. Biomagnification and tissue distribution of perfluoroalkyl substances (PFASs) in market-size rainbow trout (*Oncorhynchus mykiss*) Environmental Toxicology and Chemistry, Vol. 32, No. 9, pp. 2078–2088, 2013
- Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, Toppari J, Zoeller RT. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev. 2015 Dec; 36(6):E1-E150. doi: 10.1210/er.2015-1010.
- Guillette TC, McCord J, Guillette M, Polera ME, Rachels KT, Morgeson C, Kotlarz N, Knappe DRU, Reading BJ, Strynar M, Belcher SM. Elevated levels of per- and polyfluoroalkyl substances in Cape Fear River Striped Bass (Morone saxatilis) are associated with biomarkers of altered immune and liver function. Environ Int. 2020 Mar; 136:105358. https://doi.org/10.1016/j.envint.2019.105358
- Hsu C-N, Tain Y-L. Adverse Impact of Environmental Chemicals on Developmental Origins of Kidney Disease and Hypertension. Front. Endocrinol. 2021. https://doi.org/10.3389/fendo.2021.745716
- Jackson SJ, Andrews N, Ball D, et al. Does age matter? The impact of rodent age on study outcomes. Laboratory Animals. 2017;51(2):160-169. doi:10.1177/0023677216653984
- Kataria A, Trachtman H, Malaga-Dieguez L, Trasande L. Association between perfluoroalkyl acids and kidney function in a cross-sectional study of adolescents. Environ Health. 2015 Nov 21; 14:89. doi: 10.1186/s12940-015-0077-9.
- Kowalczyk, J., Göckener, B., Eichhorn, M., Kotthoff, M., Bücking, M., Schafft, H., Lahrssen-Wiederholt, M., Numata, J. Agric. Food Chem 2020 68 (45), 12539-12548 DOI: 10.1021/acs.jafc.0c04485
- Kwiatkowski CF, Andrews DQ, Birnbaum LS, Bruton TA, DeWitt JC, Knappe DRU, Maffini MV, Miller MF, Pelch KE, Reade A, Soehl A, Trier X, Venier M, Wagner CC, Wang Z, Blum A. Scientific Basis for Managing PFAS as a Chemical Class. Environ. Sci. Techn. Letters. 2020. 7(8), 532-543.
- Leeson A, Thompson T, Stroo HF, Anderson RH, Speicher J, Mills MA, Willey J, Coyle C, Ghosh R, Lebrón C, Patton C. Identifying and Managing Aqueous Film-Forming Foam-Derived Per- and

Polyfluoroalkyl Substances in the Environment. Environ Toxicol Chem. 2021 Jan;40(1):24-36. doi: 10.1002/etc.4894.

- Lin, Z., Li, M., Wanng, Y-S., Tell, L.A., Baynes, R.E., Davis, J.L., Vickroy, T.W., Rivere, J.E. et al. Physiological parameter values for physiologically based pharmacokinetic models in food-producing animals. Part I: Cattle and swine. Journal of Veterinary Pharmacology and Therapeutics 43, 385–420 (2020).
- Lupton, S. J., Huwe, J. K., Smith, D. J., Dearfield, K. L. & Johnston, J. J. Distribution and Excretion of Perfluorooctane Sulfonate (PFOS) in Beef Cattle (Bos taurus). J. Agric. Food Chem. 62, 1167–1173 (2014).
- Morales-McDevitt ME, Jitka Becanova, Arlene Blum, Thomas A. Bruton, Simon Vojta, Melissa Woodward, and Rainer Lohmann. The Air That We Breathe: Neutral and Volatile PFAS in Indoor Air. Environmental Science & Technology Letters 2021 8 (10), 897-902. DOI: 10.1021/acs.estlett.1c00481
- NTP (National Toxicology Program). 2016. Monograph on Immunotoxicity Associated with Exposure to Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf
- Numata, J., Kowalczyk, J., Adolphs, J., Ehlers, Schaff, H., Fuers, P., Muller-Graf, C., Lahrssen-Wiederholt, M., and Greiner, M. Toxicokinetics of seven perfluoroalkyl sulfonic and carboxylic acids in pigs fed a contaminated diet. Journal Agric. Agric. Food Che. 2014, 62:6861-6870
- Patlewicz G, Richard AM, Williams AJ, Grulke CM, Sams R, Lambert J, Noyes PD, DeVito MJ, Hines RN, Strynar M, Guiseppi-Elie A, Thomas RS. A Chemical Category-Based Prioritization Approach for Selecting 75 Per- and Polyfluoroalkyl Substances (PFAS) for Tiered Toxicity and Toxicokinetic Testing. Environ. Health Perspect. 2019. 127:1 CID: 014501 https://doi.org/10.1289/EHP4555
- Rice P. Human health risk assessment of perfluorinated chemicals. In: Kempisty DM, Xing Y, Racz L, editors. Environmental and Occupational Health Series—Perfluoroalkyl Substances in the Environment: Theory, Practice, and Innovation. Boca Raton, FL: CRC Press; 2019.
- Rice P.A., Aungst, J., Cooper, J., Bandele, O., and Kabadi, S.V. (2020) Comparative analysis of the toxicological databases for 6:2 fluorotelomer alcohol (6:2 FTOH) and perfluorohexanoic acid (PFHxA). Food Chem. Toxicol., 138: 111210.
- Rice PA, Cooper J, Koh-Fallet SE, Kabadi SV. Comparative analysis of the physicochemical, toxicokinetic and toxicological properties of ether-PFAS. Toxicol Appl. Pharmacol. 2021; 422: 115531
- Rickard BP, Rizvi I, Fenton SE. Per- and poly-fluoroalkyl substances (PFAS) and female reproductive outcomes: PFAS elimination, endocrine-mediated effects, and disease. Toxicology. 2022 Jan 15; 465:153031. doi: 10.1016/j.tox.2021.153031.
- Rickard BP, Tan X, Fenton SE, Rizvi I. Select Per- and Polyfluoroalkyl Substances (PFAS) Induce Resistance to Carboplatin in Ovarian Cancer Cell Lines. Int J Mol Sci. 2022 May 5;23(9):5176. doi: 10.3390/ijms23095176.
- Rushing BR, Hu Q, Franklin JN, McMahen RL, Dagnino S, Higgins CP, et al. Evaluation of the Immunomodulatory Effects of 2,3,3,3-Tetrafluoro-2-(Heptafluoropropoxy)-Propanoate in C57BL/6 Mice. Toxicol Sci. 2017;156(1):179-89

- S.V. Kabadi et al. Characterizing biopersistence potential of the metabolite 5:3 fluorotelomer carboxylic acid after repeated oral exposure to the 6:2 fluorotelomer alcohol. Toxicology and Applied Pharmacology. 388: 114878 (2020).
- Stanifer et al (2018) Perfluorinated Chemicals as Emerging Environmental Threats to Kidney Health. CJASN October 2018, 13 (10) 1479-1492; DOI: https://doi.org/10.2215/CJN.04670418
- Steenland K, Winquist A. PFAS and cancer, a scoping review of the epidemiologic evidence. Environ Res. 2021 Mar; 194:110690. doi: 10.1016/j.envres.2020.110690.
- Vestergren R, Orata F, Berger U, Cousins IT. Bioaccumulation of perfluoroalkyl acids in dairy cows in a naturally contaminated environment. Environ Sci Pollut Res Int. 2013 Nov;20(11):7959-69.
- Wagner WE, Gold SC. Legal obstacles to toxic chemical research. Science. 2022;375(6577):138-141.
- Wang 2021 https://doi.org/10.1016/j.envint.2020.106247
- Williams Antony J., Gaines Linda G. T., Grulke Christopher M., Lowe Charles N., Sinclair Gabriel F. B., Samano Vicente, Thillainadarajah Inthirany, Meyer Bryan, Patlewicz Grace, Richard Ann M. Assembly and Curation of Lists of Per- and Polyfluoroalkyl Substances (PFAS) to Support Environmental Science Research. Front. Environ. Sci., 05 April 2022 | https://doi.org/10.3389/fenvs.2022.850019
- Worley RR, Fisher J. Application of physiologically-based pharmacokinetic modeling to explore the role of kidney transporters in renal reabsorption of perfluorooctanoic acid in the rat. Toxicology and Applied Pharmacology. 289(3): 428—41 (2015).
- Yu WG, Liu W, Jin YH, Liu XH, Wang FQ, Liu L, Nakayama SF. Prenatal and postnatal impact of perfluorooctane sulfonate (PFOS) on rat development: a cross-foster study on chemical burden and thyroid hormone system. Environ Sci Technol. 2009 Nov 1;43(21):8416-22. doi: 10.1021/es901602d. PMID: 19924978.Zhao W et al., Organic Anion Transporting Polypeptides Contribute to the Disposition of Perfluoroalkyl Acids in Humans and Rats. Toxicological Sciences. 156(1): 84-95 (2017).

<u>Ecotoxicology Data</u>

- Ahrens, L. 2011. Polyfluoroalkyl compounds in the aquatic environment: a review of their occurrence and fate. J Environ Monit. 13(1): 20-31.
- Ahrens, L. and M. Bundschuh. 2014. Fate and effects of poly- and perfluoroalkyl substances in the aquatic environment: a review. Environ Toxicol C3 (po)3 (ly)d (e)-1* (l)-1.8 (u)-2.5 (o)1 2.4 (P)-2.3 (MI9.1-1* (.-2.3 (

GenX) and perfluorooctane sulfonate (PFOS). *Environ Int*. 2022;160:107056. doi:10.1016/j.envint.2021.107056

- Death C, Bell C, Champness D, Milne C, Reichman S, Hagen T. Per- and polyfluoroalkyl substances (PFAS) in livestock and game species: A review. Sci Total Environ. 2021;774:144795. doi:10.1016/j.scitotenv.2020.144795
- De Silva, A.O., Armitage, J.M., Bruton, T.A., Dassuncao, C., Heiger-Bernays, W., Hu, X.C., Kärrman, A., Kelly, B., Ng, C., Robuck, A., Sun, M., Webster, T.F. and Sunderland, E.M. (2021), PFAS Exposure Pathways for Humans and Wildlife: A Synthesis of Current Knowledge and Key Gaps in Understanding. Environ Toxicol Chem, 40: 631-657. https://doi.org/10.1002/etc.4935
- de Vos, M. G., M. A. Huijbregts, M. J. van den Heuvel-Greve, A. D. Vethaak, K. I. Van de Vijver, P. E. Leonards, S. P. van Leeuwen, P. de Voogt and A. J. Hendriks. 2008. Accumulation of perfluorooctane sulfonate (PFOS) in the food chain of the Western Scheldt estuary: Comparing field measurements with kinetic modeling. Chemosphere. 70(10): 1766-1773.
- Giesy, J. P. and K. Kannan. 2001. Global distribution of perfluorooctane sulfonate in wildlife. Environmental science & technology. 35(7): 1339-1342.
- Giesy, J. P. and K. Kannan. 2002. Peer reviewed: perfluorochemical surfactants in the environment. Environmental science & technology. 36(7): 146A-152A.
- Greaves AK, Letcher RJ, Sonne C, Dietz R. Brain region distribution and patterns of bioaccumulative perfluoroalkyl carboxylates and sulfonates in east greenland polar bears (Ursus maritimus). Environ Toxicol Chem. 2013;32(3):713-722. doi:10.1002/etc.2107
- Grønnestad R, Vázquez BP, Arukwe A, Jaspers VLB, Jenssen BM, Karimi M, Lyche JL, Krøkje Å. Levels, Patterns, and Biomagnification Potential of Perfluoroalkyl Substances in a Terrestrial Food Chain in a Nordic Skiing Area. Environ Sci Technol. 2019 Nov 19;53(22):13390-13397. doi: 10.1021/acs.est.9b02533. Epub 2019 Nov 6. PMID: 31691564.
- Houde, M., J. W. Martin, R. J. Letcher, K. R. Solomon and D. C. Muir. 2006. Biological monitoring of polyfluoroalkyl substances: A review. Environ Sci Technol. 40(11): 3463-3473.
- Huang, K. Li, Y., Bu, D., Fu, J., Wang, M., Zhou, W., Gu, L., Fu, L., Cong, Z., Hu, B., Fu, J., Zhang, A., Jiang, G.. 2022. Trophic Magnification of Short-Chain Per- and Polyfluoroalkyl Substances in a Terrestrial Food Chain from the Tibetan Plateau. Environ Sci Technol Lett. *9* (2), 147-152. DOI: 10.1021/acs.estlett.1c01009
- Kannan, K., L. Tao, E. Sinclair, S. D. Pastva, D. J. Jude and J. P. Giesy. 2005. Perfluorinated compounds in aquatic organisms at various trophic levels in a Great Lakes food chain. Arch Environ Contam Toxicol. 48(4): 559-566.
- Keiter, S., L. Baumann, H. Farber, H. Holbech, D. Skutlarek, M. Engwall and T. Braunbeck. 2012. Long-Term Effects of a Binary Mixture of Perfluorooctane Sulfonate (PFOS) and Bisphenol A (BPA) in Zebrafish (Danio rerio). Aquat. Toxicol. 118/119: 116-129.
- Loi, E. I., L. W. Yeung, S. Taniyasu, P. K. Lam, K. Kannan and N. Yamashita. 2011. Trophic Magnification of Poly- and Perfluorinated Compounds in a Subtropical Food Web. Environ. Sci. Technol.(45): 5506-5513.
- Martin, J. W., M. M. Smithwick, B. M. Braune, P. F. Hoekstra, D. C. Muir and S. A. Mabury. 2004. Identification of long-chain perfluorinated acids in biota from the Canadian Arctic. Environmental science & technology. 38(2): 373-380.

polyfluoroalkyl substances among adults with overweight and obesity in the United States: Results from the diabetes prevention program and NHANES. *Environment International, 157*, 106789. https://doi.org/10.1016/j.envint.2021.106789.

- Pinney, S. M., Windham, G. C., Xie, C., Herrick, R. L., Calafat, A. M., McWhorter, K., Fassler, C. S., Hiatt, R. A., Kushi, L. H., & Biro, F. M. (2019). Perfluorooctanoate and changes in anthropometric parameters with age in young girls in the Greater Cincinnati and San Francisco Bay Area. *International Journal of Hygiene and Environmental Health*, *222*(7), 1038–1046. https://doi.org/10.1016/j.ijheh.2019.07.002.

Appendix E:

Table E-1a. Field Implemented Water Treatment Technologies for the Removal and Destruction of PFAS (Adapted from ITRC 2021)

Technology	Challenges	Research Needs
Granular Activated Carbon (GAC)	• Competitive adsorption with other contaminants, including unidentified PFAS species • Pretreatment may be necessary to remove competing constituents or fouling agents • Faster breakthrough times for shorter versus longer-chain PFAS • May be less economical at higher influent concentrations • Spent GAC requires further treatment via reactivation or incineration and may result in PFAS releases	More comprehensive performance data, including: • Adsorption capacity for shorter-chains and other PFAS of interest • Competition with other contaminants and aqueous species
Ion Exchange (IX)	• Competitive adsorption with other ions, including unidentified PFAS species • Pretreatment may be necessary to remove competing constituents or fouling agents • Can have faster breakthrough times for shorter versus longer-chain PFAS • Virgin media cost higher than GAC, performance must make up for increased media cost • Removal efficiencies are compound specific • Potentially more economical at higher influent concentrations than GAC because of the higher loading capacity for the anionic resins • Spent IX resin must be removed for off-site disposal or on-site regeneration, which produces concentrated regeneration-brine requiring additional treatment • Incineration of spent media may be costly and result in PFAS releases	• Similar research needs as GAC • Improved cost-benefit analysis to compare single use, regenerable, and combined use IX resin approaches to address PFAS mixtures

Technology	Challenges	Research Needs
Reverse Osmosis (RO)	• Membranes are highly susceptible to fouling • Pretreatment is necessary to remove suspended solids and other fouling agents in the feedwater such as colloidal and organic matter, inorganic salts, and/or microbial growth • Multistage membrane arrays may be necessary increase removal efficiency • Membrane cleaning and replacement are essential to maintaining the performance of membrane systems • Typically generates high concentration, high volume reject stream • Membrane reject stream and cleaning solutions containing PFAS must be properly managed and disposed • The temperature of the feedwater can affect the performance of membrane systems • Post treatment of product water to avoid corrosion issues within the distribution system for all water qualities and existing corrosion scales • Cost of treatment (for situation amenable to GAC or IX treatment, RO treatment will have a higher cost of treatment)	• Further development and evaluation of membrane technologies and performance in removing a wide range of PFAS under a wide variety of water qualities • Identification and evaluation of cost-effective disposal or treatment technologies for high concentration, high volume reject streams
Nanofiltration (NF)	• In general, rejection performance will be less than with RO membranes • Challenges identical to RO membranes	• Determination if the advantages of NF membranes can be realized – either for NF only systems or in conjunction with other technologies. • Similar needs as RO treatment above

Table E-1b. Novel Water Treatment Technologies for the Removal and Destruction of PFAS (Adapted from ITRC 2021)

Process	Technology	Challenges	Research Needs
Adsorption	Novel adsorbents (e.g., biochar, carbon nanotubes, Cyclodextrin polymers, polymer-coated sand, Zeolites, clay minerals	• Need to develop inexpensive adsorbents with high capacities • Need to certify novel adsorbents for drinking water applications • Competitive adsorption with other contaminants, including unidentified PFAS species • Virgin media cost higher than GAC, performance must make up for increased media cost • Pretreatment may be necessary • Possible faster breakthrough times for select PFAS • May be less economical at higher influent concentrations	• Development of new adsorbents with a combination including cost, adsorption capacity, adsorption kinetics, and ability to manage spent media. • Performance data for a wide range of PFAS, water qualities, and conditions • Data on the cost of treatment

Process	Technology	Challenges	Research Needs
		• Spent adsorbents will require further treatment via regeneration or incineration and may result in PFAS releases	
	Precipitation-Coagulation-Flocculation (conventional treatment) with adsorbent addition	• Current adsorbents such as PAC cannot achieve high percentage removal rates at reasonable PAC loading rates. • Difficulty in evaluating proprietary formulations that can be quickly modified • Novel adsorbents will have issues such as that indicated above.	• Development of adsorbents with higher capacities to be used in conjunction with the conventional treatment process.
	Ultrafiltration (UF) or Microfiltration (MF) in conjunction with adsorbents	• Will not be effective for PFAS control unless they are used in conjunction with other technologies such as powdered activated carbon. They may find usefulness as a pretreatment for other processes such as RO or NF. • Novel adsorbents will have issues such as that indicated above.	• Evaluation of adsorbents that can be used in conjunction with UF membranes. • Secondary need of determining the pretreatment applications.
Separation and Concentration	Foam Fractionation	• Less effective for short-chain PFAS • Integration into treatment train (pretreatment and or residual stream treatment)	• Performance data for a wide range of water qualities and conditions • Data on the cost of treatment • Determination of optimal place within a treatment train
	Membrane distillation	• Membrane fouling • Full-scale design • High energy use • Cost of treatment	• Full-scale demonstration • Long-term performance • Performance data for a wide range of water qualities • Cost of treatment data
	Forward Osmosis	• Draw regeneration is difficult • Pretreatment is necessary to remove suspended solids and other fouling agents in the feedwater such as colloidal and organic matter, inorganic salts, and/or microbial growth • Full-scale design questions • Membrane reject stream and cleaning solutions containing PFAS must be properly managed and disposed • The temperature of the feedwater can affect the performance of membrane systems	• Full-scale demonstration • Long-term performance • Performance data for a wide range of water qualities • Cost of treatment data •

Process	Technology	Challenges	Research Needs
		• Post treatment of product water to avoid corrosion issues within the distribution system for all water qualities and existing corrosion scales • Cost of treatment (for situation amenable to GAC or IX treatment, RO treatment will have a higher cost of treatment)	
	Electrodialysis	• No validation for PFAS • High energy use • Membrane reject stream and cleaning solutions containing PFAS must be properly managed and disposed • Post treatment of product water to avoid corrosion issues within the distribution system for all water qualities and existing corrosion scales • Cost of treatment (for situation amenable to GAC or IX treatment, RO treatment will have a higher cost of treatment)	• Demonstration • Long-term performance • Performance data for a wide range of water qualities • Cost of treatment data
	Electro-coagulation	• High energy use • Passivation of electrode • Optimal operating conditions • Cost of treatment • Full-scale design questions	• Determination of optimal place within a treatment train • Long-term performance • Performance data for a wide range of water qualities • Cost of treatment data
	Evaporation ponds	• Time needed to achieve treatment • Climate dependent • Potential groundwater contamination	• Large area requirement • Possible PFAS air emissions
	Brine concentrators and crystallizers	• High energy use • Full-scale design • Full-scale design still in development	• Determination of optimal place within a treatment train • Long-term performance • Performance data for a wide range of water qualities • Cost of treatment data
Destruction / Defluorination	Ozone-Based Systems	• Poor performance, high doses needed • Need to combine with other technologies as a pretreatment or to create hydroxyl radicals • Potential bromate formation when bromide is present • Byproduct formation likely	• Determination of optimal place within a treatment train • Byproduct identification • Cost of treatment data

Process	Technology	Challenges	Research Needs
	Advanced oxidation (hydroxyl radicals)	• Quenching of the reaction due to other constituents • Limited success to date • Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed
	Hydrated electrons	• Quenching of the reaction due to other constituents • Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities • Full-scale design • Byproduct identification • Cost of treatment needed
	Plasma-based Technology	• Recirculation of argon • Performance data for a wide range of water qualities • Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed
	Catalyzed Hydrogen Peroxide (CHP)–Based Systems	• Quenching of the reaction due to other constituents • Less effective for certain PFAS • Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed
	Activated Persulfate	• Quenching of the reaction due to other constituents • Byproduct formation likely • Full-scale design questions Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed

Process	Technology	Challenges	Research Needs
	Sonochemical Oxidation/Ultrasound	• Quenching of the reaction due to other constituents • Less effective for certain PFAS • Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed
	Photocatalysis	• Breakdown products • Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed
	Zero-Valent Iron (ZVI)/Doped-ZVI	• Limited applicability • Less effective for certain PFAS • Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed
	Alkaline Metal Reduction	• Requires heat and elevated pH to improve efficiency • Byproduct formation likely • Less effective for certain PFAS (linear alkyl chains) • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed

Process	**Technology**	**Challenges**	**Research Needs**
	High-Energy Electron Beam (eBeam)	• Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed
	High Temperature and Supercritical Water Oxidation	• Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determination of optimal combination of technologies • Performance data for a wide range of water qualities and flow rates • Full-scale design • Byproduct identification • Cost of treatment needed
	Biodegradation	• Not demonstrated • Difficulty in distinguishing between destruction and absorption to microbes or extracellular materials • Unclear performance in various water qualities and temperatures • Slow kinetics • Byproduct formation likely • Full-scale design questions	• Determining optimal operation for high-rate treatment systems • Performance data for a wide range of water qualities and temperatures • Optimal full-scale design • Byproduct identification
	Enzymes from bacterial or fungal sources	• Not demonstrated • Unclear performance in various water qualities and temperatures • Unclear production and separation of enzymes • Byproduct formation likely • Full-scale design questions • Cost of treatment	• Determining optimal operation for high-rate treatment systems • Performance data for a wide range of water qualities and temperatures • Optimal full-scale design • Byproduct identification
	Incineration (see solids and air/gases sections)	• Only useful for small volumes of liquids and sludges • Potential air releases containing PFAS and their transformation products • Cost of treatment	• Breakdown product identification • Cost of treatment • See solid and air/gases section for more details.

Process	Technology	Challenges	Research Needs
		• See solid and air/gases section for more details.	
Sequestration	In Situ sequestration with adsorbents (e.g.,		

Process	Technology	Challenges	Research Needs
Separation	Excavation and Disposal	• Limited disposal options for excavated materials in landfills, confined disposal facilities for sediments, etc. • Not a destructive technology therefore requires further treatment or stabilization/isolation	• Cost comparison of "dig and haul" approaches with in-situ and destructive technologies. • Cost effective disposal/destructive technologies needed for ultimate disposition of the PFAS. • Shares many of the research needs with landfilling of PFAS contaminated wastes
	Soil Sieving / Washing	• Technology not fully demonstrated for a range of PFAS under a range of soil properties and co-contaminants • As a volume reduction technology, treatment of the residual and waste streams required.	• Performance for a range of PFAS under various soil properties • Cost/performance data needed • Disposal options for residuals and wastes generated during the process
Sorption and Stabilization	Colloidal Activated Carbon (CAC) and other amendments	• Competitive adsorption with other contaminants • Pretreatment may be necessary • Spent GAC must be reactivated or incinerated	• Determine adsorption efficiency of CAC for various PFAS species • Assess incineration/reactivation of GAC material for disposal/reuse
Destruction / Defluorination	Incineration	• Wide variety of full-scale system configurations makes acquisition and comparison of meaningful data difficult • Assessment of full-scale systems requires holistic approach: sampling all phases of feeds, treated materials, and emissions along with combination of targeted/non-targeted/non-specific PFAS analysis	• Bench-scale incineration data to inform development of models and design of full-scale studies • Full scale demonstration to quantify destruction and possible emissions/waste residuals • Best practice operating conditions to maximize PFAS mineralization

Table E-1d. Novel Solids Treatment Technologies for the Removal and Destruction of PFAS (Adapted from ITRC 2021)

Process	Technology	Challenges	Research Needs
Destruction/ Defluorination	Pyrolysis / Gasification	• Full-scale pyrolysis/gasification systems are not common • No standardized system configuration • Low-oxygen conditions, high chance of products of incomplete combustion (PICs) formation	• Information on fate of PFAS in pyrolysis conditions • Bench-scale data needed
	Ultrasound	• Includes a broad range of chemical, electrochemical, photochemical, sonochemical, etc. technologies that have potential in laboratory scale studies but are unproven under real world conditions. • Limited technologies available that have demonstrated efficacy in treatment and cost at pilot or full scale.	• Bench-scale data needed
	In-situ Smoldering / Combustion	• Low-oxygen conditions, high chance of products of incomplete combustion (PICs) formation	• Bench-scale data needed
	Plasma	• Limited biodegrade availability and unique capital equipment • Limited cost, performance, and design information available	• Cost and performance data needed for various matrices with various PFAS compositions • Characterizing possible emissions or residuals
	High-Energy Electron Beam (eBeam)	• Limited access to e-beam facilities • Reconfiguring reactors and facilities to optimize destruction and manage residuals/emissions	• Bench-scale data needed • Cost and performance data needed for various matrices with various PFAS compositions • Characterizing possible emissions or residuals

Process	Technology	Challenges	Research Needs
Separation	Soil Sieving / Washing with Advanced Oxidative Process (AOP)	• Lack of bench or demonstration data to allow design or cost comparisons	• Characterizing the performance under various soil conditions and PFAS compositions • Optimization of treatment train for performance and cost
	Thermal Desorption	• Lack of design criteria for various soils and PFAS contaminants • Demonstrating mass balance or management of PIDs • Cost and performance data	• Characterizing the performance of the technologies under varying soils, conditions, and PFAS compositions • Demonstration of technology and emission control technologies.
	Sorption and Stabilization	• Not a destruction technology and requires either further treatment or validation/demonstration that the PFAS are permanently stabilized • Demonstrated performance and costs of both in-situ and ex-situ stabilization • Varying geochemical parameters of the soils and sediments targeted for stabilization can impact the performance and permanence of S/S technologies	• Standard protocols for leaching tests to demonstrate sequestration or potential for releases. • Understanding the long-term performance of stabilized PFAS under real world conditions • Delivery methods for in-situ methods and cost-effective ex-situ disposal of stabilized materials • Efficacy for PFAS not currently measured in standard targeted methods including anionic, cationic, and zwitterionic compounds in both long and short chain chemistries
	Foam Fractionation	• Requires novel reactor designs that are not off-the-shelf designs • Not a destruction technology and requires further treatment of residuals and wastes	• Understanding the performance under various water quality conditions, PFAS compositions, and impacts of co-contaminants • Characterizing the possible air emissions

Process	Technology	Challenges	Research Needs
			• Characterizing the potential transformations of precursors and other PFAS materials
	Biodegradation	• Many PFAS have demonstrated limited to no biodegradability under environmental conditions •	

Readiness Level	Process	Technology	Challenges	Research Needs
			• Certain particulate disposal methods could lead to release of PFAS to the environment	• Evaluate disposal options for particulate
		Electrostatic Precipitation	• Solid residuals require further treatment/disposal • Certain particulate disposal methods could lead to release of PFAS to the environment	• Determine partitioning of PFAS in particulate • Evaluate disposal options for particulate
		Vapor Phase GAC	• Competitive adsorption with other contaminants • Pretreatment may be necessary • Spent GAC must be reactivated or incinerated	• Determine adsorption efficiency of vapor phase GAC for various PFAS species • Assess incineration/reactivation of GAC material for disposal/reuse
	Destruction / Defluorination	Incineration	• Wide variety of full-scale system configurations makes acquisition and comparison of meaningful data difficult • Assessment of full-scale systems requires holistic approach: sampling all phases of feeds, treated materials, and emissions along with combination of targeted/non-targeted/non-specific PFAS analysis	• Bench-scale incineration data (temperatures and residence times needed for full mineralization) to inform full-scale studies • Best practice operating conditions to maximize PFAS mineralization

Table E-2. Analytical Methods

Table E-3. Emerging and Data Poor PFAS Identified in US EPA's Systematic Evidence Map[a] With at Least 1 Animal or Human Study Summarized in the 150 Chemical Literature Inventory.

Chemical Name	Chemical Abstracts Service Registry Number (CASRN)	Animal Evidence	Human Evidence
1-Butanesulfonic acid, 1,1,2,2,3,3,4,4,4-nonafluoro-, salt with sulfonium, dimethylphenyl- (1:1)	220133-51-7	x	-
1H,1H,2H-Perfluorocyclopentane	15290-77-4	x	-
1H,1H,5H-Perfluoropentanol	355-80-6	x	-
2-Chloro-1,1,1,2-tetrafluoroethane	2837-89-0	x	-
3,3,4,4,5,5,6,6,6-Nonafluorohexene	19430-93-4	x	-
3-Methoxyperfluoro(2-methylpentane)	132182-92-4	x	-
6:2 Fluorotelomer alcohol	647-42-7	x	-
6:2 Fluorotelomer methacrylate	2144-53-8	x	-
6:2 Fluorotelomer sulfonic acid	27619-97-2	x	x
8:2 Fluorotelomer alcohol	678-39-7	x	x
Dodecafluoroheptanol	335-99-9	x	-
Methyl perfluoro(3-(1-ethenyloxypropan-2-yloxy) propanoate)	63863-43-4	x	-
Nafion	31175-20-9	x	x
N-Ethyl-N-(2-hydroxyethyl)perfluorooctanesulfonamide	1691-99-2	x	-
N-Ethylperfluorooctanesulfonamide	4151-50-2	x	-
N-Methyl-N-(2-hydroxyethyl)perfluorooctanesulfonamide	24448-09-7	x	-

Perfluamine	338-83-0	x	-
Perfluoro(4-methoxybutanoic) acid	863090-89-5	x	-
Perfluoro(N-methylmorpholine)	382-28-5	x	-
Perfluoro(propyl vinyl ether)	1623-05-8	x	-
Perfluoro-1,3-dimethylcyclohexane	335-27-3	x	-
Perfluoro-1-iodohexane	355-43-1	x	-
Perfluoro-2,5-dimethyl-3,6-dioxanonanoic acid	13252-14-7	x	x
Perfluoro-3-methoxypropanoic acid	377-73-1	x	
Perfluoro-3-(1H-perfluoroethoxy)propane	3330-15-2	x	-
Perfluorobutanesulfonyl fluoride	375-72-4	x	-
Perfluorocyclohexanecarbonyl fluoride	6588-63-2	x	-
Perfluoroheptanesulfonate	146689-46-5	-	x
Perfluoroheptanesulfonic acid	375-92-8	-	x
Perfluoroheptanoic acid	375-85-9	-	x
Perfluoromethylcyclopentane	1805-22-7	x	-
Perfluorooctanesulfonamide	754-91-6	x	x
Perfluorooctanesulfonyl fluoride	307-35-7	x	x
Perfluoropentanoic acid	2706-90-3	x	x
Perfluoropropanoic acid	422-64-0	-	x
Perfluorotetradecanoic acid	376-06-7	x	x
Perfluorotridecanoic acid	72629-94-8	x	x
Perfluoroundecanoic acid	2058-94-8	x	x
Sodium perfluorodecanesulfonate	2806-15-7	-	x
Tetrabutylphosphonium perfluorobutanesulfonate	220689-12-3	x	-
Tetraethylammonium perfluorooctanesulfonate	56773-42-3	x	-
Trichloro((perfluorohexyl)ethyl)silane	78560-45-9	x	-
Triethoxy((perfluorohexyl)ethyl)silane	51851-37-7	x	-
Trifluoroacetic acid	76-05-1	x	x
Trifluoromethanesulfonic acid	1493-13-6	x	-

[a] Table 5 as published in: Carlson LM, Angrish M, Shirke AV, Radke EG, Schulz B, Kraft A, Judson R, Patlewicz G, Blain R, Lin C, Vetter N, Lemeris C, Hartman P, Hubbard H, Arzuaga X, Davis A, Dishaw LV, Druwe IL, Hollinger H, Jones R, Kaiser JP, Lizarraga L, Noyes PD, Taylor M, Shapiro AJ, Williams AJ, Thayer KA. Systematic Evidence Map for Over One Hundred and Fifty Per- and Polyfluoroalkyl Substances (PFAS). *Environ Health Perspect*. 2022 May; 130(5):56001.

Table E-4. Current Status PFAS Ecotoxicity Studies*

Biotic Components Assessed for PFAS Toxicity	FW Fish	SW Fish	FW Invert	SW Invert	Algae	Plant	Amphibian	Terrestrial Invert	Reptile	Bird	Mammal (aquatic/ terrestrial) (to include cell/ tissue in vitro studies)
Types of Exposures											
Acute laboratory testing											
Mortality (LC50/LD50)	H	M	H	M	n/a	L	M	M	L	M	L
Cell/molec biomarker	M	M	M	M	L	L	L	M	L	M	L
Chronic laboratory testing											
Growth/ Development	M	M	M	M	M	L	L	M	L	M	L
Reproduction	M	L	L	L	n/a	L	L	M	L	M	L
Behavior	L	L	L	L	n/a	n/a	L	L	L	L	L
Cell/molec biomarker	M	M	M	M	L	L	L	M	L	M	L
Histology	M	L	L	L	n/a	L	L	L	L	L	L
Spiked sediment testing	n/a	n/a	L	L	n/a	L	n/a	M	n/a	n/a	n/a
Mesocosm testing											
Freshwater/ terrestrial	L	L	L	L	L	L	L	L	L	L	L
Estuarine/marine	L	L	L	L	L	L	L	n/a	n/a	n/a	n/a
Field assessments											
Tissue chemistry paired with biomarkers	M	M	M	M	n/a	n/a	L	L	L	L	L
Chemistry paired with	L	L	L	L	n/a	n/a	L	L	L	L	L

reproductive measure									[redacted]
Caged animal studies	L	L	L	L	n/a	n/a	L	L	[redacted]

*H – information available and actionable; M – some information available; L – limited or no information

PFAS testing = PFOS, PFOA, or other common PFAS; Mixture = testing multiple PFAS in mixture; Multistressor = tes[redacted]iotic components can be FW or SW unless specified; Mesocosm = multiple species, simulated ecosystem; n/a = not applicab[redacted]