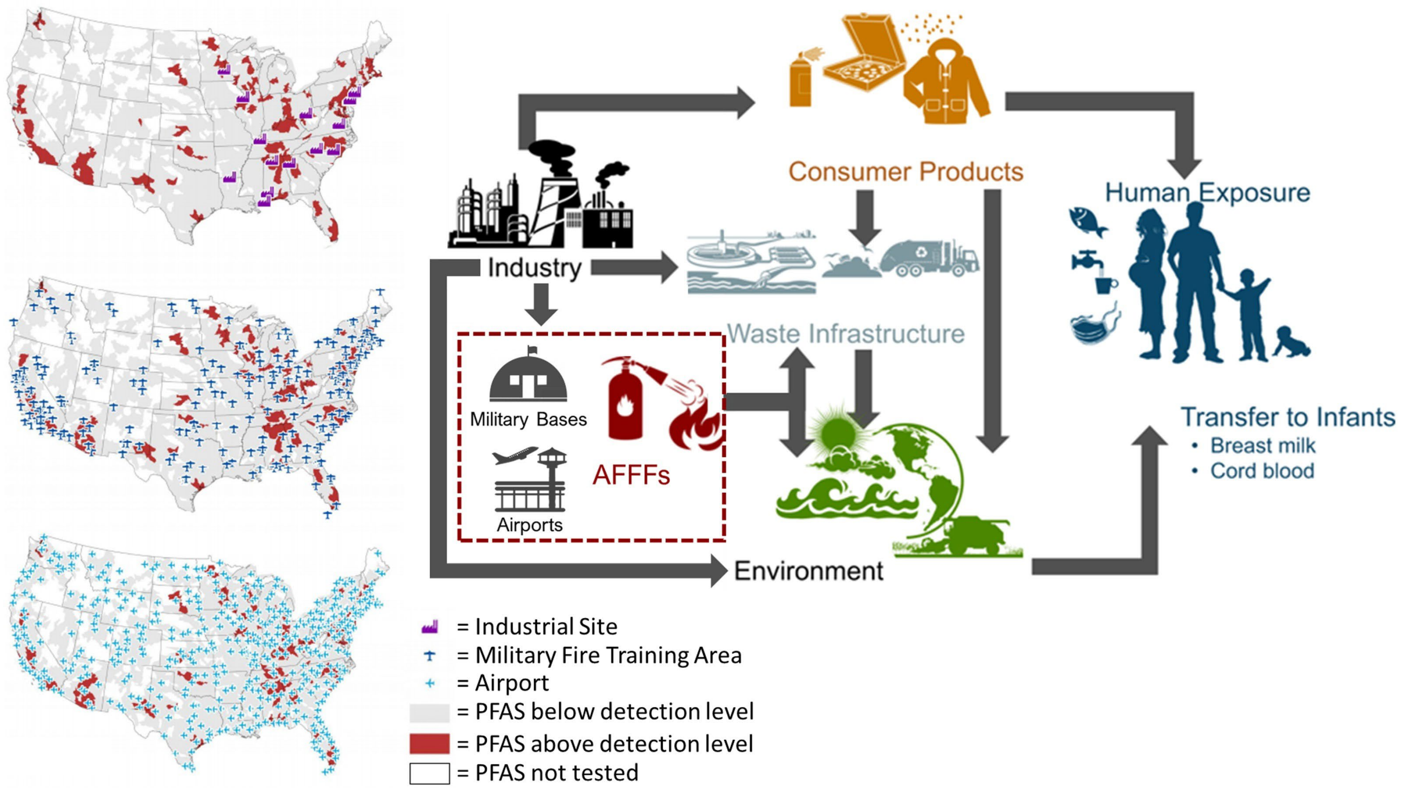
ICCVAM PFAS WG

DoD, EPA, FDA

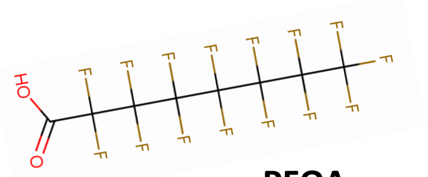
SACATM Meeting
NIEHS, September 21-22, 2023

Per- and Poly fluoroalkyl Substances (PFAS)

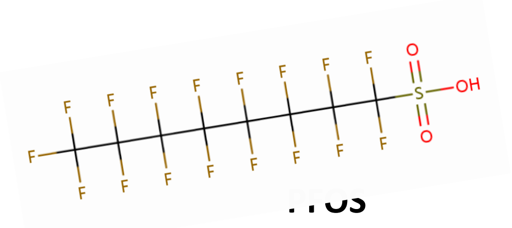


Blake and Fenton, 2020 *Toxicology*

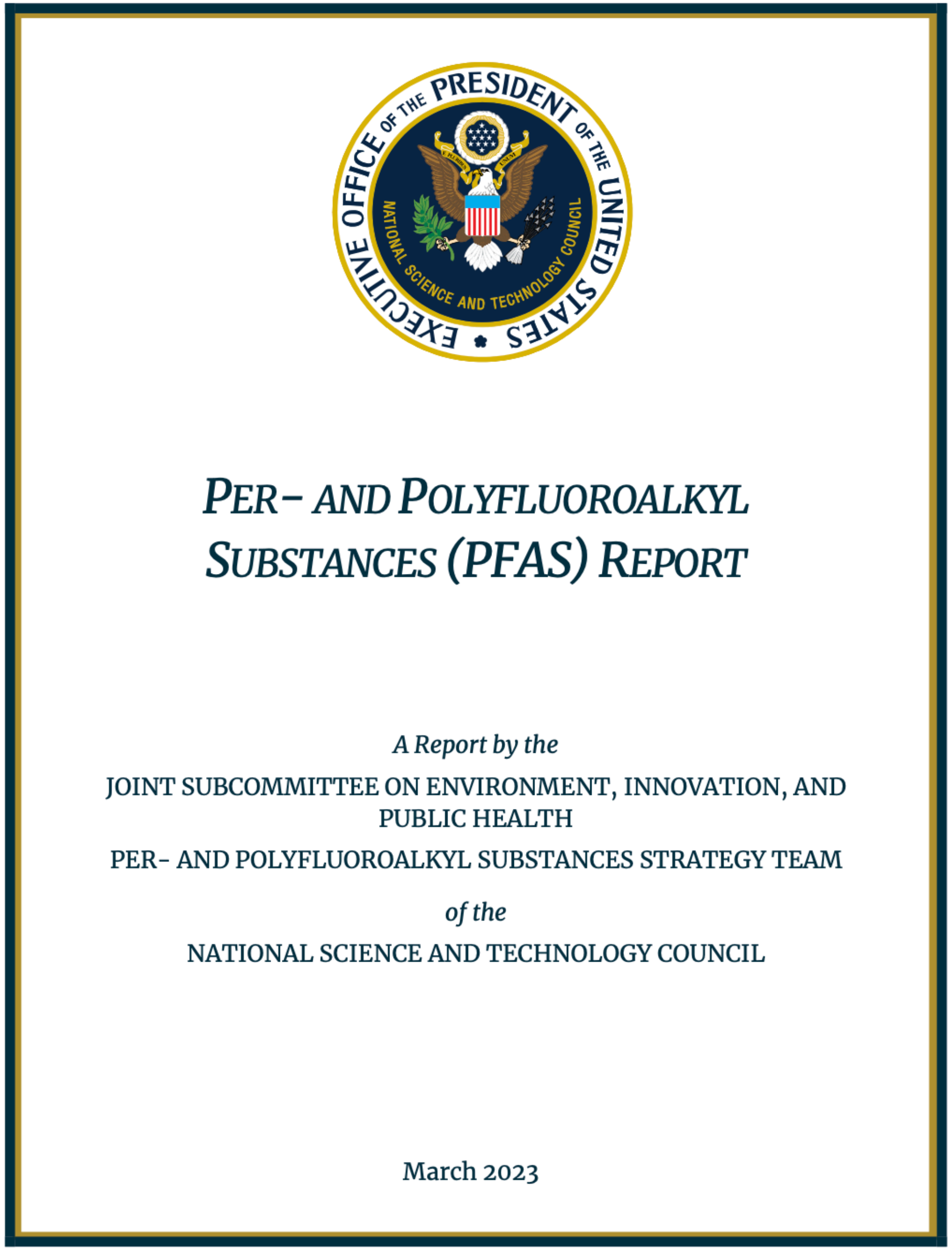
- **PFAS have widespread commercial and industrial applications**, such as water- and oil- repellents, surfactants, surface protectors, and fire-fighting foams.
- Core structure of PFAS: per- or poly- fluorinated carbon chains bonded to different functional groups (e.g. carboxylic or sulfonic acid).
- Long-chain PFAS have been identified as **highly persistent and bioaccumulative** and have been **detected in the environment, biota, and humans**.
- Only a small number of PFAS have been extensively evaluated for adverse human health potential, such as perfluorooctanoic acid (**PFOA**) and perfluorooctane sulfonic acid (**PFOS**), which are **currently under regulation internationally**.
- The **paucity of experimental data evaluating a large number of PFAS** is a discernable limitation in understanding human health effects of PFAS in the developing brain.



PFOA



- The Report to Congress provides a high-level overview of research on PFAS as a chemical class
- This state-of-the-science report includes gaps and opportunities for the Federal government in the above-mentioned areas.
- OSTP and the PFAS ST engaged over 60 Federal experts to identify critical research gaps and needs for PFAS, and issued a Request for Information (RFI) to gather public opinions and comments.



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

March 2023

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).

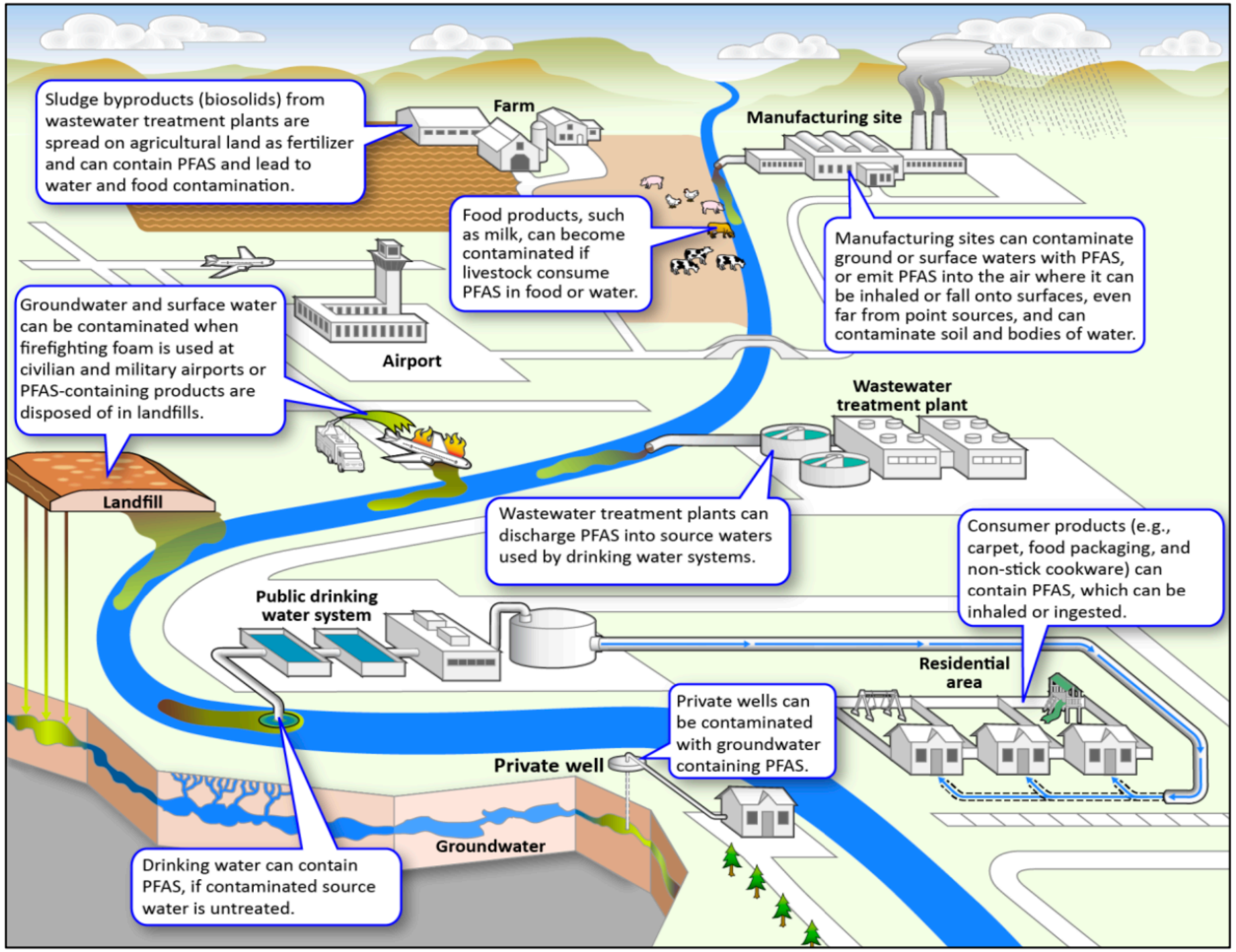


Figure 1: Possible routes for PFAS release into the environment (https://www.gao.gov/assets/gao-22-105088.pdf). This figure does not include all potential sources of PFAS releases, such as air emission and transport, uptake into plants, and permitted industrial discharges. (Source: Government Accountability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

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).

Research & Development

In this report, the term "*PFAS research and development*" is defined by Section 332 of the NDAA for FY 2021 and includes "any research or project that has the goal of accomplishing the following:

- The removal of PFAS from the environment,
- The safe destruction or degradation of PFAS,
- The development and deployment of safer and more environmentally friendly alternative substances that are functionally similar to those made with PFAS,
- Understanding the sources of environmental PFAS contamination and pathways to exposure for the public, or
- Understanding the toxicity of PFAS to humans and animals."

Toxicity

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	•	•		•	•	•	•		•	•	•	•	•	•	•
Respiratory	•	•		•	•	•				•	•	•	•		
Cardiovascular	•	•		•	•					•	•		•		•
Gastrointestinal	•	•		•	•					•	•	•	•		•
Hematological	•	•		•	•	•				•	•		•	•	•
Musculoskeletal	•	•		•	•					•	•				
Hepatic	•	•		•	•	•	•	•	•	•	•	•	•	•	•
Renal	•	•		•	•	•		•		•	•	•	•	•	•
Dermal	•					•		•		•	•				
Ocular	•	•		•		•				•	•				
Endocrine	•	•		•	•	•		•		•	•	•	•		•
Immunological	•	•		•	•	•	•	•		•	•	•	•		
Neurological	•	•		•	•	•			•	•	•		•		•
Reproductive	•	•		•	•	•	•	•		•	•	•	•		•
Developmental	•	•		•	•	•	•		•	•	•	•	•	•	•
Other noncancer						•				•		•			
Cancer						•				•	•				

Shared Challenges & Areas for Opportunity

- Analytical Technology
- Communication
- Alternatives
- Mixtures
- Reporting
  - Shared data systems
- New Approach Methodologies (NAMs)
  - PFAS-specific high throughput assays
- Ambient Levels

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* 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."

Priority Areas for Opportunity

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:

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*.

PFAS and NAMs testing

ELSEVIER
Toxicology and Applied Pharmacology
Volume 459, 15 January 2023, 116355

Targeted *Per*- and Polyfluoroalkyl substances (PFAS) assessments for high throughput screening: Analytical and testing considerations to inform a PFAS stock quality evaluation framework

Marci G. Smeltz [a], M. Scott Clifton [b], W. Matthew Henderson [c], Larry McMillan [d], Barbara A. Wetmore [a]

ELSEVIER
Computational Toxicology
Volume 24, November 2022, 100250

Towards reproducible structure-based chemical categories for PFAS to inform and evaluate toxicity and toxicokinetic testing

Grace Patlewicz, Ann M. Richard, Antony J. Williams, Richard S. Judson, Russell S. Thomas

Chemical Research in Toxicology
pubs.acs.org/crt
Article

Evaluation of Per- and Polyfluoroalkyl Substances (PFAS) *In Vitro* Toxicity Testing for Developmental Neurotoxicity

Kelly E. Carstens,* Theresa Freudenrich, Kathleen Wallace, Seline Choo, Amy Carpenter, Marci Smeltz, Matthew S. Clifton, W. Matthew Henderson, Ann M. Richard, Grace Patlewicz, Barbara A. Wetmore, Katie Paul Friedman, and Timothy Shafer

Cite This: *Chem. Res. Toxicol.* 2023, 36, 402–419
Read Online

Charges

- Evaluate the state of the science of current PFAS definitions and groupings
- Evaluate which NAMs are currently being applied for PFAS by national and international regulatory agencies, and assess their potential to fulfill regulatory testing requirements and to address the current regulatory questions for their risk assessment
- Identify requirements of different agencies for the use of NAMs for PFAS testing and risk assessment.
- Identify toxicity endpoints needed or being considered by each federal agency and commonalities and differences between agencies
- Identify research challenges and data gaps for the use of specific NAMs for testing and risk assessment of different PFAS

Scope

Although the detailed work plans for these projects are being developed by the working group, it is envisioned that the group will first contribute to a summary of agency needs for assessing PFAS and how those can be met using NAMs.

This summary will then be used to advance the development and evaluation of defined approaches for screening, testing and assessment of relevant endpoints.

Additionally, the workgroup will address the development and implementation of alternative approaches to reduce and replace animal use for PFAS testing following four key steps:

(1) reviewing current PFAS definition(s);

(2) identifying testing efforts among regulatory and non-regulatory agencies and related challenges;

(3) identifying data gaps and opportunities in application of alternative approaches; and

(4) identifying and addressing both scientific and non-scientific (including regulatory) needs and challenges. These evaluations and supporting documentation will be made available to the public and may also be submitted to OECD to facilitate international harmonization and global implementation of alternative approaches for PFAS testing and risk assessment.

Deliverables

- Interim (timeline: 6-9 months) – a brief state of knowledge white paper or report on definitions and groupings of PFAS, current NAMs used for testing and risk assessment of specific PFAS and the overarching challenges and data gaps for applying NAMs for PFAS.
- Follow up (timeline: 1-1.5 years) – a workshop or conference session on application of different NAMs for specific PFAS, specifically broken up into three sections/segments: successes, challenges and opportunities of expanding the utility of NAMs for different PFAS
- Long term (timeline: 2-3 years) – a manuscript to be published in a scientific journal that discusses outcome of the workshop followed by a description of challenges and data gaps for applying NAMs for different PFAS, and ideas to overcome these challenges with specific case examples based on NAMs identified after performing a deeper dive of published literature and regulatory efforts over the years.

Acknowledgements

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U.S. Department of Health and Human Services

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