Wolf Sustainability

21 Thibault Parkway
Burlington, Vermont 05401
+1 (802) 598-8370
info@wolfsustainability.com
www.wolfsustainability.com

Date: February 12, 2025

To: Rep. Amy Sheldon, Chair
House Committee on Environment

cc: Rep. Larry Labor, Vice Chair
Rep. Larry Satcowitz, Ranking Member
Rep. Sarah "Sarita" Austin, Clerk
Rep. John L. Bartholomew
Rep. Ela Chapin
Rep. Kate Logan
Rep. Kristi Morris
Rep. Rob North
Rep. Christopher "Chris" Pritchard
Rep. Michael "Mike" Tagliavia
Anika Adams, Committee Assistant

From: Martin Wolf, Principal
Wolf Sustainability
Burlington, VT 05401

and

Advisor, Safer Chemicals and Circular Economy
The American Sustainable Business Network
Washington, DC 20002

RE: Testimony on the Agency of Natural Resources Report on implementation of Act 131 regulating consumer products containing perfluoroalkyl and polyfluoroalkyl substances or other chemicals

---

Dear Rep. Sheldon and Committee Members:

Thank you for this opportunity to testify on the Agency of Natural Resources (ANR) Report on implementation of Act 131 regulating consumer products containing perfluoroalkyl and polyfluoroalkyl substances (PFAS) or other chemicals.

For the record, my name is Martin Wolf, Principal, Wolf Sustainability. I am a chemist with over 50 years of industry experience studying the occurrence and fate of chemicals in the environment and designing more sustainable consumer products.

I also represent the American Sustainable Business Network, a multi-issue membership organization advocating on behalf of businesses, business associations, and the investor community, whose members collectively represent over 250,000 businesses.

PFAS are substances containing fluorine atoms covalently bonded to carbon atoms. The exact definition has varied. The definition recommended here is that of the Organization for Economic Cooperation and Development (OECD), "PFAS are defined as fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it).[1] The definition proposed in the ANR Report excludes a large number of PFAS in commercial use[2] and opens a door for companies to engineer new molecules with the adverse impacts of PFAS but without the legislative restrictions needed to avoid human health and environmental harms.

The use of the term "Intentionally Added" is imprecise and confusing because it is seldom the intent of a manufacturer to add "byproducts or impurities." It is suggested here that terminology consistent with other laws and regulations be used. Specifically, "Intentionally added ingredient" means a chemical that a manufacturer has intentionally added to a product and that has a functional or technical effect on the product, including the intentional breakdown products of an added chemical that also have a functional or technical effect in the product.[3] A substance that is present in a product that has no functional or technical effect on the product may be referred to as an "incidental ingredient" (or simply "incidental") or as a "byproduct" or "impurity."

Companies are appropriately concerned that their products may be held to a higher standard than municipal, ground, or surface water used to manufacture their products. According to the Agency for Toxic Substances and Disease Registry (ATSDR) ingestion of food and water is a main route of PFAS exposure.[4] Therefore it is recommended that any thresholds established by the Secretary for PFAS in a product or a product component be higher than the maximum contaminant level (MCL) of PFAS set for municipal drinking water, ground water, or surface water.

---

[1] Organization for Economic Co-operation and Development (OECD). 2021. Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance. Series on Risk Management No. 61. https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/terminology-per-and-polyfluoroalkyl-substances.pdf (accessed 2021/9/1)

[2] Zhanyun Wang, Andreas M. Buser, Ian T. Cousins, Silvia Demattio, Wiebke Drost, Olof Johansson, Koichi Ohno, Grace Patlewicz, Ann M. Richard, Glen W. Walker, Graham S. White, and Eeva Leinala *A New OECD Definition for Per- and Polyfluoroalkyl Substances*, Environmental Science & Technology 2021 55 (23), 15575-15578 DOI: 10.1021/acs.est.1c06896

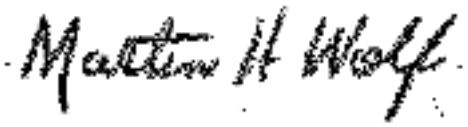
[3] California Cleaning Product Right to Know Act of 2017

[4] Human Exposure: PFAS Information for Clinicians - 2024 | PFAS and Your Health | ATSDR. Downloaded 12 February 2025

For most consumer applications, the economic impacts of remediating harm to human health and harm to the environment from PFAS far exceed the economic value of transitioning to less hazardous alternatives. The benefit to PFAS manufacturers has been estimated as $2billion per year.[5] Health-related costs for the United States are estimated to be $37−59 billion annually, not including indirect social costs such as lost wages; lost years of life; reduced quality of life; increased stress, anxiety, and depression; and subsequent impacts on families and communities.[6] Thus, there is not a business case for continued use of PFAS and it is recommended that their use be phased out rapidly.

Thank you for your attention to, and consideration of, these comments.

Respectfully submitted,



Martin H. Wolf
Principal
Wolf Sustainability

and

Advisor, Safer Chemicals and Circular Economy
American Sustainable Business Network

[5] Alissa Cordner, Gretta Goldenman, Linda S. Birnbaum, Phil Brown, Mark F. Miller, Rosie Mueller, Sharyle Patton, Derrick H. Salvatore, and Leonardo Trasande, *The True Cost of PFAS and the Benefits of Acting Now*, Environmental Science & Technology 2021 55 (14), 9630-9633. DOI: 10.1021/acs.est.1c03565
[6] Ibid.

Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2021)25

Unclassified

English - Or. English

9 July 2021

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance

Series on Risk Management
No.61

JT03479350

OECD Environment, Health and Safety Publications
Series on Risk Management
No. 61

Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

Environment Directorate
ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT
Paris 2021

About the OECD

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental organisation in which representatives of 38 industrialised countries in North and South America, Europe and the Asia and Pacific region, as well as the European Commission, meet to co-ordinate and harmonise policies, discuss issues of mutual concern, and work together to respond to international problems. Most of the OECD's work is carried out by more than 200 specialised committees and working groups composed of member country delegates. Observers from several countries with special status at the OECD, and from interested international organisations, attend many of the OECD's workshops and other meetings. Committees and working groups are served by the OECD Secretariat, located in Paris, France, which is organised into directorates and divisions.

The Environment, Health and Safety Division publishes free-of-charge documents in eleven different series: **Testing and Assessment**; **Good Laboratory Practice and Compliance Monitoring**; **Pesticides**; **Biocides**; **Risk Management**; **Harmonisation of Regulatory Oversight in Biotechnology**; **Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents;** and **Safety of Manufactured Nanomaterials.** More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/chemicalsafety/).

This publication was developed in the IOMC context. The contents do not necessarily reflect the views or stated policies of individual IOMC Participating Organizations.

The Inter-Organisation Programme for the Sound Management of Chemicals (IOMC) was established in 1995 following recommendations made by the 1992 UN Conference on Environment and Development to strengthen co-operation and increase international co-ordination in the field of chemical safety. The Participating Organisations are FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD. The purpose of the IOMC is to promote co-ordination of the policies and activities pursued by the Participating Organisations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

This publication is available electronically, at no charge.

Also published in the Testing and Assessment link

For this and many other Environment, Health and Safety publications, consult the OECD's World Wide Web site (www.oecd.org/chemicalsafety/)

or contact:

OECD Environment Directorate,
Environment, Health and Safety Division
2 rue André-Pascal
75775 Paris Cedex 16
France

Fax: (33-1) 44 30 61 80

E-mail: ehscont@oecd.org

Acknowledgements: This report was prepared under the framework of the OECD/UNEP Global PFC Group and developed with financial support of Switzerland. In particular, the report was prepared by a writing group of the following members, led by Zhanyun Wang (ETH Zürich, Switzerland) and benefited from the review and input of other members of the group:

Robert C. Buck (Chemours), Andreas Buser (Swiss Federal Office for the Environment), Ian T. Cousins (Stockholm University, Sweden), Silvia Demattio (European Chemicals Agency), Wiebke Drost (German Environment Agency), Audun Heggelund (Norwegian Environment Agency), Olof Johansson (Swedish Chemicals Agency), Eeva Leinala (OECD), Koichi Ohno (National Institute for Environmental Studies, Japan), Grace Patlewicz (US EPA), Ann Richard (US EPA), Simone Schalles (German Environment Agency), Glen Walker (Australian Department of Agriculture, Water and the Environment), Graham White (Health Canada), with earlier contributions by Urs Berger (UFZ, Germany), Stellan Fischer (Swedish Chemicals Agency) and Laurence Libelo (US EPA).

The report is published under the responsibility of the OECD Chemicals and Biotechnology Committee.


The OECD Per- and Polyfluoroalkyl Substances (PFAS) project has been produced with the financial assistance of the European Union. The views expressed herein can in no way be taken to reflect the official opinion of the European Union.

Executive Summary

This report summarizes recent efforts by the OECD/UNEP Global PFC Group between June 2018 and March 2021 in reviewing the universe and terminology of per- and polyfluoroalkyl substances (PFASs) to provide recommendations and practical guidance to all stakeholders with regard to the terminology of PFASs. In particular, this report highlights (1) a revised PFAS definition to comprehensively reflect the universe of PFASs and a comprehensive overview of the PFAS universe (Chapter 2), (2) practical guidance on how to use the PFAS terminology (Chapter 3), (3) a systematic approach to characterization of PFASs based on molecular structural traits to assist stakeholders, including non-experts, in making their own categorization based on their needs (Chapter 4), and (4) areas in relation to the PFAS terminology that warrant further development (Chapter 5). It should be noted that this report does not address the nomenclature and understanding of individual PFASs, including the sources of exposure and the actual composition of commercial products.

PFASs comprise a class of synthetic compounds that have attracted much public attention since the late 1990s and early 2000s, when the hazards and ubiquitous occurrence of two PFASs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), started to be reported and recognized. Since then, research and risk management measures have expanded from these two PFASs to a wider range of PFASs. Early communications used many different terminologies (e.g. per- and polyfluorinated chemicals, perfluorinated organics, perfluorochemical surfactants, highly fluorinated compounds). In 2011, to unify and harmonize communication on PFASs, Buck et al. published a milestone paper, providing a first clear structural definition of PFASs and recommendations on names and acronyms for over 200 individual PFASs.

Currently, there is a growing interest by regulators and scientists across the globe to assess legacy and novel PFASs. In 2018, the OECD/UNEP Global PFC Group prepared a new list of PFASs that may have been on the global market. In total, a set of substances with over 4730 CAS numbers have been identified, including substances that contain such fully fluorinated carbon moieties, but do not meet the PFAS definition in Buck et al. (2011) due to a lack of a $–CF_3$ group in the molecular structures. In addition, recent advancement of non-target screening analytical techniques using high-resolution mass spectrometry has enabled identification of many unknown substances in different environmental and product samples. The identification of these substances motivates the present work to reconcile the terminology of the universe of PFASs, including a renewed look at the PFAS definition in Buck et al. (2011).

It is key to have a coherent and consistent logic behind the PFAS definition to adequately reflect all compounds with the same structural traits, i.e. the PFAS universe. Building on the OECD 2018 PFAS List and recent non-target screening studies, Chapter 2 first identifies four major gaps in the previous PFAS definition by Buck et al. (2011) in representing the PFAS universe. Then, Chapter 2 recommends a revised PFAS definition, with detailed elaboration on individual changes provided:

> PFASs are defined as fluorinated substances that contain at least one **fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I 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**.**

The rationale behind the revision is to have a general PFAS definition that is coherent and consistent

across compounds from the chemical structure point of view and is easily implementable for distinguishing between PFASs and non-PFASs, also by non-experts. The decision to broaden the definition compared to Buck et al. is not connected to decisions on how PFASs should be grouped in regulatory and voluntary actions. Based on the revised definition of PFASs, Chapter 2 further illustrates (1) how PFASs fit into organofluorine compounds, (2) a comprehensive overview of PFAS groups, their structural traits, examples and notes on whether common nomenclatures (including acronyms) exist for them, and (3) some common synthesis routes of different individual or groups of PFASs.

As PFASs are a chemical class with diverse molecular structures and physical, chemical and biological properties, it is highly recommended that such diversity be properly recognized and communicated in a clear, specific and descriptive manner. The term "PFASs" is a broad, general, non-specific term, which does not inform whether a compound is harmful or not, but only communicates that the compounds under this term share the same trait for having a fully fluorinated methyl or methylene carbon moiety. In particular, Chapter 3 provides practical guidance to governments and other stakeholders on how to use the PFAS terminology, starting from the distinction between the general definition and user-specific working scopes of PFASs. In particular, the general definition of PFASs is based on molecular structure alone and serves as a starting and reference point to guide individual users to have a comprehensive understanding of the PFAS universe and to keep the big picture of the PFAS universe in mind. At the same time, individual users may define their own working scope of PFASs for specific activities according to their specific needs by combining the general definition of PFASs with additional considerations (e.g. specific properties, use areas). This report does not make any recommendation on how working scopes should be set up, in terms of which factors to be considered (which depends highly on specific local context), nor on PFAS grouping. However, when a working scope of PFASs is used, this report highly recommends that users clearly provide the context and rationale for selecting their PFAS working scope in order to provide transparency and avoid confusion by others. Further, the report recommends to use and build upon existing common terminologies such as in this report, in Buck et al. (2011) and common practices in organic chemistry as set by IUPAC and CAS, unless it is essential to deviate from existing naming conventions, in order to keep the consistence and coherence of the PFAS terminology.

As users often define their own working scope of PFASs according to their specific needs, they need to characterize PFASs based on pre-defined traits and categorize them (e.g. whether a compound with certain traits falls or does not fall into their working scope). However, given the high complexity and diversity of PFASs, it can be a challenging task to characterize and categorize PFASs based on chemical structures in a coherent and consistent manner, particularly for non-experts. In addition, different users may have very different needs, and there is no single categorization/grouping system that can meet all needs. Therefore, Chapter 4 provides a standardized approach for systematic characterization of different PFASs based on molecular structural traits that will allow stakeholders to make their own categorization in a coherent and consistent manner. In addition to the manual application of the system to characterize and categorize PFASs, the elements presented here may also be used as inputs for developing cheminformatic tools that would allow automated characterization and categorization of PFASs.

While this report makes advancement on several important points regarding PFAS terminology and practical guidance of how to use the PFAS terminology, Chapter 5 also recognizes four areas that warrant further work, in order to facilitate clear and unambiguous communication of PFASs and

beyond: (1) a centralized PFAS nomenclature database/platform; (2) further development of cheminformatics-based tools for automated systematic characterizing and categorizing PFASs; (3) further work on the characterization and reporting of polymers; and (4) work on organofluorine compounds other than PFASs including many fluorinated aromatics.

List of Acronyms

ADONA	Ammonium 4,8-dioxa-3H-perfluorononanoate
Br	Bromine atom
CAS	Chemical Abstracts Service
CAS Nos.	Chemical Abstracts Service registry numbers
Cl	Chlorine atom
CTFE	Chlorotrifluoroethylene
ECHA	European Chemicals Agency
ETFE	Ethylene-tetrafluoroethylene copolymer
EU	European Union
FASAs	Perfluoroalkane sulfonamides
FASEs	Perfluoroalkane sulfonamidoethanols
FEP	Fluorinated ethylene propylene co-polymer
FPs	Fluoropolymers
FTABs	Fluorotelomer sulfonamide alkylbetaines
FTEOs	Fluorotelomer ethoxylates
FTIs	Fluorotelomer iodides
FT(MA)ACs	Fluorotelomer (meth)acrylates
FTOs	Fluorotelomer olefins
FTOHs	Fluorotelomer alcohols
FTSAs	Fluorotelomer sulfonic acids
HFCs	Hydrofluorocarbons
HFEs	Hydrofluoroethers
HFOs	Hydrofluoroolefins
HFP	Hexafluoropropylene
HFPO	Hexafluoropropylene oxide
HFPO-DA	Hexafluoropropylene oxide dimer acid
H	Hydrogen atom
I	Iodine atom
ICCM	International Conference on Chemicals Management
InChI	International chemical identifier
InChIKey	A hashed version of the full InChI
ITRC	Interstate Technology & Regulatory Council in the United States
IUPAC	International Union of Pure and Applied Chemistry
OBS	Sodium *p*-perfluorous noenoxybenzenesulfonate
OECD	Organisation for Economic Co-operation and Development
PACFs	Perfluoroalkanoyl fluorides

PASFs	Perfluoroalkane sulfonyl fluorides
PCTFE	Polychlorotrifluoroethylene
PFA	Perfluoroalkoxyl polymer
PFAAs	Perfluoroalkyl acids
PFAIs	Perfluoroalkyl iodides
PFASs	Per- and polyfluoroalkyl substances
PFCAs	Perfluoroalkyl carboxylic acids
PFdiCAs	Perfluoroalkyl dicarboxylic acids
PFdiSAs	Perfluoroalkane disulfonic acids
PFECAs	Perfluoroalkylether carboxylic acids
PFEI	Perfluoroethyl iodide
PFESAs	Perfluoroalkylether sulfonic acids
PFHxS	Perfluorohexane sulfonic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFPAs	Perfluoroalkyl phosphonic acids
PFPEs	Perfluoropolyethers
PFPIAs	Perfluoroalkyl phosphinic acids
PFSAs	Perfluoroalkane sulfonic acids
PFSIAs	Perfluoroalkane sulfinic acids
PolyFCAs	Polyfluoroalkyl carboxylic acids
PolyECAs	Polyfluoroalkylether carboxylic acids
PolyESAs	Polyfluoroalkylether sulfonic acids
POPs	Persistent Organic Pollutants
POSF	Perfluoroctane sulfonyl fluoride
PPVE	Perfluoropropylvinyl ether
PTFE	Polytetrafluoroethylene
PVDF	Polyvinylidene fluoride
PVF	Polyvinyl fluoride
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (EC 1907/2006)
SaMPAPs	Perfluorooctane sulfonamidoethanol phosphate esters
SFAs	Semifluorinated alkanes
SMILES	Simplified molecular input line entry specification
TFE	Tetrafluoroethylene
THV	Terpolymer of tetrafluoroethylene, hexafluoropropylene and vinylidene fluoride
UNEP	United Nations Environment Programme
VDF	Vinylidene fluoride

Table of contents

FIGURES

TABLES

1. Background, motivation and scope

The OECD/UNEP Global PFC[1] Group was established to respond to the Resolution II/5 adopted at the second session of the UN International Conference on Chemicals Management (ICCM 2) in 2009, which calls upon intergovernmental organizations, governments and other stakeholders to "consider the development, facilitation and promotion in an open, transparent and inclusive manner of national and international stewardship programmes and regulatory approaches to reduce emissions and the content of relevant perfluorinated chemicals of concern in products and to work toward global elimination, where appropriate and technically feasible". Further work on this resolution was reaffirmed in Resolution III/3 adopted at ICCM 3 in 2012 noting that a significant need remains for additional work to support implementation of Resolution II/5. This report is prepared within the framework of the Group. For more details on the Group and its work, see the OECD PFAS web portal (https://oe.cd/2M9).

This report summarizes recent efforts by the OECD/UNEP Global PFC Group between June 2018 and March 2021 in reviewing the universe and terminology of per- and polyfluoroalkyl substances (PFASs[2]) to provide recommendations and practical guidance to all stakeholders (governments, industry, academia, civil society organizations, etc.) regarding the terminology of PFASs. In particular, this report highlights (1) a revised PFAS definition to comprehensively reflect the universe of PFASs and a comprehensive overview of the PFAS universe (Chapter 2), (2) a practical guidance on how to use the PFAS terminology, from a general PFAS definition to user-specific working scopes to naming conventions of individual PFASs (Chapter 3), (3) a systematic approach to characterization of PFASs based on molecular structural traits to assist stakeholders, including non-experts, in making their own categorization based on their needs (Chapter 4), and (4) areas in relation to the PFAS terminology that warrant future work (Chapter 5). It should be noted that this report does not address the nomenclature and understanding of individual PFASs, including the sources of exposure and the actual composition of commercial products. It also does not address organofluorine compounds other than PFASs.

PFASs comprise a class of synthetic compounds that have attracted much public attention since the late 1990s and early 2000s, when the hazards and ubiquitous occurrence of two PFASs, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), started to be reported and recognized. Since then, research and risk management measures have expanded from these two PFASs to a wider range of PFASs [e.g. 3M's voluntary global phase-out of $C_{6–10}$ perfluoroalkane sulfonic acids (PFSAs), PFOA and related chemistries in 2000–2002]. It is noted that early communications

[1] "PFCs" here refer to "per- and polyfluorinated chemicals", and not to "perfluorocarbons". As stated below, "per- and polyfluorinated chemicals" was a term commonly used before the term "per- and polyfluoroalkyl substances" was recommended by Buck et al.. As it is part of the Group official name, it remains unchanged.

[2] This report uses the acronym "PFASs" for "per- and polyfluoroalkyl substances" as stated in Buck et al. (2011), and its corresponding singular form "PFAS" refers to either a perfluoroalkyl or polyfluoroalkyl substance. It is noted that there is a notion of using "PFAS" as the acronym for both the singular and plural forms. This report does not make any recommendation to address this notion, as it is a trivial point that is difficult for everyone to comprehend, particularly for non-PFAS experts and non-English native speakers. While recognizing that readers may make their own decision which acronym they would use, this report encourages readers to always use the acronym consistently in their documents (for more details on practice guidance on how to identify and use the PFAS terminology, see Section 3.2 below).

used many different terminologies (e.g. per- and polyfluorinated chemicals, perfluorinated organics, perfluorochemical surfactants, highly fluorinated compounds).

In 2011, to unify and harmonize communication on PFASs, Buck et al. published a milestone paper on a first comprehensive overview of PFASs detected in the environment, wildlife, and humans. It provided a first clear structural definition of PFASs. A particular emphasis of Buck et al. (2011) was placed on long-chain perfluoroalkyl acids [PFAAs, i.e., perfluoroalkyl carboxylic acids (PFCAs) with seven or more perfluorinated carbons and PFSAs with six or more perfluorinated carbons][3], substances related to the long-chain PFAAs, and substances intended as alternatives to the long-chain PFAAs or their precursors[4]. In addition, Buck et al. (2011) provided a list of 42 families and subfamilies[5] of PFASs and 268 selected individual compounds, including recommended names and acronyms, structural formulas, and Chemical Abstracts Service registry numbers (CAS Nos.).

Today, several long-chain PFAAs have been recognized as global contaminants of high concern. For example, PFOS, its salts, and perfluorooctane sulfonyl fluoride (POSF[6]), as well as PFOA, its salts, and PFOA-related compounds have been listed under the Stockholm Convention on Persistent Organic Pollutants (POPs) for global actions. In addition, the POPs Review Committee to the Stockholm Convention decided in 2019 to recommend that the Conference of the Parties to the Stockholm Convention consider listing perfluorohexane sulfonic acid (PFHxS, C_6 PFSA), its salts and PFHxS-related compounds at its tenth meeting. In response to these actions, an industrial transition has taken place to replace long-chain PFAAs and their precursors with alternative chemicals, many of which are still PFASs, including short-chain PFAAs and their precursors as well as perfluoroalkylether-based substances (for examples, see Buck et al., 2011, Wang et al., 2013, 2016 and references therein). It is noted that there is a growing interest by regulators[7] and scientists across the globe to assess legacy and novel PFASs other than long-chain PFAAs and their well-known precursors.

In particular, various efforts have been made to identify overlooked PFASs. In 2018, the OECD/UNEP Global PFC Group prepared a new list of PFASs[8] that may have been

[3] Note that the definition of "long-chain PFAAs" here is based on the OECD definition (https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/aboutpfass/), and the definitions of "long-chain PFAAs" may differ by jurisdiction.

[4] PFAA precursors refer to chemicals that can transform and form PFAAs in the environment and biota.

[5] Note that in the literature, some authors have used other taxonomy terminologies, e.g. "groups and subgroups" instead of "families and subfamilies". This report does not propose a new taxonomy terminology for PFASs, but makes some practical guidance on how to use taxonomy terminologies (see Chapter 3 below).

[6] Note that the acronym "POSF" here is used in accordance with the recommendations by Buck et al. (2011), whereas under the Stockholm Convention, another acronym "PFOSF" is used.

[7] For example, five European Union (EU) member states have agreed to prepare a joint REACH restriction proposal to limit the risks to the environment and human health from the manufacture and use of a wide range of PFASs, and thus launched a public call for evidence in May 2020 with regard to substances that contain at least one aliphatic $–CF_2–$ or $–CF_3$ element. For more details, see https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas. In addition, multiple PFASs other than long-chain PFAAs and their precursors are listed in ECHA's Public Activities Coordination Tool (PACT) to be assessed by ECHA or EU member states (https://echa.europa.eu/pact).

[8] The Excel Spreadsheet version of the OECD 2018 PFAS list can be found at https://www.oecd.org/chemicalsafety/risk-management/global-database-of-per-and-polyfluoroalkyl-substances.xlsx. In addition, several other entities have curated the OECD 2018 PFAS list into their databases, with features such as an easier overview of chemical structures and links to other information, including the US EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard/chemical_lists/PFASOECD),

on the global market using a systematic search of substances that have a $–C_nF_{2n}–$ ($n \geq 3$) or $–C_nF_{2n}OC_mF_{2m}–$ (n and $m \geq 1$) moiety in different publicly accessible sources. In total, a set of substances with over 4730 CAS Nos. have been identified, including substances that contain fully fluorinated carbon moieties and are structurally similar to or related to commonly known PFASs [e.g. perfluoroalkyl dicarboxylic acids (PFdiCAs) to PFCAs], but do not meet the PFAS definition in Buck et al. (2011) due to a lack of a $–CF_3$ group in the molecular structures (for more details, see Section 2.2). Meanwhile, recent advancement of non-target screening analytical techniques using high-resolution mass spectrometry has enabled identification of many unknown substances in different environmental and product samples [e.g. $H–(CF_2CH_2)_n–CF_2COOH$ by Newton et al. (2017)].

The identification of overlooked PFASs motivates the present work to reconcile the terminology of the universe of PFASs, including a renewed look at the PFAS definition in Buck et al. (2011) (see Chapter 2). In light of these newly identified substances and building on existing common terminology provided in Buck et al. (2011), this report and others, this report also looks into practical guidance on how to use the PFAS terminology, including uses of user-specific working scopes (see Chapter 3). In addition, the OECD 2018 PFAS List and recent non-target screening studies show the complexity and diversity of the PFAS universe, resulting in challenges for non-experts in conducting their own categorization of PFASs based on molecular structures. Therefore, this report also looks into systematic approaches to characterization and categorization of PFASs to assist stakeholders in making their own categorization based on their needs (see Chapter 4). Further, this report highlights open questions in relation to PFAS terminology for future consideration (see Chapter 5).

NORMAN Network (https://www.norman-network.com/?q=suspect-list-exchange) and PubChem (https://pubchem.ncbi.nlm.nih.gov/classification/#hid=101).

In addition, the US EPA CompTox Chemicals Dashboard also provides a number of other PFAS lists intended to address different research and regulatory interests, including PFASSTRUCT that is compiled from all the records with a structure assigned in the Dashboard using a pre-defined set of substructural filters and contains over 8000 compounds, as of 23 November, 2020 (for more details including the list of substructural filters, see https://comptox.epa.gov/dashboard/chemical_lists/PFASSTRUCT). Note that these lists may also include substances that are not regarded as PFASs in accordance with the revised PFAS definition below.

2. Reconciling Terminology of the Universe of PFASs

2.1. The previous PFAS definition in Buck et al. (2011)

In Buck et al. (2011), **PFASs** were defined as "the **highly fluorinated aliphatic substances** that contain **1 or more C atoms** on which all the H substituents (present in the nonfluorinated analogues from which they are notionally derived) have been replaced by F atoms, in such a manner that they contain the perfluoroalkyl moiety **C_nF_{2n+1}–**" (i.e. must contain at least $-CF_3$). The definition highlights the presence of at least one fully fluorinated saturated carbon atom in the PFAS molecules.

2.2. Gaps in the previous PFAS definition by Buck et al. (2011)

It is key to have a coherent and consistent logic behind the PFAS definition to reflect all compounds with shared structural traits, i.e. the PFAS universe. Building on the OECD 2018 PFAS List and recent non-target screening studies, this section identifies gaps in the previous PFAS definition by Buck et al. (2011) in representing the PFAS universe. Note that the gaps identified in this report are not exhaustive and additional gaps in the PFAS definition may be identified in the future; therefore, an iterative approach is guaranteed to ensure the consistency between the PFAS universe and terminology when new knowledge of gaps in the PFAS definition is generated.

Case 1: The fully fluorinated saturated carbon moiety[9] is connected with functional groups on both ends, including having a single H/Br/Cl atom on one end. As such, it does not meet the structural requirement of **"–C_nF_{2n+1}"** in the previous definition. In the example of a1 in Figure 1, it is a PFdiCA with a similar structure to PFCAs (e.g. PFOA in the example of A in Figure 1), but having carboxylic groups on both ends of the perfluoroalkanediyl moiety. In addition, for the example of a2 in Figure 1, it would meet the previous definition if the H atom was moved to a secondary carbon atom (i.e. $CF_3CFHCF_2CF_2CF_2CF_2COOH$, a positional isomer).

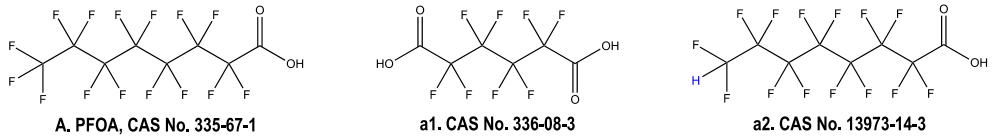


Figure 1. PFOA and examples of substances with similar molecular structures, but having functional groups (including single atoms such as hydrogen) on both ends of the perfluoroalkanediyl moiety.

Furthermore**,** functionalized fluoropolymers and perfluoropolyethers[10] (i.e. those that have functional groups on both ends of the polymer backbone, e.g. Fomblin HC/P2 1000[11]) do not meet the structural requirement of **"–C_nF_{2n+1}"** in the previous definition,

[9] Note that a "saturated carbon moiety" means no unsaturated bonds occurring in the moiety, including double bond (=), triple bond (≡) or aromatic rings, and thus, a saturated carbon moiety is always considered aliphatic.

[10] According to Buck et al., fluoropolymers are "*carbon-only* polymer backbone with F directly attached to backbone C atoms", whereas perfluoropolyethers are "*ether* polymer backbone with F atoms directly attached" (i.e. having –C–O–C– moieties on the polymer backbone).

[11] $(HO)_2(O)PO–(CH_2CH_2O)_n–CH_2CF_2–(OCF_2)_p–(OCF_2CF_2)_q–OCF_2CH_2–(OCH_2CH_2)_n–OP(O)(OH)_2$; Trier X, Granby K, Christensen JH. Polyfluorinated surfactants (PFS) in paper and board coatings for food packaging. *Environ Sci Pollut Res Int*. 2011;18(7):1108-1120. doi:10.1007/s11356-010-0439-3

whereas their closely related analogues with only fluorine atoms on each end of the polymer backbone would meet the previous definition.

Case 2: The substance is a fully fluorinated aliphatic cyclic compound which may or may not have a fully fluorinated alkyl side chain. As such, it may not meet the structural requirement of **"–C_nF_{2n+1}"** in the previous definition. For example, b1 in Figure 2 meets the previous definition, whereas its shorter-chain homologue, b2 in Figure 2, does not meet the previous definition.

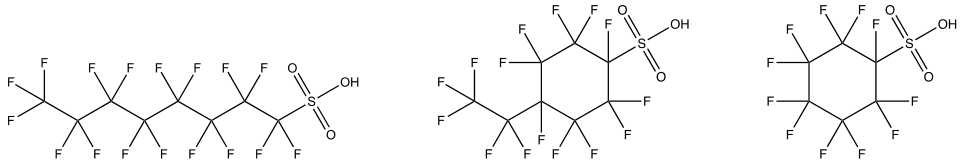


Figure 2. PFOS, an example of a cyclic PFSA, and a shorter-chain homologue of the cyclic PFSA

Case 3: The functional group contains an aromatic ring. Thus, it may not meet the term **"aliphatic substances**" in the previous definition, although the example of c1 in Figure 3 is a derivative of 6:2 fluorotelomer iodide, i.e. a 6:2 fluorotelomer-based compound.

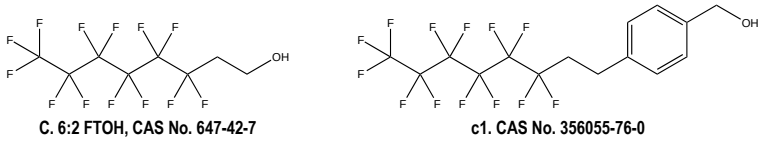


Figure 3. 6:2 FTOH, and a 6:2 fluorotelomer iodide derivative with one aromatic ring in the functional group

Case 4: The description "highly fluorinated" in the previous definition is an ambiguous, problematic term. It cannot and should not be literally translated to, e.g., the weight percentage of fluorine atoms in the molecules, using three 6:2 fluorotelomer-based compounds as an example (see Figure 4):

- $C_6F_{13}C_2H_4OH$ (6:2 FTOH; CAS No. 647-42-7) has a fluorine content of 67.8 wt%,
- $C_6F_{13}C_2H_4SO_2NHC_3H_6N(O)(CH_3)_2$ used in Forafac® 1183 (CAS No. 80475-32-7) has a fluorine content of 46.7 wt%, and
- 6:2 fluorotelomer ethoxylates [C_6F_{13}–$(CH_2CH_2O)_n$–H, n = 0–13] in a commercial product (Frömel and Knepper, 2010) would have even lower fluorine content when n>4.

But they are all 6:2 fluorotelomer-based compounds and may act as precursors to perfluorohexanoic acid (PFHxA) in the environment and biota.

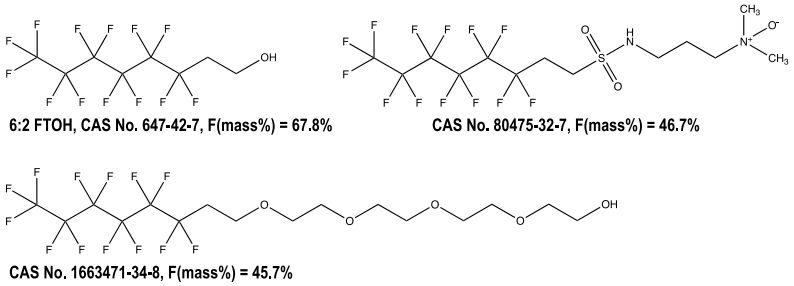


Figure 4. 6:2 FTOH and two 6:2 fluorotelomer derivatives, and their corresponding fluorine contents

2.3. A revised PFAS definition

Therefore, there is a need to revisit the previous definition in Buck et al. (2011) to address these gaps (i.e. the previous definition was not comprehensive enough and contained ambiguous descriptions). A clear distinction of the logical relationship needs to be made here: the intention of the revision of the PFAS definition is not to expand the PFAS universe, but to comprehensively reflect it. More concretely, the rationale behind the revision is to have a general PFAS definition that is coherent and consistent across compounds from the chemical structure point of view and is easily implementable for distinguishing between PFASs and non-PFASs, also by non-experts.

This revised PFAS definition reads,

PFASs are defined as fluorinated substances that contain at least one **fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I 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**.**

Both a perfluorinated methyl group and a perfluorinated methylene group are saturated and aliphatic. Note that the carbon in a $R–CF_2–O–$ or $R–CF_2–Si–$ group ($R \neq H/Cl/Br/I$) is a perfluorinated methylene carbon. A perfluorinated methylene group may also be represented as "$>CF_2$", where ">" denotes two single bonds. A fully fluorinated carbon that is bound to the rest of the molecule by a double bond is a perfluorinated methyl*idene* carbon atom ($=CF_2$). This distinction is important. Further, a perfluorinated methine carbon moiety ($>CF–$) alone does not meet this revised PFAS definition.

It should be noted that this general PFAS definition is based only on chemical structure, and the decision to broaden this definition compared to Buck et al. (2011) is not connected to decisions on how PFASs should be grouped and managed in regulatory and voluntary actions. For further practical guidance on how to use this general PFAS definition, see Section 3.1.

Figure 5 illustrates substances that are PFASs, and Figure 6 shows those that are not PFASs. Note that tetrafluoroethylene (TFE, CAS No. 116-14-3, $CF_2=CF_2$) is not a PFAS as both fully fluorinated carbon atoms are unsaturated; its longer-chain homologue hexafluoropropylene (HFP, CAS No. 116-15-4, $CF_2=CF–CF_3$) is a PFAS due to the presence of a fully fluorinated methyl carbon atom ($–CF_3$).

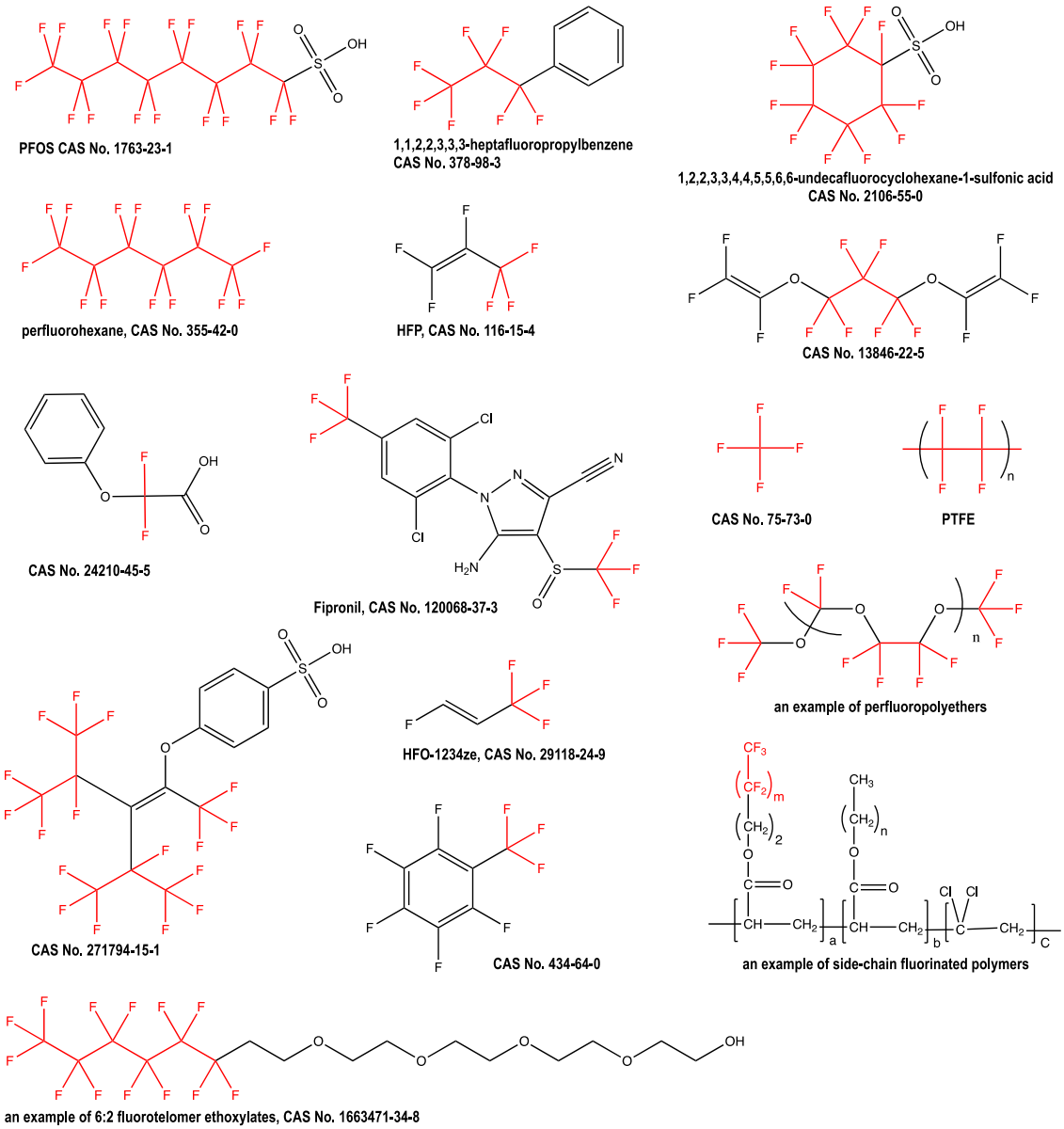


Figure 5. Examples of PFASs. The fully fluorinated methyl or methylene carbon atoms are highlighted in red.

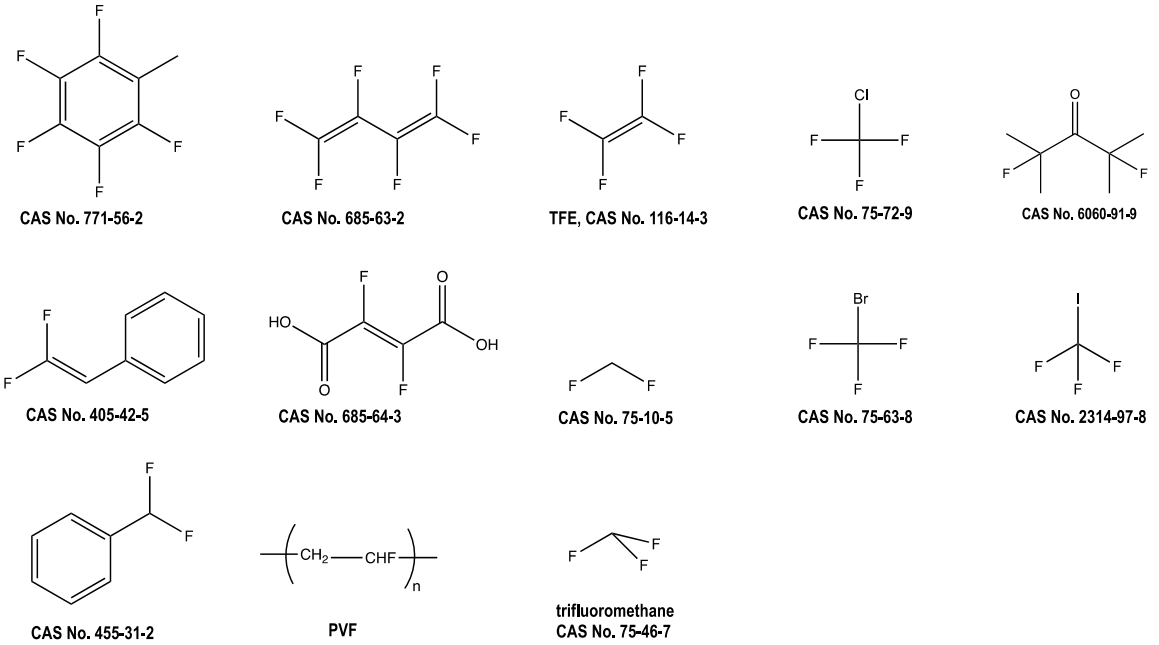


Figure 6. Examples of compounds that are not PFASs due to a lack of fully fluorinated methyl or methylene carbon atoms.

The rationale for making such changes is detailed as follows.

- **Change from "highly fluorinated aliphatic substances" to "fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it)":**

  First, the qualifier "highly" is removed from the definition, as it is not meaningful when the fluorinated carbon chain can cleave from the substance to produce a new molecule that is more highly fluorinated [see Section II in FOEN (2017) and references therein].

  Second, the term "aliphatic" is removed from the definition. As shown in Case 3 in Figure 3, aromatic ring(s) may be present as a part of the functional group connecting to a fully fluorinated methyl or methylene carbon moiety. Using the previous definition by Buck et al. (2011), such compounds would not be recognized as PFASs, whereas compounds with similar structures but without aromatic ring(s) are recognized as PFASs. This may easily create confusion as to when a substance is or is not a PFAS, particularly for non-experts. The change of wording here is also to make the definition more straightforward. At the same time, the new wording "substances that contain at least one fully fluorinated methyl or methylene carbon atom" means that this revised definition is still constrained to the key trait of having an aliphatic fully fluorinated saturated carbon moiety and excluding those fluorinated aromatics that only have fluorine directly attached to the aromatic rings. Overall, this revised definition includes side-chain fluorinated aromatics [i.e. aromatics that have one or more aliphatic fully fluorinated saturated carbon moiety on the side chain(s) attached to the aromatic ring(s), an analogy to "side-chain fluorinated polymers"[12] as in Buck et al. 2011] as PFASs; for examples, see c1 in Figure 3 and Figure 7 below.

[12] In Buck et al. (2011), side-chain fluorinated polymers are defined as "nonfluorinated polymer backbone with fluorinated side chains".

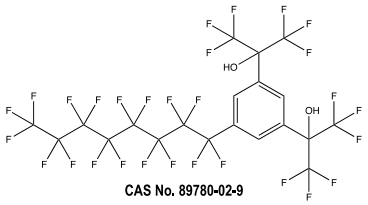


Figure 7. An example of side-chain fluorinated aromatics.

- **Change from "the perfluoroalkyl moiety C_nF_{2n+1}–" to "at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it)":**

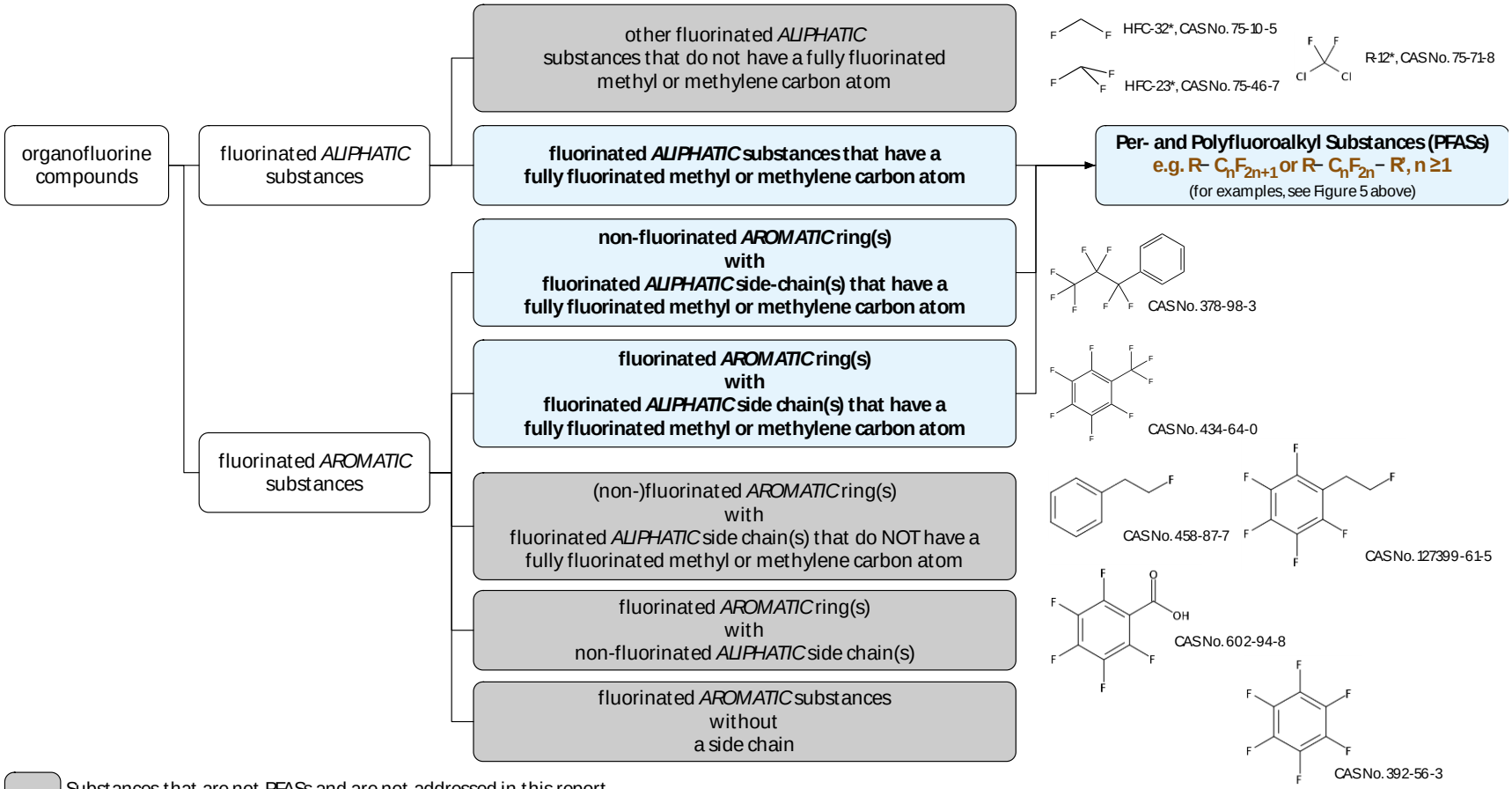
  This change is to accommodate those that have functional groups on both ends of the fully fluorinated saturated carbon moieties (Case 1) and those that have cyclic structure(s) at the end of the fully fluorinated saturated carbon moieties (Case 2).

  In addition, two more specific descriptions are made here to make the definition clearer. First, the term "methyl or methylene carbon atom" is added to describe the fully fluorinated saturated carbon moiety, which was not clear from the description "that contain only 1 or more C atoms on which all the H substituents … have been replaced by F atoms", but only implicitly mentioned in the description "in such a manner that they contain the perfluoroalkyl moiety C_nF_{2n+1}–". Second, adding "without any H/Cl/Br/I atom attached to it" highlights that the carbon atom is considered non-fully fluorinated, when a H/Cl/Br/I atom is attached to it.

2.4. A comprehensive overview of the PFAS universe

Based on this revised definition of PFASs, a first scheme can be drawn to illustrate how PFASs fit into organofluorine compounds (see Figure 8). It can be seen that besides PFASs, there are many other organofluorine compounds, including (1) fluorinated aliphatic substances that do not have a fully fluorinated methyl or methylene carbon atom [e.g. trifluoromethane (HFC-23) and difluoromethane (HFC-32)], (2) fluorinated aromatic substances with no side chain(s) (e.g. hexafluorobenzene, CAS No. 392-56-3), and (3) fluorinated aromatic substances with non-fluorinated side chain(s) (e.g. pentafluorobenzoic acid, CAS No. 602-94-8). These other organofluorine compounds are beyond the scope of this report, and future work on them is encouraged.

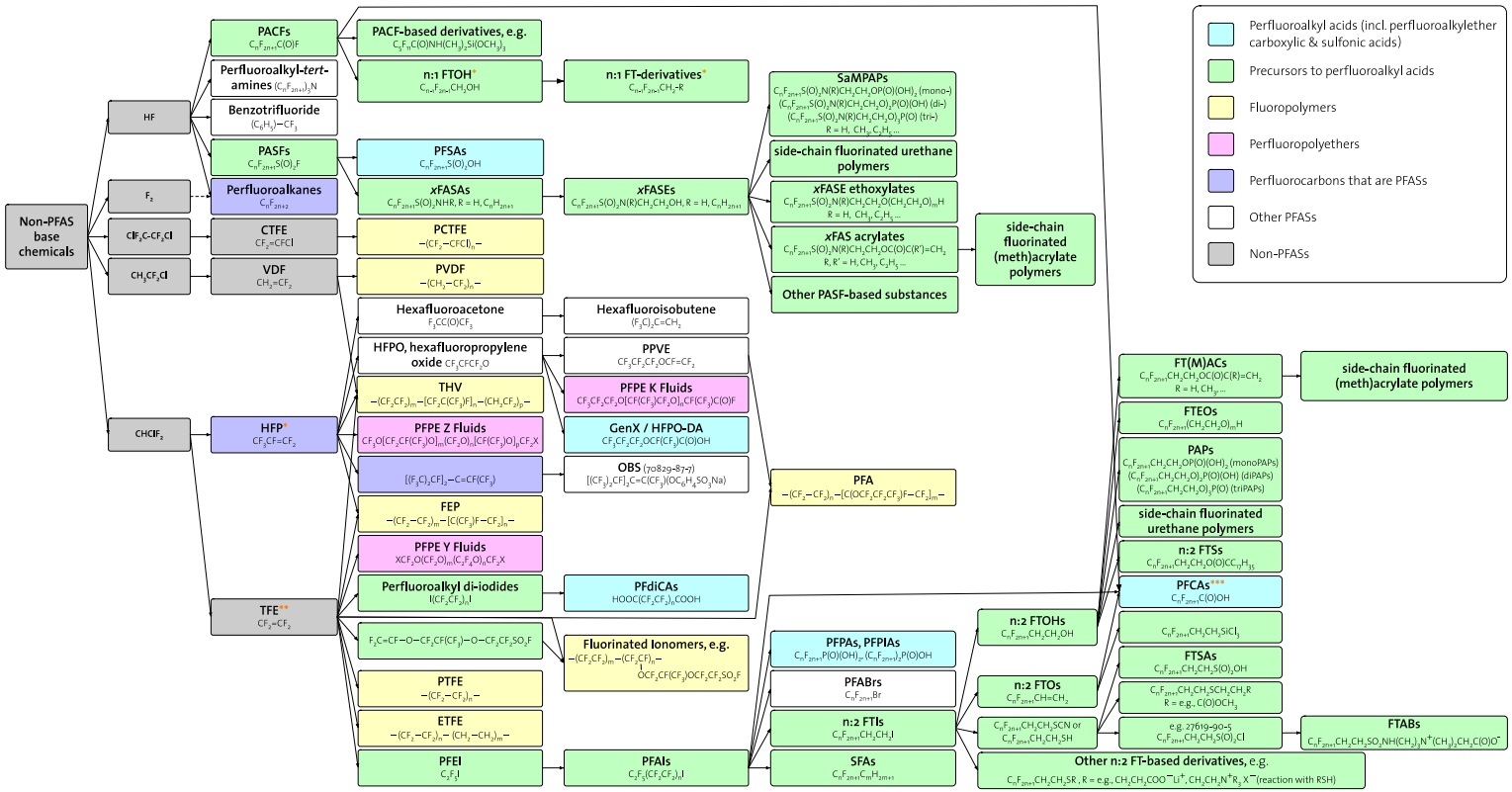
Looking at the PFAS universe, it is a highly complex chemical class with compounds having diverse functional groups attached to the fully fluorinated saturated carbon moiety/-ies. Figure 9 provides a comprehensive overview of PFAS groups, their structural traits, examples and notes on whether common nomenclatures (including acronyms) exist for them, building on Buck et al. (2011) and the OECD 2018 List. Figure 10 illustrates some common synthesis routes of different individual or groups of PFASs based on publicly accessible sources. It should be noted that, while Figures 9 and 10 aim to be comprehensive, they are by no means exhaustive. For more information on individual PFAS groups (e.g. major compounds in the group, synthesis routes, major uses, regulatory status, environmental occurrence, etc.), readers may consult the PFAS Fact Cards published on the OECD PFAS Web portal: https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/.



* HFC-32, HFC-23 and R-12 are not PFASs, despite the presence of moieties such as $-CF_2-$ or $-CF_3$, because not all H on the fluorinated carbon atom are replaced by F, i.e., they do not have a fully fluorinated carbon atom.

Figure 8. An illustrative scheme of how PFASs fit into the universe of organofluorine compounds

Figure 9. A comprehensive overview of PFAS groups, their structural traits, examples and notes on whether corresponding common nomenclatures (including acronyms) exist.



* Strictly speaking, these substances are not fluorotelomers, as they are not derived from the telomerization process. Despite this, they are termed here "n:1 fluorotelomer-based" substances for readability. Future work may consider to identify more proper terminology for this group of PFASs.
** Note that for many compounds such as HFP and TFE, there are different synthesis routes with different starting materials, and here shows only one of them.
*** Note that there are three synthesis routes shown here for manufacturing of PFCAs, from PACFs, PFAIs and n:2 FTIs. Note that different synthesis routes may generate PFCAs with different perfluorocarbon chain lengths.

Sources: (1) Siegemund G, Schwertfeger W, Feiring A, Smart B, Behr F, Vogel H, McKusick B. *Fluorine Compounds, Organic*, 3rd ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2000; Vol. 33. (2) Banks RE, Smart BE, Tatlow JC. Organofluorine Chemistry: Principles and Commercial Applications. New York: Plenum, 1994. (3) Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, De Voogt P, Jensen AA, Kannan K, Mabury SA, van Leeuwen SPJ. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. *Integr Environ Assess Manag* **2011**, 7 (4), 513–541. (4) Wang Z, Cousins IT, Scheringer M, Buck RC, Hungerbühler K. Global emission inventories for C4-C14 perfluoroalkyl carboxylic acid (PFCA) homologues from 1951 to 2030, Part I: production and emissions from quantifiable sources. *Environ Int* **2014**, 70, 62–75. (5) Moffett RH, Howell JL, Hoerter JM, Shtarov AB, Jannerfeldt G, Johnston SB, Keenan J, Warriner C, Closser DM. *Perfluoroalkylpolyethers* in *Synthetics, Mineral Oils, and Bio-Based Lubricants: Chemistry and Technology* (third edition), Edited by Rudnick LR. 2020. CRC Press. ISBN: 978-1-138-06821-6. (6) Grot W. *Fluorinated Ionomers*. William Andrew 2011. ISBN: 978-1-437-74457-6.

Figure 10. An overview of some common synthesis routes of different individual or groups of PFASs based on publicly accessible source

3. Practical Guidance on How to Use the PFAS Terminology

As shown above, PFASs are a chemical class with diverse molecular structures (e.g. neutral, anionic, cationic or zwitterionic; with or without aromatic rings; non-polymers or polymers; low molecular weight or high molecular weight) and thus diverse physical, chemical and biological properties (e.g. involatile or volatile; water soluble or water insoluble; reactive vs. inert; bioaccumulative or non-bioaccumulative). Therefore, it is highly recommended that such diversity be properly recognized and communicated in a clear, specific and descriptive manner. The following sections aim to provide practical guidance to governments and other stakeholders on how to use the PFAS terminology, starting from the distinction between the general definition described here and user-specific working scopes of PFASs. An overarching rationale behind the practical guidance is to use and build upon existing common terminologies such as in this report, in Buck et al. (2011) and common practices in organic chemistry as set by IUPAC and CAS, unless it is essential to deviate from existing naming conventions in order to keep the consistence and coherence of the PFAS terminology.

3.1. Distinction between the General Definition and User-Specific Working Scopes of PFASs

It should be noted that the revised definition of PFASs in Section 2.3 refers to a general definition of PFASs that is coherent and consistent across compounds based on chemical structure and is easily implementable for distinguishing between PFASs and non-PFASs, also by non-experts. It does not include any minimal or maximal chain length requirements, or any other considerations beyond chemistry. It also does not conclude that all PFASs have the same properties, uses, exposure and risks.

While this general definition of PFASs may be viewed as too broad, encompassing thousands or more compounds, for anyone to address all of them at once, it serves as a starting and reference point to guide individual users to have a comprehensive understanding of the PFAS universe and to keep the big picture of the PFAS universe in mind. At the same time, individual users may define their own PFAS working scope for a specific activity according to their specific needs by combining this general definition of PFASs with additional considerations (e.g. specific properties, use areas). For example, the US Interstate Technology & Regulatory Council (ITRC)[13] used a working scope of "C_nF_{2n+1}" (n>2) in making its own PFAS fact sheets. Another example is the working scope used in compiling the OECD 2018 PFAS List, namely $–C_nF_{2n}–$ (n ≥3) and $–C_nF_{2n}OC_mF_{2m}–$ (n and m ≥1). Also, the addition of criteria such as bioavailability and persistence in Gore Fabrics' Goal and Roadmap[14] for Eliminating PFCs of Environmental Concern may be regarded as a way of setting working scopes.

This report does not make any recommendation on how a working scope should be set up regarding which factors to consider (which depend on specific local context)[15], nor

[13] The latest version of the fact sheet on naming conventions of PFASs is from April 2020: https://pfas-1.itrcweb.org/fact_sheets_page/PFAS_Fact_Sheet_Naming_Conventions_April2020.pdf

[14] Here it refers to the version published on January 31, 2017, which can be found at: https://drive.google.com/file/d/0BxvQ_I44P_9eeTlwYUJCekhLNlE/view

[15] Future work compiling various existing practices of defining working scope under different context may be beneficial to provide further guidance to governments and other stakeholders on this matter.

on PFAS grouping[16]. However, when a working scope of PFASs is used, this report highly recommends that users clearly provide the context and rationale for selecting their PFAS working scope in order to provide transparency and avoid confusion by others.

3.2. Practical guidance on how to identify and use suitable PFAS terms

The term "PFASs" does not inform whether a compound is harmful or not, but only communicates that the compounds under this term share the same trait for having a fully fluorinated methyl or methylene carbon moiety. In addition, particularly for PFASs without an assigned CAS No., a lot of parallel and often non-intuitive acronyms are employed, potentially prohibiting effective communication and creating barriers for synthesizing knowledge. This section aims to provide practical guidance on how to identify and use suitable terms to foster communication around PFASs with the aim of being accurate, precise, understandable by others, and consistent.

First, it is strongly recommended that the PFAS terminology be used in a clear, specific and descriptive manner. It should be noted that "PFASs" is a broad, general, non-specific term, which should only be used when talking about all the substances included in the PFAS definition described here (or the user should clearly define the scope of which substances are being referred to as PFASs in the documents they prepare). Otherwise, it would introduce ambiguity and even factual error in the statements (as occurred sometimes in past literature). For example, not all PFASs are surfactants, and thus, a statement "PFASs are surfactants" is factually inaccurate. Table 1 highlights examples of ambiguous statements, which when are overgeneralized may lead to ambiguity, and factual inaccuracies and miscommunication in some cases. Therefore, it is recommended that users always ask the following two questions when drafting a statement: (1) Am I referring to all PFASs or not? (2) If not, what term(s) would mostly clearly describe the substance(s) that my statement is referring to? There could be multiple ways by users to locate the right levels of terms that are clear, specific and descriptive for specific statements, by combining and ordering traits such as polymeric vs. non-polymeric, PFAAs vs. PFAA precursors, or side-chain fluorinated polymers vs. fluoropolymers vs. perfluoropolyethers. Figure 11 shows different levels of PFAS terms and their respective characteristics in terms of clarity and specificity, along with examples; one may either start from Level 1 (most general) and move downwards (with the question of whether it is specific enough), or Level 5 (most specific) and move upwards (with the question of whether it can be further generalized), to locate the right level of terms for a specific statement. Table 1 also includes examples of good practice to refine ambiguous statements using more suitable terms. Furthermore, individual PFASs need to be named in a clear, specific and descriptive manner.

[16] In a recent scientific article, various grouping strategies for PFASs were reviewed and the motivations, advantages and disadvantages for each approach were discussed; for more details, see Cousins et al. 2020. *Environmental Science: Processes & Impacts*, 22, 1444–1460, https://doi.org/10.1039/D0EM00147C

Table 1. Examples of ambiguous statements and associated good practices of using more specific PFAS terminology to refine these statements

Examples of ambiguous statements (which may also result in factual inaccuracy in some cases)	**Examples of good practices of using the PFAS terminology to avoid errors and reduce ambiguity**	
	(1) Using more specific PFAS terms	**(2) Adding qualifiers (less favorable than (1), as it remains quite ambiguous)**
PFASs were investigated in human milk.	**C_4–C_{14} PFCAs** were investigated in human milk.	**15 non-polymeric** PFASs were investigated in human milk.
PFASs are used to make protective coatings on common household products.	**Fluorotelomer-based side-chain fluorinated polymers** are used to make protective coatings on common household products.	**A number of polymeric** PFASs are used to make protective coatings on common household products.
PFASs are relatively ubiquitous in the environment at low concentrations. (factually inaccurate)	**PFCAs** are relatively ubiquitous in the environment at low concentrations.	**A number of** PFASs are relatively ubiquitous in the environment at low concentrations.
PFASs are water repellent, oil, grease and dirt repellent surfactants. (factually inaccurate)	**Many perfluorooctane sulfonyl fluoride-based derivatives** are water-, as well as oil-, grease- and dirt-repellent surfactants.	**A number of** PFASs are water-, as well as oil-, grease- and dirt-repellent surfactants.

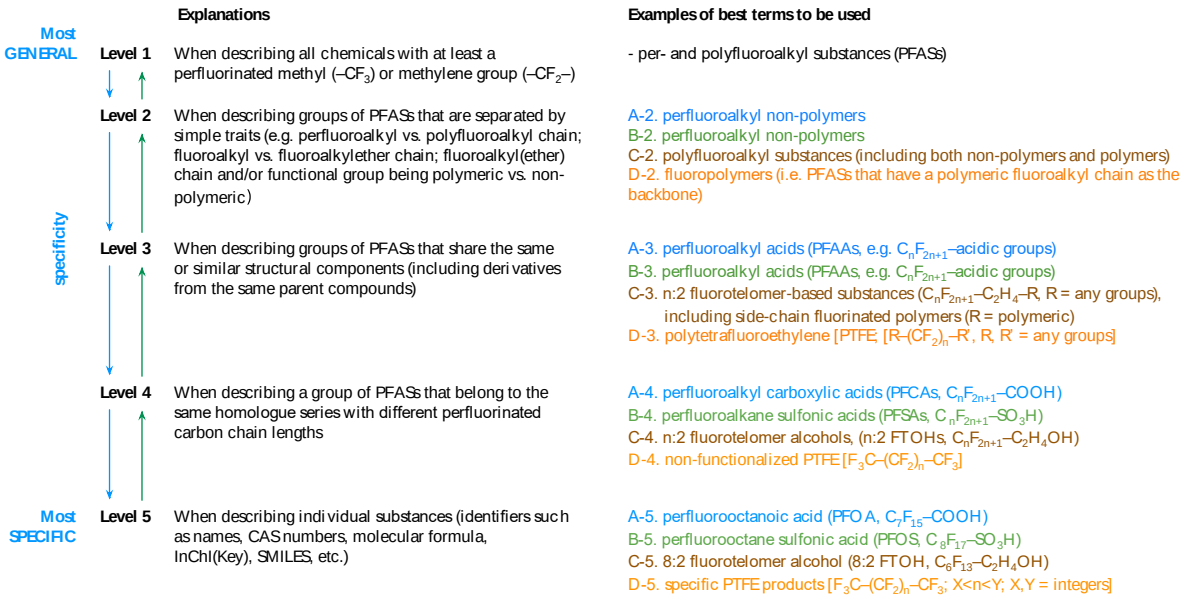


Figure 11. A visual guide to identify the best terms to use for a specific statement with four examples (increasing level of specificity illustrated with same colour within examples).

Second, if users are not sure about how to name a specific compound, it is recommended to first check whether a common nomenclature (including a common acronym) already exists, e.g., in Buck et al. (2011), Barzen-Hanson et al. (2017)[17], this report and other studies, before creating their own naming conventions. For example, for CAS No. 678-39-7, a common name "8:2 fluorotelomer alcohol" and a common acronym "8:2 FTOH" already exist, and should be used instead of other synonyms.

[17] In the Supporting Information, Barzen-Hanson et al. developed a simplified, manual IUPAC-based naming system for the PFASs that they identified in their non-target screening. For more details, see Barzen-Hanson et al. 2017. *Environmental Science & Technology*. 51(4), 2047–2057. https://doi.org/10.1021/acs.est.6b05843

Third, acronyms are often necessary in communicating PFASs to avoid writing very long names all the time; however, the same acronym may refer to different full names or different forms of the same substance (e.g. the parent acid, the anion form, and various salt forms), depending on context and personal understanding. To avoid confusion, it is recommended that acronyms be spelled out when being mentioned for the first time in the text and used consistently throughout the text.

Fourth, while chemical names and associated acronyms are the most common chemical identifiers being used, it is also recommended that other more specific identifiers such as CAS No., SMILES (simplified molecular input line entry specification), InChI (international chemical identifier), InChIkey (a hashed version of the full InChI) and/or structural formula[18] are provided for possibilities of cross-checking. This may also be useful in reporting the chemical identities of PFASs that have been registered as substances of unknown or variable composition, complex reaction products, or biological materials (UVCBs, e.g., CAS No. 69991-67-9 = 1-propene, 1,1,2,3,3,3-hexafluoro-oxidized, polymd.)[8].

[18] These identifiers may be found and verified using online databases, such as the CAS Common Chemistry (https://commonchemistry.cas.org), ChemSpider (http://www.chemspider.com), NORMAN Suspect List Exchange (https://www.norman-network.com/?q=suspect-list-exchange), OECD eChemPortal (https://www.echemportal.org/echemportal/), PubChem (https://pubchem.ncbi.nlm.nih.gov/classification/#hid=101), SciFinder (http://scifinder.cas.org) and US EPA CompTox Chemicals Dashboard (https://comptox.epa.gov/dashboard/chemical_lists/PFASOECD).

4. Systematic characterization and categorization of PFASs

As users often define their own working scope of PFASs according to their specific needs (see Section 3.1), they need to characterize PFASs based on molecular structures (and other considerations) and then categorize them by comparing characterization traits against specific needs (e.g. whether a compound falls or does not fall into their working scope). For example, the recent listing of PFOA and PFOA-related compounds under the Stockholm Convention requires regulators across the world to be able to identify PFOA-related compounds from a pool of PFASs.

However, given the high complexity and diversity of PFASs, it can be a challenging task to characterize and categorize PFASs based on their chemical structures in a coherent and consistent manner, particularly for non-experts. Detailed challenges may include needs of specialized chemistry knowledge (e.g. on transformation), different interpretations of structural traits by users for different groups of PFASs, and potential for human errors including oversights and typing errors (Sha et al. 2019). In addition, different users may have very different needs, and there is no single categorization/grouping system that can meet all needs.

Therefore, this section provides a standardized system for systematic characterization of different PFASs based on molecular structural traits that will allow stakeholders to make their own categorization in a coherent and consistent manner. Molecular structure-based elements of such a characterization system are provided in Table 2, with some examples of applications given in Table 3. For example, if someone would like to have the grouping of linear PFCAs, they would just need to search for molecules with the right characterization traits as defined in Table 3: under "fluorinated carbon chain (A)", having "alkyl", "perfluoro", "linear", "saturated", "non-polymeric"; under "functional group B", having "COOH" and "non-polymeric"; and under "stoichiometry between A and B", having "1:1". The system is flexible for future refinement including possible addition of new elements as needed and also applications to new groups of PFASs as identified.

In addition to manual application of the system to characterize and categorize PFASs, the elements presented here may also be used as inputs for developing cheminformatic tools that would allow automatized characterization and categorization of PFASs, as demonstrated in Sha et al. (2019).

In that study, an algorithm was developed to systematically parse a PFAS molecule into three fragments namely C_nF_{2n+1}–X–R, where C_nF_{2n+1}– refers to the fluorinated carbon moiety and –X–R refers to functional group moiety. X was used to identify whether a PFAS molecule falls into the target group of perfluoroalkane sulfonyl fluoride-derivatives (where X = SO_2), perfluoroalkanoyl fluoride derivatives (where X = CO), n:1 fluorotelomer-based compounds (where X = CH_2 and R does not have a CH_2 or CH moiety connecting with X), or n:2 fluorotelomer-based compounds (where X = CH_2CH_2). The algorithm was applied to a set of 770 PFASs from the OECD 2018 PFAS List and identified PFASs from the target four groups as intended. The algorithm was also able to identify PFASs that were mis-categorized in the OECD 2018 PFAS List, as the original categorization was done manually.

The algorithm developed in Sha et al. (2019) serves as a proof-of-concept, and thus has its limitations in terms of its purpose (i.e. to identify whether a PFAS falls into one of the four target groups) and function (e.g. it cannot handle PFASs with more than one

functional group moieties). However, it shows the potential of such cheminformatics approaches, which can be expanded using the elements provided here for systematic characterization and categorization of PFASs in a coherent and consist manner, particularly for non-PFAS experts. It needs to be noted that tools proposed here that integrate the concept presented in Sha et al. (2019) and the proposed elements of a characterization system is one way of developing cheminformatics-based tools for systematic characterization and categorization of PFASs. Depending on the needs, there may also be other ways of doing so, including adding other elements into consideration (e.g. a ToxPrints approach that also considers structures related to adverse outcomes[19]) or implementing in other ways (e.g. using Markush structures to annotate existing lists[20]). An outlook of future developments is provided in the next section.

Table 2. Molecular structure-based elements of a characterization system for PFASs.

PFASs may be parsed into the following two structural parts	Molecular structure-based elements to be considered	Note
Fluorinated carbon chain (A)	alkyl vs. alkylether	Whether the fluorinated carbon chain is carbon only or has oxygen-linkage(s) between fluorinated carbons e.g., $–C_nF_{2n}–$ vs. $–C_nF_{2n}–O–C_mF_{2m}–$
	perfluoro vs. polyfluoro	Whether all hydrogen on the fluorinated carbon chain are replaced by fluorine (i.e. perfluoro) or not (i.e. polyfluoro) e.g., $H–C_2F_4–$, $Cl–C_2F_4–$, $CF_3CF_2–C_2H_4–C_2F_4–C_2H_4–$, $CF_3CF_2–CH_2–CF_2–CH_2–CF_2–$, etc. = polyfluoro
	linear vs. branched vs. cyclic	Whether the fluorinated carbon chain is linear, branched or cyclic e.g., $–C_6F_{13}$ vs. $–C_3F_6CF(CF_3)_2$ vs. $–cyclo(C_6F_{12})$
	saturated vs. non-saturated	Whether there is any unsaturated bond (a double or triple bond) in the fluorinated carbon chain e.g., $–CF_2CF_2-$ vs. $–CF=CF–$

[19] For an example, see https://figshare.com/articles/presentation/PFAS_Toxprints_A_Hierarchical_Structure-Based_Categorization_Method_for_Characterization_of_Per-_and_Polyfluoroalkyl_Substances/12834329. Currently, the US EPA is preparing a manuscript on this approach, including means for applying it.

[20] A Markush structure is a generic type of description of chemicals used to summarize a potentially very large set of closely related chemicals in a single condensed representation. It may consist of a "core" chemical structure and a list of possible substituents attached to it, with four substituent options: substituent variation (allowing different substituents at a position), position variation (allowing different attachment points for a substituent), frequency variation (allowing substituents to occur multiple times) and homology variation (using generic expressions covering many specific substituents like "alkyl"). For more details, see, e.g., Geyer P. 2013. *World Patent Information*, 35(3), 178–182, https://doi.org/10.1016/j.wpi.2013.05.022.

The US EPA CompTox Chemicals Dashboard uses "Markush structures" to organize its PFAS list. In brief, the Dashboard has curated 112 PFAS Markush structures with unique DTXSIDs assigned (e.g. DTXSID80893896 $HOOC–(CF_2)_n–COOH$ for perfluoroalkyl (linear) dicarboxylic acids, i.e. homology variation). Each PFAS Markush structure is considered a generalized substance or "parent ID" that can be associated with one or many "child IDs" within the Dashboard (e.g. DTXSID80893896 are linked to 12 linear perfluoroalkyl dicarboxylic acids with different fluorinated carbon chain lengths in the Dashboard). For more details, see https://comptox.epa.gov/dashboard/chemical_lists/EPAPFASCAT.

	polymeric vs. non-polymeric	Whether the fluorinated carbon chain is polymeric or non-polymeric e.g. using the OECD definition (http://www.oecd.org/env/ehs/oecddefinitionofpolymer.htm) [Note: this may require additional consideration, e.g. whether a minimum perfluorocarbon moiety chain length of 20 would be required][21]
	chain length of the fluorinated carbon chain	e.g., for perfluoroalkylether-based substances, the total length of perfluoroalkylether moieties including both carbon and oxygen atoms will be counted, and additional information on the number of oxygen atoms will be provided as supplementary information, similarly to what is in the OECD 2018 list.
Functional group (B)	types and structures of functional groups	As there is no common classification system of functional groups, here a simplified scheme is proposed that is intended to distinguish those reactive and non-reactive (or those not so reactive) groups under natural conditions, which can be used to differentiate e.g. PFAAs and PFAA precursors. 1. Non-reactive groups (or those not so reactive) 1.1. H, Cl, Br 1.2. N, P 1.3. COOH 1.4. SO_3H 1.5. PO_3H_2 2. Reactive groups 2.1. I 2.2. SO_2H – sulfinic acids 2.3. PO_2H 2.4. CH_2–R – possibly n:1 fluorotelomers 2.5. CH_2CH_2–R – possibly n:2 fluorotelomers 2.6. CO–R (other than COOH) – alkanoyl fluoride-derivatives 2.7. SO_2–R (other than SO_2OH) – sulfonyl fluoride-derivatives 2.8. C_mH_{2m+1}, OC_mH_{2m+1}, C_mH_{2m-1} 3. Others (which may be refined in future work)
	polymeric vs. non-polymeric	Whether the non-fluorinated functional group is polymeric or non-polymeric, e.g. using the OECD definition (http://www.oecd.org/env/ehs/oecddefinitionofpolymer.htm) [Note: this may require additional consideration of additional qualifier, e.g. whether a minimum chain length of 20 would be required]
stoichiometry between A and B	How are fluorinated carbon chain(s) connected with non-fluorinated carbon chain(s)/functional groups?	1:0 = no functional group
		1:1/1:2/1:3 = one fluorinated carbon chain connected with 1/2/3 functional group(s)
		2:1 = two fluorinated carbon chains connected with one functional group, e.g. PFPIAs

[21] In many jurisdictions, a polymer is defined as a substance that has over 50 percent of the weight consisting of polymer molecules and the amount of polymer molecules presenting the same molecular weight must be less than 50 weight percent of the substance. A polymer molecule is defined as a molecule that contains a sequence of at least 3 monomer units, which are covalently bound to at least one other monomer unit or other reactant. Thus, a mixture of 8:2, 10:2 and 12:2 fluorotelomers (each 33%) can theoretically be regarded as a polymer.

Table 3. Examples using the proposed characterization system.

	Possible elements to be considered	Example 1: Linear PFCAs	Example 2: PFOA precursors	Example 3: ADONA	Example 4: 6:2 FT-acrylate polymer	Example 5: PTFE with –COOH on each end
Fluorinated carbon chain (A)	alkyl vs. alkylether	Alkyl	Alkyl	Alkylether	Alkyl	Alkyl
	perfluoro vs. polyfluoro	Perfluoro	Perfluoro	Polyfluoro	Perfluoro	Perfluoro
	linear vs. branched vs. cyclic	Linear	Linear + Branched	Linear	Linear	Linear
	saturated vs. non-saturated	Saturated	Saturated	Saturated	Saturated	Saturated
	polymeric vs. non-polymeric	Non-polymeric	Non-polymeric	Non-polymeric	Non-polymeric	Polymeric
	chain length	1–20	>=7 (in the case of when A and B connects via a carbon atom); >=8 (in the case of when A and B connects via other atoms other than a carbon atom)	6 + 2O	6	XX
Non-fluorinated functional group (B)	types and structures of functional groups	1.3 COOH	2 Reactive groups	1.3 COOH	2.5 CH_2CH_2–R – possibly n:2 fluorotelomers	1.3 COOH
	polymeric vs. non-polymeric	Non-polymeric	Non-polymeric; polymeric	Non-polymeric	Polymeric	Non-polymeric
Connection between A and B	How are fluorinated carbon chain(s) connected with non-fluorinated carbon chain(s)?	1:1	1:1	1:1	n:1	1:2

5. Areas for Future Work

While this report makes advancement on several important points regarding the PFAS terminology and practical guidance of how to use the PFAS terminology, it also recognizes that the following four areas warrant further work within the field of PFASs (i.e. areas one and two) and beyond (i.e. areas three and four), in order to facilitate clear and unambiguous communication of PFASs.

First, a centralized PFAS nomenclature database/platform may be considered. With the further advancement and application of non-target screening methods, many more unknown PFASs are expected to be discovered in the future. Such a centralized nomenclature database/platform can help foster the use of harmonized names and acronyms for the same compounds. It can also help to link different common names and acronyms that have been used over time to specific substances.

Second, further development of cheminformatics-based tools for automated systematic characterizing and categorizing PFASs would advance the field. A solely structure-based approach proposed in the report (i.e. Chapter 4) may serve as one starting point for possible joint development of an open source tool by experts from different online databases/platforms so that such a tool may be compatible for different online databases/platforms. In addition, as cheminformatics is a fast-developing field, future work may be conducted to monitor, assess and communicate which cheminformatics tools are developed for which purposes.

Third, further work on the characterization and reporting of polymers should be considered, as well as assessment of their properties. The current definitions of polymers in many jurisdictions originate from the OECD definition of polymer that was developed in the early 1990s, and in some cases, substances containing a significant fraction of low-molecular-weight molecules may be identified as polymers, as indicated in Footnote 21. This may impact how individual substances are registered (or not registered) and subsequent regulatory requirements of safety information. Thus, chemical compositions in substances that are identified as polymers may warrant a closer look, particularly in terms of their low-molecular-weight content, based on lessons learned in the past three decades. In addition, the current reporting of many polymers are often rather ambiguous (e.g. a polymer may be named as a co-polymer of three monomers A, B and C without indicating how the monomers are connected and in which molecular ratios, reaction schemes and molecular weight range of individual compositions, which could have implications on assessing the fate, behavior and risks of specific polymer products). Thus, future international efforts are needed to look into ways to improve the understanding of polymer structures including access to necessary information, focusing on polymeric PFASs or on polymers in general.

Fourth, as shown in Figure 8, there are many groups of organofluorine substances other than PFASs. Future work could also look into these compounds, including the terminology of many fluorinated aromatics.

References

Barzen-Hanson KA, Roberts SC, Choyke S, Oetjen K, McAlees A, Riddell N, et al. 2017. Discovery of 40 classes of per- and polyfluoroalkyl substances in historical aqueous film-forming foams (AFFFs) and AFFF-impacted groundwater. Environ Sci Technol 51(4), 2047–2057. https://doi.org/10.1021/acs.est.6b05843

Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, De Voogt P, et al. 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integrated Environmental Assessment and Management 7(4), 513–541, https://doi.org/10.1002/ieam.258

FOEN (Swiss Federal Office for the Environment). 2017. Additional information in relation to the risk management evaluation of PFOA, its salts, and related compounds. http://www.pops.int/TheConvention/POPsReviewCommittee/Meetings/POPRC12/POPRC12Followup/PFOAComments/tabid/5950/Default.aspx. (submitted on 31 May 2017).

Newton S, McMahen R, Stoeckel JA, Chislock M, Lindstrom A, Strynar M. 2017. Novel polyfluorinated compounds identified using high resolution mass spectrometry downstream of manufacturing facilities near Decatur, Alabama. Environ Sci Technol 51(3), 1544–1552. https://doi.org/10.1021/acs.est.6b05330.

Sha B, Schymanski EL, Ruttkies C, Cousins IT, Wang Z. 2019. Exploring open cheminformatics approaches for categorizing per- and polyfluoroalkyl substances (PFASs). Environmental Science: Processes & Impacts 21(11), 1835–1851. https://doi.org/10.1039/C9EM00321E.

Wang Z, Cousins IT, Scheringer M, Hungerbuehler K. 2013. Fluorinated alternatives to long-chain perfluorocarboxylic acids (PFCAs), perfluorosulfonic acids (PFSAs) and their potential precursors. Environ Int, 60, 242. https://doi.org/10.1016/j.envint.2013.08.021.

Wang Z, Cousins IT, Berger U, Hungerbühler K, Scheringer M. 2016. Comparative assessment of the environmental hazards of and exposure to perfluoroalkyl phosphonic and phosphinic acids (PFPAs and PFPiAs): Current knowledge, gaps, challenges and research needs. Environ Int, 89, 235. https://doi.org/10.1016/j.envint.2016.01.023.

Environmental Science & Technology

pubs.acs.org/est

Viewpoint

A New OECD Definition for Per- and Polyfluoroalkyl Substances

Zhanyun Wang,* Andreas M. Buser, Ian T. Cousins, Silvia Dematttio, Wiebke Drost, Olof Johansson, Koichi Ohno, Grace Patlewicz, Ann M. Richard, Glen W. Walker, Graham S. White, and Eeva Leinala

Cite This: *Environ. Sci. Technol.* 2021, 55, 15575−15578

Read Online

ACCESS | Metrics & More | Article Recommendations

KEYWORDS: *PFAS definition, cheminformatic tools, PFAS synthesis, PFAS universe, PFAS terminology*

Per- and polyfluoroalkyl substances (PFASs) comprise a class of chemicals that has attracted much attention since the early 2000s, when the hazards and ubiquitous occurrence of two PFASs—perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS)—were reported. Early communications used multiple terms such as "per- and polyfluorinated chemicals", "perfluorinated organics", "perfluorochemical surfactants", and "highly fluorinated compounds". In 2011, to harmonize communication, Buck et al.[1] published a milestone paper, providing the first clear structural definition of PFASs and recommendations on the names and acronyms for over 200 individual PFASs. Since then, research and regulation has expanded from PFOA and PFOS to a much wider range of substances.

In 2018, the so-called "Global PFC Group" led by the Organisation for Economic Co-operation and Development (OECD) and the United Nations Environment Programme (UNEP) published a list of over 4700 PFASs that contain a $-C_nF_{2n}-$ ($n \geq 3$) or $-C_nF_{2n}OC_mF_{2m}-$ (n and $m \geq 1$) moiety and that were known or likely to have been on the global market.[2] The list included substances that contain fully fluorinated carbon moieties, but do not meet the PFAS definition in Buck et al. (2011) due to a lack of a $-CF_3$ group in the molecule. Additionally, recent advancement of nontargeted analytical techniques enabled identification of many unknown PFASs in environmental and product samples. These developments provided motivation to reconcile the terminology of the PFAS universe, including a renewed look at the PFAS definition.

Against this backdrop, a report on the terminology of PFASs was recently published under the framework of the Global PFC Group.[3] This report reflects a three-year multistakeholder

Received: October 12, 2021
Published: November 9, 2021

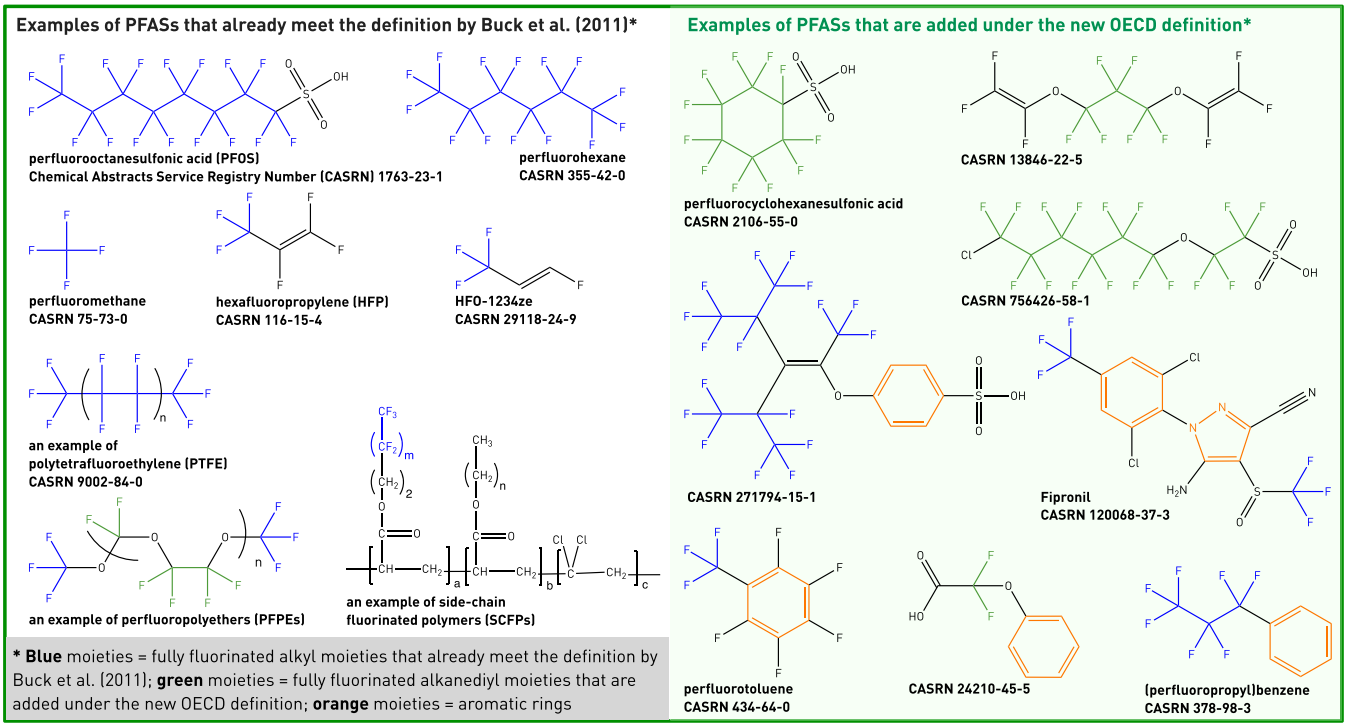


Figure 1. Examples of substances that are, and are not, PFASs based on the new definition.

international effort in reviewing the universe and terminology of PFASs to provide recommendations and practical guidance. We encourage stakeholders from academia, civil society, industry, and government to read the report and consider adopting its recommendations, wherever feasible, to help enable the coherent and consistent use of PFAS terminology across sectors and around the world. This Viewpoint provides an overview of the report.

A REVISED PFAS DEFINITION

The report details four major limitations with the previous definition in representing the PFAS universe: (1) omission of substances that have functional groups on both ends of the fully fluorinated carbon moiety (e.g., perfluoroalkyldicarboxylic acids); (2) inconsistencies in dealing with homologues that are fully fluorinated aliphatic cyclic compounds with or without a fully fluorinated alkyl side chain; (3) omission of substances with aromatic ring(s) in the nonfluorinated functional group(s) that can be cleaved in the environment and biota; and (4) use of the ambiguous term "highly fluorinated".

To address these concerns, the report presents a revised, broadly inclusive PFAS definition: "*PFASs are defined as fluorinated substances that contain at least one* **fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I 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*". The "noted exceptions" refer to a carbon atom with a H/Cl/Br/I atom attached to it.

The rationale behind the revision is to have a coherent and consistent definition across compounds from the view of the chemical structure. The new definition was required to be easily implementable for distinguishing between PFASs and non-PFASs, and easily understood by experts and nonexperts alike. Figure 1 illustrates examples that are, and are not, PFASs. This revised definition captures the broadness of the PFAS universe, ranging from small molecules, to more complex aromatics with a perfluorinated methyl/methylene group on the side chain(s), to diverse polymers.

Building on the revised definition, the report further provides (1) an explanation of how PFASs relate to other organofluorine compounds, (2) a comprehensive overview of known PFAS groups and their structural traits, including examples and notes on whether common names and acronyms

https://doi.org/10.1021/acs.est.1c06896
Environ. Sci. Technol. 2021, 55, 15575−15578

exist, and (3) some common synthesis routes of individual or groups of PFASs.

PRACTICAL GUIDANCE ON HOW TO USE THE PFAS TERMINOLOGY

The report highlights the need to distinguish between the general definition and user-specific working scopes of PFASs. The general definition is based on molecular structure alone and serves as a starting and reference point to guide individual users to have a comprehensive understanding of the scale and diversity of chemicals in the PFAS universe. Meanwhile, users may define their own working scope of PFASs for specific activities according to their specific needs by combining the general definition with additional considerations (e.g., specific properties, use areas). When such a working scope of PFASs is used, the report recommends that respective users clearly provide the context and rationale for selecting their working scope to ensure transparency and avoid confusion by others.

The report further recommends using and building upon existing common terminologies such as in Buck et al. (2011) and well-defined common practices in organic chemistry, unless it is essential to deviate from them, to keep the consistent and coherent use of the PFAS terminology. As PFASs are a chemical class with diverse molecular structures and thus properties, it is recommended to properly recognize and communicate such diversity in a clear, specific and descriptive manner.

A SYSTEMATIC MOLECULAR STRUCTURE-BASED APPROACH TO CHARACTERIZING PFASS

When users define their own working scope of PFASs, they need to determine whether a compound falls or does not fall into their working scope. However, given the complexity and diversity of PFASs, it can be a challenging task to characterize and categorize PFASs based on chemical structures in a coherent and consistent manner, particularly for nonexperts. Different users may have different construction of working scopes, and there is no single categorization/grouping system that suits all. Therefore, the report provides a standardized approach for systematically characterizing PFASs based on molecular structural traits that will allow stakeholders to make their own categorization in a coherent and consistent manner. This system can be used to manually characterize and categorize PFASs, but the approach could also be used as inputs for developing automated cheminformatic tools.[4]

FUTURE WORK ON PFAS TERMINOLOGY

Four areas are recognized for further work to facilitate clear and unambiguous communication: (1) a centralized PFAS nomenclature database/platform; (2) development of cheminformatic tools for automated, structure-based systematic characterizaing and categorizing of PFASs; (3) work on the characterization and reporting of polymers; and (4) work on organofluorine compounds not currently defined as PFASs, including many fluorinated aromatics.

AUTHOR INFORMATION

Corresponding Author

Zhanyun Wang − *Chair of Ecological Systems Design, Institute of Environmental Engineering, ETH Zürich, 8093 Zürich, Switzerland;* orcid.org/0000-0001-9914-7659; Email: zhanyun.wang@ifu.baug.ethz.ch

Authors

Andreas M. Buser − *Swiss Federal Office for the Environment (FOEN), 3063 Ittigen, Switzerland*

Ian T. Cousins − *Department of Environmental Science and Analytical Chemistry (ACES), Stockholm University, SE-10691 Stockholm, Sweden;* orcid.org/0000-0002-7035-8660

Silvia Demattio − *European Chemicals Agency, 00150 Helsinki, Finland*

Wiebke Drost − *German Environment Agency, 06844 Dessau-Roßlau, Germany*

Olof Johansson − *Swedish Chemicals Agency, 172 67 Sundbyberg, Sweden*

Koichi Ohno − *Health and Environmental Risk Division, National Institute for Environmental Studies, Tsukuba, Ibaraki 305-8506, Japan*

Grace Patlewicz − *Center for Computational Toxicology and Exposure, Office of Research and Development, U.S. Environmental Protection Agency, Durham, North Carolina 27711, United States*

Ann M. Richard − *Center for Computational Toxicology and Exposure, Office of Research and Development, U.S. Environmental Protection Agency, Durham, North Carolina 27711, United States;* orcid.org/0000-0003-2116-2300

Glen W. Walker − *Department of Agriculture, Water and the Environment, Australian Government, Canberra, Australian Capital Territory 2601, Australia*

Graham S. White − *New Substances Assessment and Control Bureau, Safe Environments Directorate, Health Canada, Ottawa K1A 0K9, Canada*

Eeva Leinala − *Environment, Health and Safety Division, Environment Directorate, Organisation for Economic Cooperation and Development, 75016 Paris, France*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.est.1c06896

Notes

The authors declare no competing financial interest.

Biography

Dr. Zhanyun Wang is a senior researcher in the Ecological Systems Design Group at ETH Zürich, Switzerland. As an environmental chemist by training, his research interests focus primarily on understanding the life cycles and risks of various anthropogenic chemicals in the technosphere and natural environment. He is also very interested in exploring novel and pragmatic approaches to advancing sound chemicals management, enabling a sustainable

https://doi.org/10.1021/acs.est.1c06896
Environ. Sci. Technol. 2021, 55, 15575−15578

circular economy, and strengthening science-policy interface on chemicals and waste.

■ ACKNOWLEDGMENTS

Z.W. gratefully acknowledges financial support for his work from the Swiss Federal Office for the Environment (FOEN). We gratefully acknowledge Robert C. Buck (Chemours), Audun Heggelund (Norwegian Environment Agency), and Simone Schalles (German Environment Agency) for their contribution in drafting and finalizing the report, Urs Berger (UFZ, Germany), Stellan Fischer (Swedish Chemicals Agency), Linda Gaines and Laurence Libelo (USEPA) for their contribution to the early development of the project, and members of the OECD/UNEP Global PFC Group for their review and contributions to the report. The views expressed are those of the authors and do not necessarily reflect the views or official policies of their organizations and/or governments.

■ REFERENCES

(1) Buck, R. C.; Franklin, J.; Berger, U.; Conder, J. M.; Cousins, I. T.; de Voogt, P.; Jensen, A. A.; Kannan, K.; Mabury, S. A.; van Leeuwen, S. P. J. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification and origins. *Integr. Environ. Assess. Manage.* **2011**, *7* (4), 513−541.

(2) Organisation for Economic Co-operation and Development (OECD). 2018. Toward a new comprehensive global database of per- and polyfluoroalkyl substances (PFASs). http://www.oecd.org/chemicalsafety/risk-management/global-database-of-per-and-polyfluoroalkyl-substances.xlsx; http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV-JM-MONO(2018)7&doclanguage=en (methodology report) (021/9/1).

(3) Organisation for Economic Co-operation and Development (OECD). 2021. Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance. Series on Risk Management No. 61. https://www.oecd.org/chemicalsafety/portal-perfluorinated-chemicals/terminology-per-and-polyfluoroalkyl-substances.pdf (accessed 2021/9/1)

(4) Sha, B.; Schymanski, E. L.; Ruttkies, C.; Cousins, I. T.; Wang, Z. Exploring open cheminformatics approaches for categorizing per- and polyfluoroalkyl substances (PFASs). *Environmental Science: Processes & Impacts* **2019**, *21* (11), 1835−1851.

https://doi.org/10.1021/acs.est.1c06896
Environ. Sci. Technol. 2021, 55, 15575−15578

Exposure and Health (2023) 15:373–394
https://doi.org/10.1007/s12403-022-00496-y

ORIGINAL PAPER

Leveraging Systematic Reviews to Explore Disease Burden and Costs of Per- and Polyfluoroalkyl Substance Exposures in the United States

Vladislav Obsekov[1] · Linda G. Kahn[1,2] · Leonardo Trasande[1,2,3,4,5]

Received: 24 March 2022 / Revised: 3 June 2022 / Accepted: 23 June 2022 / Published online: 26 July 2022

Abstract

Accelerating evidence confirms the contribution of per- and polyfluoroalkyl substances (PFAS) to disease burden and disability across the lifespan. Given that policy makers raise the high cost of remediation and of substituting PFAS with safer alternatives in consumer products as barriers to confronting adverse health outcomes associated with PFAS exposure, it is important to document the costs of inaction even in the presence of uncertainty. We therefore quantified disease burdens and related economic costs due to legacy PFAS exposures in the US in 2018. We leveraged systematic reviews and used meta-analytic inputs whenever possible, identified previously published exposure–response relationships, and calculated PFOA- and PFOS-attributable increases in 13 conditions. These increments were then applied to census data to determine total annual PFOA- and PFOS-attributable cases of disease, from which we calculated economic costs due to medical care and lost productivity using previously published cost-of-illness data. We identified PFAS-attributable disease costs in the US of $5.52 billion across five primary disease endpoints shown to be associated with PFAS exposure in meta-analyses. This estimate represented the lower bound, with sensitivity analyses revealing as much as $62.6 billion in overall costs. While further work is needed to assess probability of causation and establish with greater certainty effects of the broader category of PFAS, the results confirm further that public health and policy interventions are still necessary to reduce exposure to PFOA and PFOS and their endocrine-disrupting effects. This study demonstrates the large potential economic implications of regulatory inaction.

Keywords PFAS · Perfluoroalkyl substances · Polyfluoroalkyl substances · Environmental chemicals · Disease burden · Economic costs · Obesity · Diabetes · Metabolism · Cancer · Reproductive health · Fertility · Respiratory infection · Child health

Abbreviations

AF	Attributable fraction
ART	Assisted reproductive technology
BMI	Body mass index
CI	Confidence interval
DALY	Disability-adjusted life years
ERR	Exposure–response relationship
GDM	Gestational diabetes
IQ	Intelligence quotient
LBW	Low birth weight
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PCOS	Polycystic ovarian syndrome
PFAS	Perfluoroalkyl substances
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
ppt	Parts per trillion
QALY	Quality-adjusted life years
RR	Risk ratio
SD	Standard deviation
TTP	Time to pregnancy
T2D	Type 2 diabetes mellitus
US	United States

✉ Leonardo Trasande
leonardo.trasande@nyulangone.org

[1] Department of Pediatrics, NYU Grossman School of Medicine, New York, NY, USA

[2] Department of Population Health, NYU Grossman School of Medicine, New York, NY, USA

[3] Department of Environmental Health, NYU Grossman School of Medicine, New York, NY, USA

[4] NYU Wagner School of Public Service, New York, NY, USA

[5] NYU School of Global Public Health, New York, NY, USA

Introduction

Per- and polyfluoroalkyl substances (PFAS) are a group of over 4700 human-made fluorine-rich molecules (Birnbaum 2018). Long-chain PFAS, with a minimum of six carbons in their "backbone," were first developed in the 1940s. The polarity of their structure enhanced their utility in the production of water- and oil-resistant clothing, electronics, nonstick cookware, carpets, and food packaging materials for many years (Arbuckle et al. 2013; Holzer et al. 2008). These chemicals are widely detected in the blood of human populations worldwide (Bach et al. 2016a; Calafat et al. 2007), in part due to the biological persistence of many long-chain PFAS, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), which have half-lives in humans of at least 2 years (Bartell et al. 2010; Olsen et al. 2007; Xu et al. 2020). Although PFOA and PFOS have been added to the Stockholm Convention and PFOA use has been banned in the EU, they are still being released into the environment and are still being produced in other countries. Furthermore, both chemicals persist in the environment due to their chemical stability, resulting in ongoing human exposure (Grandjean and Clapp 2015).

Among the first to document PFAS-related effects on human health were the C8 Science Panel exposure and health studies conducted between 2005 and 2013 in mid-Ohio Valley communities where PFOA had heavily contaminated the water supply since the 1950s. These studies identified probable links with diagnosed high cholesterol, ulcerative colitis, thyroid disease, testicular cancer, kidney cancer, and pregnancy-induced hypertension (C8 Science Panel). An updated report from C8 Science Panel members and colleagues suggests that while the epidemiologic evidence for some of the associations they identified remains limited, possibly due to lower exposure levels in the general population, their findings for high cholesterol, ulcerative colitis, and kidney and testicular cancer had been reinforced by subsequent studies and impaired immune function had emerged as an additional outcome (Steenland et al. 2020). A recent scoping review of studies exclusively conducted among general population samples concluded that the weight of evidence supported associations of low-level PFAS exposure with low birth weight (LBW, < 2500 g), childhood obesity, adult obesity, adult-onset type 2 diabetes (T2D), gestational diabetes (GDM), endometriosis, polycystic ovarian syndrome (PCOS), couple infertility, and breast cancer (Kahn et al. 2020). Systematic reviews add further support for routine PFAS exposure and LBW (Bach et al. 2015; Johnson et al. 2014; Koustas et al. 2014; Lam et al. 2014; Steenland et al. 2018); childhood obesity (Liu et al. 2018b), dyslipidemia (Rappazzo et al. 2017), renal dysfunction (Rappazzo et al. 2017), respiratory infection (Rappazzo et al. 2017), and reduced immune response to vaccines (Rappazzo et al. 2017); age at menarche (Rappazzo et al. 2017); and adult thyroid dysfunction (Kim et al. 2018) and kidney (Bartell and Vieira 2021), testicular (Bartell and Vieira 2021), and breast (Wan et al. 2021) cancers. While a 2016 systematic review cast doubt on evidence for infertility due to PFAS because most of the studies that found associations were not restricted to nulliparous women (Bach et al. 2016b), the authors acknowledged that four of eight studies identified increased time to pregnancy (TTP) with PFOA or PFOS exposure. A more recent scoping review was less dismissive of the evidence and pointed out that studies conducted among parous women may still be valid if models adjust for interpregnancy interval and (in retrospective studies) gestational age at blood collection (Kahn et al. 2021). A difference-in-difference analysis of a natural experiment in which fertility and birth outcomes were compared between communities without PFAS exposure and highly exposed communities where PFOA- and PFOS-contaminated water supplies were remediated found that preterm birth and LBW rates, which had been higher in the contaminated communities, decreased following remediation and the fertility rate, which had been lower, increased (Waterfield et al. 2020).

In the United States (US), rising concerns about the health effects of PFAS have prompted calls to state and federal governments to limit ongoing PFAS use and remediate contaminated water supplies. The US Environmental Protection Agency's third Unregulated Containment Monitoring Rule report released in January 2017 found that 4% of water systems reported at least one PFAS compound detectable above the minimum reporting level, which ranged from 10 to 90 parts per trillion (ppt) for various PFAS (Crone et al. 2019). A more recent study estimates that 18–80 million people in the US receive tap water with at least 10 ppt of PFOA and PFOS combined and more than 200 million Americans have tap water contaminated with PFOA and PFOS concentrations of 1 ppt or higher (Andrews and Naidenko 2020). Although there is currently no national regulatory limit for PFOA and PFOS exposure and the US Environmental Protection Agency continues to use a lifetime health advisory level of 70 ppt for the sum of PFOA and PFOS (Environmental Protection Agency 2016), some states have banned PFAS in food packaging and lowered regulatory limits for PFAS in drinking water by two orders of magnitude to 1 ppt or lower as suggested by studies of PFAS and antibody titers in children (Grandjean and Clapp 2015; Hoylman 2020).

In considering regulatory action, the European Food Safety Authority and the US Agency for Toxic Substances and Disease Registry have suggested that the evidence is not sufficient to confirm causality and therefore to proceed with steps to reduce exposure (Rogers et al. 2021; Schrenk et al. 2020). As Bradford Hill declared in his landmark lecture on causal inference (Hill 1965), uncertainty "does not confer

upon us a freedom to ignore the knowledge we already have or to postpone the action that it appears to demand at a given time." Given that policy makers raise the high cost of remediation and of substituting PFAS with safer alternatives in consumer products as barriers to confronting adverse health outcomes associated with PFAS exposure, it is important to document the costs of inaction even in the presence of uncertainty.

Recent studies suggest that the disease-related burden due to PFAS can be substantial. In 2003–2004, PFOA exposure accounted for up to 4% of LBW in the US, with $13.7 billion in associated costs (Malits et al. 2018). The Nordic Council of Ministers estimated €52–84 billion in disease-related costs in 2019 associated with PFAS within the European Economic Area, driven substantially by occupational PFAS exposures and effects on populations living near contaminated sites (Goldenman et al. 2019). Yet, these analyses did not consider the broader scope of health effects of routine, low-level environmental PFAS exposure on human health. The aim for this analysis was therefore to quantify disease burden and associated costs of PFOA and PFOS exposure among the entire US population based on health outcomes with a substantial weight of evidence in support of associations with PFAS exposure.

Methods

Overall approach (Fig. 1)

To identify diseases and dysfunctions and their associated economic costs to be considered for possible attribution to PFAS exposure, we leveraged the PFAS-Tox Database (https://pfastoxdatabase.org/), which was built using systematic review methods, to extract relevant studies and data (Pelch et al. 2019). Given the rapidly evolving nature of the PFAS literature, we supplemented the primary source with a PubMed search using the terms "PFAS" and "systematic review" or "meta-analysis." In an additional effort to be complete, we also mined three recent scoping reviews to ensure the most comprehensive inclusion of potential disease burden and costs in sensitivity analyses (Kahn et al. 2020; Steenland et al. 2020; Steenland and Winquist 2021).

In main estimates of PFAS-attributable disease burden and cost, we only considered disease outcomes for which statistically significant associations had been derived from published meta-analyses of epidemiologic studies. These included (1) LBW due to prenatal exposure (Steenland et al. 2018); (2) childhood obesity due to prenatal exposure (Liu et al. 2018b); (3) kidney cancer due to lifetime exposure (Bartell and Vieira 2021); (4) testicular cancer due to lifetime exposure (Bartell and Vieira 2021); and (5) hypothyroidism in females due to lifetime exposure (Kim et al. 2018). For all of these outcomes except hypothyroidism, we used the meta-analytic estimates of exposure–response relationship [ERR, e.g., odd ratios (ORs) or risk ratios (RRs)] as the bases for disease burden and cost estimations. For hypothyroidism, a clear negative association was demonstrated between PFOA exposure and total T4 and T3 levels in a meta-analysis of seven papers by Kim et al., but because these are not clinical endpoints, we used an OR from a representative paper from the meta-analysis that identified a negative association with subclinical hypothyroidism (Wen et al. 2013).

In a sensitivity analysis of PFAS-attributable disease burden and cost, we expanded the scope of relevant outcomes

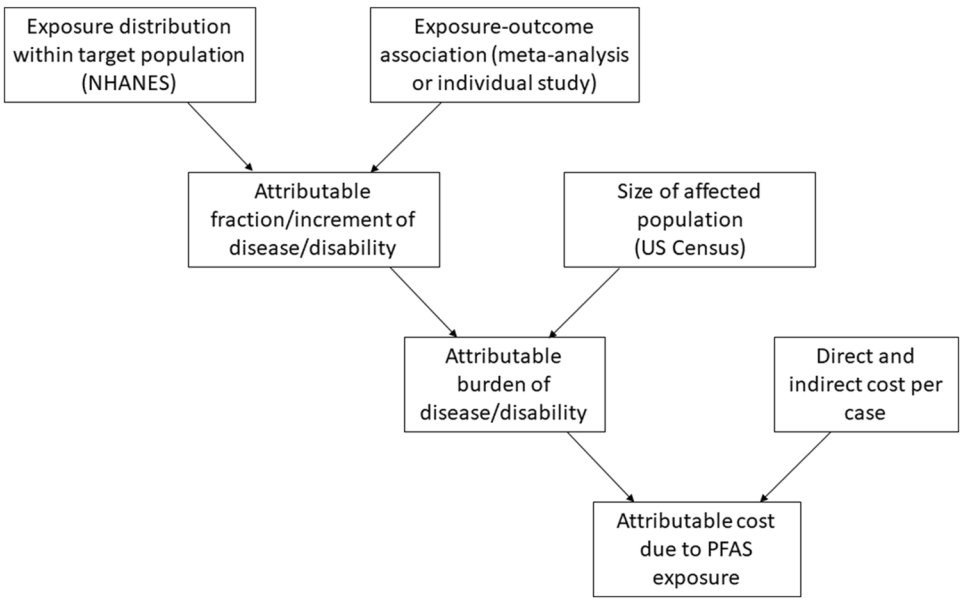


Fig. 1 Schematic of method for calculating cost of disease/disability attributable to PFAS exposure

to consider health conditions for which relations with PFAS had been identified in systematic and scoping reviews but had not been meta-analyzed. These included (6) adult obesity due to exposure over the lifespan (Kahn et al. 2020); (7) T2D in females due to exposure over the lifespan (Kahn et al. 2020); (8) GDM due to exposure measured in pregnancy (Kahn et al. 2020); (9) endometriosis due to exposure over the lifespan (Kahn et al. 2020); (10) PCOS due to exposure over the lifespan (Kahn et al. 2020); (11) couple infertility due to lifetime exposure in females (Kahn et al. 2020); (12) female breast cancer due to lifetime exposure (Wan et al. 2021); and (13) pneumonia in children due to prenatal exposure (Rappazzo et al. 2017). We did not include pediatric dyslipidemia or reduced age at menarche (Rappazzo et al. 2017), as these indicators are associated with outcomes already included in our analysis (e.g., childhood obesity and breast cancer, respectively); similarly, we did not include adult high cholesterol (Steenland et al. 2020), as it is associated with adult obesity, which is already included in our analysis. We also did not include reduced response to childhood vaccination (Grandjean et al. 2012), as reduced titers generally only require revaccination and clinical episodes of tetanus [~ 30 cases per year (CDC)] and diphtheria [2 cases between 2004 and 2017 (CDC)] are extremely rare in the US (CDC 2022a, b). Recognizing that some studies for each of the included outcomes might have reported null findings, the lower bound of economic cost added for this group of outcomes is zero. We based the upper bound of the sensitivity analysis on ERRs drawn from recent well-designed studies that reported statistically significant results from populations most similar to the current US population and extracted appropriate ERRs for our exposures and outcomes of interest (Tables 1, 2). To extrapolate most accurately effects in 2018 [the most recent year for which PFAS exposure data are available from the US National Health and Nutrition Examination Survey (NHANES)], we considered only studies published within the past 10 years and excluded those that did not control for confounding variables in the analysis, did not have PFAS exposure levels similar to our population as defined by the 2017–2018 NHANES dataset, and did not provide an RR, OR, or beta coefficient with either a 95% confidence interval or *p*-value. When multiple studies met these criteria, we modeled each separately and added the highest estimate to our cost estimate total in order to establish the upper bound of our sensitivity analysis.

Assessing Risk of Bias

A substantial literature has described and compared methods to evaluate systematic reviews (Whiting et al. 2016) and epidemiologic studies (Eick et al. 2020) for risk of bias. We used the tool developed by the National Toxicology Program's Office of Health Assessment and Translation (OHAT) (Office of Health Assessment and Translation (OHAT) 2022) to evaluate epidemiologic studies and ROBIS, the first rigorously developed tool designed specifically to assess the risk of bias in systematic reviews (Whiting et al. 2016). Two authors (LT, LK) independently evaluated each of the studies.

OHAT includes seven questions that yield graded probability assessments for risk of bias within observational studies (definitely low, probably low, probably high, definitely high). In the cases where there was a potential risk of bias, we added narrative comments to explain reasons for our concerns. ROBIS evaluates risk of bias in systematic reviews across four domains: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings. Within each domain, answers to multiple questions are used to assemble a domain-wide assessment of risk of bias (low, high, unclear). For each systematic review, two authors (LT and LK) assessed overall risk of bias in each of the four domains, identified specific concerns, and then assessed whether conclusions were supported by the evidence based on three criteria: whether the interpretation of findings addressed identified concerns in all the domains; whether the relevance of identified studies to the research question was appropriately considered; and whether authors overemphasized statistical significance. These questions were answered as yes, probably yes, probably no, no, or no information. This informed final assessments of each systematic review as low, high, or unclear.

Estimating PFAS-Attributable Disease Burden and Cost

To estimate the attributable cost of PFAS-mediated disease, we applied the model first used by the Institute of Medicine (1981) described by the equations below:

$$\text{Attributable disease burden} = \text{Increment in disease/disability} \times \text{Attributable fraction(AF)} \times \text{Population size} \quad (1)$$

$$\text{Attributable cost} = \text{Attributable disease burden} \times \text{Cost per increment.} \quad (2)$$

Table 1 Study selection

Exposure	Author (Year)	N	Study type	Date of recruitment	Location	Population	Exposure	Outcome	Covariates	Results
Low birth weight										
PFOA~	Steenland (2018)	24 studies	Meta-analysis	Varied by study	Varied by study	Varied by study	PFOA in maternal or cord blood	Birth weight	Varied by study	10.5 g (4.4, 16.7) decrease in birth weight per ng/mL PFOA increase in maternal or cord blood
PFOS*	Meng (2018)	3535 mother–infant pairs	Cross-sectional	1992–2002	Denmark	Mother–infant pairs	PFOS in maternal plasma	Birth weight	Infant sex, infant birth year, gestational week of blood draw, maternal age, parity, socio-occupational status, pre-pregnancy BMI, smoking, and alcohol use during pregnancy	45.2 g (13.6, 76.8) decrease in birth weight per doubling of ng/mL PFOS increase in maternal plasma
Childhood obesity at age 10										
PFOA~	Liu (2018a)	Nine studies with prenatal exposure	Meta-analysis	Varied by study	Varied by study	Multiple cohorts of children	PFOA in early childhood	BMI	Varied by study	0.09 (0.02, 0.17) increase in BMI *z*-score per ng/mL increase in prenatal PFOA
PFOS*	Lauritzen (2018)	412 females	Prospective cohort	1986–1988	Norway and Sweden	Pregnant women	PFOS in maternal serum	BMI	Maternal age, education, smoking at conception, pre-pregnancy BMI, weight gain at 17 weeks, interpregnancy interval, previous breastfeeding duration, and country of residence	0.18 (0.01, 0.35) increase in BMI *z*-score per ln-unit ng/mL increase in prenatal PFOA

Table 1 (continued)

Exposure	Author (Year)	N	Study type	Date of recruitment	Location	Population	Exposure	Outcome	Covariates	Results
Kidney cancer										
PFOA~	Bartell (2021)	Four studies	Meta-analysis	Varied by study	Varied by study	Varied by study	PFOA exposure	Kidney cancer incidence	Varied by study	Increase in cancer risk per 10 ng/mL increase in serum PFOA = 16% (3%, 30%)
Testicular cancer										
PFOA~	Bartell (2021)	Two studies	Meta-analysis	Varied by study	Varied by study	Varied by study	PFOA exposure	Testicular cancer incidence	Varied by study	Increase in cancer risk per 10 ng/mL increase in serum PFOA = 3% (2%, 4%)
Hypothyroidism										
PFOA~	Kim (2018)	Seven studies after excluding outliers	Cross-sectional	2007–2009	USA	Adults > 20 years old	PFOA in serum	Subclinical hypothyroidism in women	Age, race, drinking, smoking, and natural log-urinary iodine	7.42 (1.14–48.12) OR of subclinical hypothyroidism risk per ln-unit ng/mL increase in serum PFOA
PFOS*	Wen (2013)	1181 individuals	Cross-sectional	2007–2009	USA	Adults > 20 years old	PFOS in serum	Subclinical hypothyroidism in women	Age, race, drinking, smoking, and natural log-urinary iodine	3.03 (1.14–8.07) OR of subclinical hypothyroidism risk per ln-unit ng/mL increase in serum PFOA
Adult obesity										
PFOS*	Liu (2018a)	520 individuals	Randomized clinical trial	2003–2007	Boston, MA and Baton Rouge, LA	Over-weight and obese 30–70-year olds	PFOS in serum	Body weight	Age, sex, race, baseline BMI, education, smoking status, alcohol consumption, physical activity, and dietary intervention group	Higher baseline levels of PFOS associated with greater weight regain (1.5 ± 0.6–3.2 ± 0.6 kg)

Table 1 (continued)

Exposure	Author (Year)	N	Study type	Date of recruitment	Location	Population	Exposure	Outcome	Covariates	Results
Adult-onset type 2 diabetes										
PFOA*	Sun (2018)	1586 females	Prospective nested case–control study	1995–2000	USA	Female nurses 32–52 years old	PFAS in plasma	T2D	Age, month, and fasting status at sample collection and menopausal status and hormone replacement therapy	1.54 (1.04–2.28) OR of T2D in highest tertile of exposure compared to lowest
Gestational diabetes										
PFOA*	Zhang (2015)	258 females	Prospective cohort	2005–2009	Michigan and Texas	Women discontinuing contraception to become pregnant	PFOA in serum	GDM	Age, BMI, and parity conditional on gravidity	1.61 (1.05–2.49) OR of GDM per SD increment of PFOA exposure
Endometriosis										
PFOA*	Buck Louis (2012)	626 females	Prospective nested case–control study	2007–2009	Salt Lake City, UT and San Francisco, CA	Women 18–44 years old	PFOA in serum	Endometriosis	Age, BMI, and parity	1.89 (1.17–3.06) OR of endometriosis per log unit exposure of PFOA
Polycystic ovarian syndrome										
PFOA*	Vagi (2014)	102 females	Case–control	2007–2008	Los Angeles, CA	Women 18–45 years old	PFOA in serum	PCOS	Age, BMI, and race	6.93 (1.79–29.92) OR of PCOS in highest tertile compared to lowest
PFOS*	Vagi (2014)	102 females	Case–control	2007–2008	Los Angeles, CA	Women 18–45 years old	PFOS in serum	PCOS	Age, BMI, and race	5.79 (1.58–24.12) OR of PCOS in highest tertile compared to lowest
Couple infertility										
PFOA*	Bach (2015)	1601 females	Case–control	1996–2002	Denmark	Pregnant women	PFOA in serum	Time to pregnancy	Age, socio-economic status, BMI, and parity	0.67 (0.51–0.88) fecundability ratio per log unit PFOA exposure

Table 1 (continued)

Exposure	Author (Year)	N	Study type	Date of recruitment	Location	Population	Exposure	Outcome	Covariates	Results
PFOS*	Bach (2015)	1601 females	Case–control	1996–2002	Denmark	Pregnant women	PFOS in serum	Time to pregnancy	Age, socio-economic status, BMI, and parity	0.62 (0.47–0.83) fecundability ratio per log unit PFOS exposure
Breast cancer										
PFOA*	Wielsoe (2017)	161 females	Case–control	2000–2003, 2011–2014	Greenland	Inuit women	PFOA in serum	Breast cancer	Age, BMI, cotinine levels, parity, and breastfeeding	1.26 (1.01–1.58) OR of breast cancer with PFOA exposure
PFOS*	Wielsoe (2017)	161 females	Case–control	2000–2003, 2011–2014	Greenland	Inuit women	PFOS in serum	Breast cancer	Age, BMI, cotinine levels, parity, and breastfeeding	1.02 (1.01–1.03) OR of breast cancer with PFOS exposure
Pneumonia										
PFOA*	Impinen (2019)	1270 females	Cohort	1999–2008	Norway	Children	PFOA in maternal serum	Number of infections by age 3	Maternal age, maternal BMI, maternal education, parity, and smoking during pregnancy	1.27 (1.12–1.43) RR of bronchitis/pneumonia
PFOS*	Impinen (2019)	1270 females	Cohort	1999–2008	Norway	Children	PFOS in maternal serum	Number of infections by age 3	Maternal age, maternal BMI, maternal education, parity, and smoking during pregnancy	1.20 (1.07–1.34) RR of bronchitis/pneumonia

*Sensitivity analysis

˜From meta-analyses

Table 2 Exposure–response relationships

Outcome	Exposed population	Exposure	Exposure modeling (ng/mL)	ERR	Source of ERR
Low birth weight~					
	Females 18–49	PFOA	Continuous	$\beta = -10.5$ g/PFOA (ng/mL)	Steenland (2018)
		PFOS	Continuous	$\beta = -45.2$ g/doubling of PFOS (ng/mL)	Meng (2018)
Childhood obesity at age 10~					
	Females 18–49	PFOA	Continuous	$\beta = 0.09$ per PFOA (ng/mL)	Liu (2018a)
		PFOS	Continuous	$\beta = 0.18$ per ln((PFOS) (ng/mL))	Lauritzen (2018)
Kidney cancer					
	Adults 18+	PFOA	Continuous	OR = 1.16 per 10 ng/mL PFOA	Bartell (2021)
Testicular cancer					
	Males 18+	PFOA	Continuous	OR = 1.03 per 10 ng/mL PFOA	Bartel (2021)
Hypothyroidism					
	Females 18–49	PFOA	Continuous	OR = 7.42 per ln(PFOA (ng/mL))	Wen (2013)
		PFOS	Continuous	OR = 3.03 per ln(PFOA (ng/mL))	
Adult obesity					
	Adults 18+	PFOS	Tertile 1: < 19.2	$\beta = 1.5$ kg gained	Liu (2018a)
			Tertile 2: 19.2–32.1	$\beta = 3.5$ kg gained	
			Tertile 3: > 32.1	$\beta = 3.2$ kg gained	
Adult-onset type 2 diabetes					
	Females 18–49	PFOA	Tertile 1: < 3.76	OR = 1	Sun (2018)
			Tertile 2: 3.76–5.48	OR = 1.27	
			Tertile 3: > 5.48	OR = 1.54	
Gestational diabetes					
	Females 18–49	PFOA	Continuous	When ln(1 + PFOA (ng/mL) increases by 1 SD, OR increases by 1.61	Zhang (2015)
Endometriosis					
	Females 18–49	PFOA	Continuous	OR = 1.89 per log((PFOA (ng/mL))	Buck Louis (2012)
Polycystic ovarian syndrome					
	Females 15–45	PFOA	Tertile 1: < 2.6	OR = 1	Vagi (2014)
			Tertile 2: 2.6–4.1	OR = 1.65	
			Tertile 3: > 4.1	OR = 6.93	
		PFOS	Tertile 1: < 6.2	OR = 1	
			Tertile 2: 6.2–8.6	OR = 3.43	
			Tertile 3: > 8.6	OR = 5.79	
Couple infertility					
	Females 18–49	PFOA	Continuous	OR = 0.67 per log((PFOA (ng/mL))	Bach (2015)
		PFOS	Continuous	OR = 0.62 per log((PFOS (ng/mL))	
Breast cancer					
	Females 18–49	PFOA	Continuous	OR = 1.26 per PFOA (ng/mL)	Wielsoe (2017)
		PFOS	Continuous	OR = 1.02 per PFOS (ng/mL)	
Pneumonia~					
	Females 18–49	PFOA	Continuous	RR = 1.27 per PFOA (ng/mL)	Impinen (2019)
		PFOS	Continuous	RR = 1.20 per PFOS (ng/mL)	

~ Serum concentrations in females of childbearing age was used as a proxy for prenatal exposure

The AF of a risk factor can be defined as the proportional decrease in the number of cases of ill health or deaths as a result of reducing the risk factor to a reference level and can be estimated using the following equation:

$$\mathrm{AF} = \mathrm{Prevalence}_{\mathrm{exposure}} * (\text{relative risk(RR)} - 1) \Big/ \left[1 + \left(\mathrm{prevalence}_{\mathrm{exposure}} * (\mathrm{RR} - 1)\right)\right], \quad (3)$$

where RR represents the risk of morbidity associated with the specific exposure relative to the reference level (Levin 1953).

The first step in calculating attributable disease burden was to quantify exposure. We focused our analysis on PFOA and PFOS, as they are the most widely studied members of the PFAS class and evidence of their health effects is strongest. Because these two chemicals co-occur, as a conservative measure, we calculated disease burden based on PFOA and PFOS separately as proxies for long-chain PFAS exposure. Our source for distributions of exposure was the 2017–2018 cycle of NHANES, as this contains the most recent nationally representative data. For each analysis, we focused on the relevant subsection of the population (e.g., women of childbearing age when considering PCOS). For childhood obesity we used data from the 2007–2008 cycle to quantify in utero exposure among children who were age 10 in 2017–2018. NHANES measured serum concentrations of PFOA and PFOS with online solid-phase extraction coupled with high-performance liquid chromatography–tandem mass spectrometry; an extensive methodology is provided in the NHANES Laboratory Procedures Manual (CDC 2016) Main estimates used PFOA levels, while sensitivity analyses considered PFOS levels, as well.

We stratified the US population into percentile groupings of serum PFAS concentration (< 10th, 10th–24th, 25th–49th, 50th–74th, 75th–89th, 90th–99th, and > 99th). As a conservative measure, we assumed exposures within each percentile grouping to be at the lowest end of the range (e.g., corresponding to the 10th, 25th, 50th, 75th, 90th, and 99th percentile) and assumed no exposure for the lowest 10% of the population, our reference group (Table 3).

Once we established the exposure level across each percentile group, we calculated increments in disease or disability over the baseline population rate due to exposure. 2018 US Census estimates (USC Bureau 2020) were used to convert the baseline prevalence or incidence values to the appropriate population size (subsequent sections identify the sources of prevalence/incidence data for each outcome). We then applied the previously selected ERRs to quantify attributable burdens of disease within each group. If an ERR was based on continuous exposure in the literature, main analyses employed a reference level of 0.1 ng/mL below which no effects were assumed to be observed. If an ERR was based on tertiles or quartiles of exposure in the literature, we used the lowest quantile as the reference level (Table 3). ORs were converted to RRs to avoid overestimation following published practice (Knol et al. 2012), and Levin's formula was used to tabulate AFs based on RRs (Levin 1953).

Once we estimated the increase in cases attributable to PFOA/PFOS exposure for the 13 outcome measures, we calculated associated economic costs using available data on cost per case, derived from previously published estimates of direct and/or indirect healthcare and societal costs, and the size of the population at risk (Supplementary Tables 1–13). All cost estimates were adjusted to reflect the annual average for 2018 in US dollars using the All Items Consumer Price Index (US Bureau of Labor Statistics 2020).

Table 3 NHANES exposure data

Outcome	Exposed population	NHANES years of exposure	Exposure chemical	Concentrations assigned to each percentile of exposure						
				0–9	10–24	25–49	50–74	75–89	90–99	> 99
Low birth weight*, adult diabetes, gestational diabetes, endometriosis, couple infertility, breast cancer, pneumonia*, and hypothyroidism										
	Females 18–49	2017–2018	PFOA (ng/mL)	0.00	0.47	0.67	0.97	1.47	2.37	5.17
			PFOS (ng/mL)	0.00	1.10	1.70	2.60	3.90	5.70	11.9
Childhood obesity at age 10*										
	Females 18–49	2007–2008	PFOA (ng/mL)	0.00	2.30	2.70	3.50	4.60	5.90	7.10
			PFOS (ng/mL)	0.00	4.70	7.20	9.90	17.70	24.30	32.20
Adult obesity and kidney cancer										
	Adults 18+	2017–2018	PFOA (ng/mL)	0.00	0.67	0.97	1.47	2.17	3.07	8.30
			PFOS (ng/mL)	0.00	1.60	2.70	4.70	7.80	12.0	26.2
Polycystic ovarian syndrome										
	Females 15–45	2017–2018	PFOA (ng/mL)	0.00	0.47	0.67	0.87	1.37	2.07	5.17
			PFOS (ng/mL)	0.00	1.10	1.70	2.50	3.60	5.30	10.7
Testicular cancer										
	Males 18+	2017–2018	PFOA (ng/mL)	0.00	0.87	1.17	1.67	2.27	3.27	8.30
			PFOS (ng/mL)	0.00	2.60	3.60	5.80	9.20	13.0	26.2

*Serum concentrations in females of childbearing age were used as a proxy for prenatal exposure

Table 4 Total disease burden and costs in 2017–2018

	Primary analysis	Sensitivity analysis	
	Main estimate from meta-analyses	Low estimate	High estimate
Low birth weight			
Attributable incident cases per year	10,053	–	96,847
Attributable fraction	3.17%	–	30.7%
Total cost per annual incident case	$1,420,000,000	–	$13,700,000,000
Direct cost of hospitalization	$305,000,000	–	$2,940,000,000
Indirect cost due to lost IQ points	$1,110,000,000	–	$10,700,000,000
Childhood obesity at age 10			
Attributable incident cases per year	127,362	–	462,119
Attributable fraction	3.78%	–	13.70%
Incremental lifetime medical cost of an obese child relative to normal weight child due to annual incident cases	$2,650,000,000	–	$9,600,000,000
Kidney cancer			
Attributable incident cases per year	142	–	–
Attributable fraction	0.34%	–	–
Total cost per annual incident case	$184,000,000	–	–
Direct medical cost during 1st year of diagnosis	$4,740,000	–	–
Indirect cost as DALY lost over 10 years	$180,000,000	–	–
Testicular cancer			
Attributable incident cases per year	5	–	–
Attributable fraction	0.076%	–	–
Total cost per annual incident case	$6,850,000	–	–
Direct medical cost of treatment	$139,000	–	–
Indirect cost as DALY lost over 10 years	$6,710,000	–	–
Hypothyroidism in females			
Attributable incident cases per year	14,572	–	59,939
Attributable fraction	5.0%	–	20.7%
Total cost per annual incident case	$1,260,000,000	–	$5,180,000,000
Direct cost of new cases of hypothyroidism annually	$42,100,000	–	$173,000,000
Indirect cost as DALY lost over 10 years	$1,220,000,000	–	$5,000,000,000
Adult obesity			
Attributable incident cases per year	–	4,294,379	–
Attributable fraction	–	2.98%	–
Total 15-year cost per annual incident case	–	$17,000,000,000	–
Direct medical cost for newly obese 35-year olds	–	$3,210,000,000	–
Indirect cost of QALY lost over 15 years	–	$13,800,000,000	–
Adult type II diabetes in females			
Attributable incident cases per year	–	1728	–
Attributable fraction	–	0.37%	–
Lifetime cost of treating type II diabetes and associated complications due to annual incident cases	–	$140,000,000	–
Gestational diabetes			
Attributable incident cases per year	–	6061	12,474
Attributable fraction	–	2.85%	5.87%
Total cost per annual incident case	–	$414,000,000	$852,000,000
Direct medical cost	–	$73,300,000	$150,000,000
Indirect cost of lost productivity from adverse birth effects	–	$341,000,000	$702,000,000
Endometriosis			

Table 4 (continued)

	Primary analysis	Sensitivity analysis	
	Main estimate from meta-analyses	Low estimate	High estimate
Attributable incident cases per year	–	696	18,062
Attributable fraction	–	0.43%	11.27%
Total 10-year cost per annual incident case	–	$397,000,000	$10,200,000,000
Direct medical cost over 10 years	–	$21,100,000	$547,000,000
Indirect cost as DALY lost over 10 years	–	$376,000,000	$9,760,000,000
Polycystic ovarian syndrome			
Attributable incident cases per year	–	7209	7505
Attributable fraction	–	5.92%	6.16%
Annual cost of initial PCOS evaluation and treatment of comorbidities due to annual incident cases	–	$10,500,000	$10,900,000
Couple infertility			
Attributable cases of ART SET utilized per year	–	593	26,160
Attributable fraction	–	0.25%	10.86%
Cost of attributable ART SET utilization per annual incident case	–	$37,600,000	$1,660,000,000
Breast cancer			
Attributable incident cases per year	–	421	3095
Attributable fraction	–	0.50%	3.65%
Total 10-year cost per annual incident case	–	$555,000,000	$4,080,000,000
Direct medical cost for 6 months following diagnosis per annual incident cases	–	$21,700,000	$159,000,000
Indirect cost as DALY lost over 10 years	–	$533,000,000	$3,920,000,000
Pneumonia			
Attributable incident cases per year in children 0–3 years old	–	447	6759
Attributable fraction	–	0.58%	8.81%
Total cost per incident case of pneumonia in 0–3-year olds	–	$1,490,000	$22,500,000
Direct medical cost of case across all healthcare settings	–	$1,320,000	$20,000,000
Indirect cost of parental absenteeism	–	$166,000	$2,510,000
Total cost	$5.52 billion	($5.52 billion–$62.6 billion)	

Sensitivity Analyses

As our main result, we reported the PFOA disease burden and cost estimates for the five disease outcomes with meta-analytic associations and then summed them. We then generated alternative estimates through multiway sensitivity analyses to provide the most accurate range of possible costs (Table 4). First, we calculated disease burden and cost estimates using ERRs for PFOS and serum levels from NHANES for the same group of outcomes. We then calculated disease burden and cost estimates for PFOA using an expanded group of outcomes that included both those conditions for which there were meta-analytic results and those for which there were results from systematic or scoping reviews. We also examined the influence of a higher reference level (1.0 ng/mL) on disease burden and costs for which ERRs were based on continuous exposure. Finally, we repeated this analysis for the expanded group of conditions, substituting PFOS for PFOA. The boundaries of the sensitivity analysis were identified using the lowest and highest values for each of the adverse endpoints studied, which were aggregated to create a range for probable disease costs due to PFAS.

The following sections elaborate details of our methods specific to each disease outcome.

Low Birth Weight

We updated a previously published approach to quantifying PFAS-attributable LBW (Malits et al. 2018) to include new literature and an estimate for PFOS, which we used in a sensitivity analysis. Briefly, we compared observed LBW in 2017–2018 to LBW in a counterfactual scenario in which PFOA/PFOS-attributable reductions in birth weight were eliminated, with the difference representing PFOA/PFOS-attributable LBW. For each 1.0 ng/mL of PFOA exposure above 0.1 ng/mL, a 10.5 g decrease [95% confidence interval

(CI) − 16.7, − 4.4] in birth weight was applied in main analyses, based on the results of an updated meta-analysis (Steenland et al. 2018). Sensitivity analyses applied the lower 3.3 g decrement identified in a subset of studies with later pregnancy measures. For PFOS, we applied a 45.2 g decrease (95% CI − 76.8, − 13.6) in birth weight per doubling of early pregnancy maternal plasma concentrations from a study of 3535 mother–infant pairs in the Danish National Birth Cohort study (Meng et al. 2018). We used natality data from the National Vital Statistics System of the National Center for Health Statistics (CDC/NCHS 2014, 2018) to determine the actual mean birth weight, total number of births, and number of LBW births for 2017 and 2018 (the exposed scenario) and then increased mean birth weight in each PFOA/PFOS centile by the absolute value of the attributable decrement to calculate the number of LBW births in a scenario free of PFOA/PFOS effects. The PFOA/PFOS-attributable LBW disease burden was the difference in LBW births between the two, assuming a normal distribution of birth weight (Table S1). The average of results for 2017 and 2018 was calculated to represent PFAS-attributable LBW in 2018.

We calculated the total cost of LBW attributable to in utero PFAS exposure by adding the LBW-associated costs of hospitalization for medical concerns (direct cost) to the lost lifetime economic productivity, operationalized as loss of IQ points due to LBW (indirect cost). The direct cost of hospitalization was estimated at $30,364 per case in 2018 (Kowlessar et al. 2011). LBW has been associated with a 4.98 point loss in IQ (95% CI 3.20, 6.77) (Kormos et al. 2014). Applying a 3% discount rate for lifetime earnings, each IQ point loss was valued at $22,190 in 2018 (Gould 2009; Max et al. 2004). Both costs were multiplied by the number of additional LBW babies born over the 2 years attributable to PFOA and PFOS exposure to get the total cost.

Childhood Obesity

We first quantified changes in body mass index (BMI) *Z*-score in subpopulations of children with increasing prenatal PFOA exposure by applying results of a meta-analysis of ten cohort studies, which identified a 0.09 increase in BMI *Z*-score for each ng/mL increase in PFOA (Liu et al. 2018b). For PFOS, we utilized a cohort study of 412 Norwegian and Swedish mother–infant pairs in which a 1 ng/mL increase in maternal serum levels was associated with 0.18 increase in BMI *Z*-score (Lauritzen et al. 2018). A 0.1 ng/mL reference level was applied in all analyses, below which no effects on BMI *Z*-score were included. The distribution of PFOA and PFOS in US women age 18–49 years in 2007–2008 was used as a proxy for the distribution in pregnant women during that time period. To estimate increases in childhood obesity in 10-year olds due to prenatal PFOA/PFOS exposure, we calculated increases in BMI *Z*-score and quantified incremental increases in $Z > 1.64$ (95th percentile).

Incremental increases in obesity were calculated from PFOA/PFOS-attributable increases in BMI *Z*-score using the NORMDIST function in Excel, assuming a mean = 0 and standard deviation (SD) = 1 without exposure. Increases in percent obese individuals were then multiplied by the number of 10-year olds in 2018 identified in US Census population estimates (Table S2) (USC Bureau 2020; Hales et al. 2017). We calculated the economic burden of PFOA/PFOS-attributable cases of childhood obesity based on an estimated lifetime medical cost of childhood obesity at age 10 of $20,780 in 2018 dollars (Finkelstein et al. 2014).

Kidney Cancer

We utilized the ERR from Bartell et al. to identify the PFOA-attributable increased odds of kidney cancer based on a pooled increased risk of 16% per 10 ng/mL of PFOA exposure from a meta-analysis of four papers demonstrating the link between PFOA and kidney cancer (Bartell and Vieira 2021). We calculated ORs for PFOA in each percentile grouping based upon exposure levels in NHANES 2017–2018, applying a reference level of 0.1 ng/mL below which we assumed there was no increase in odds of kidney cancer. We then converted the ORs to RRs and adjusted for a kidney cancer prevalence of 12.89 per 10,000 adults in the US (Surveillance Research Program Surveillance, Epidemiology, and End Results Program). Afterward, we weighted the RRs by exposure percentile to calculate the AFs across all exposure percentiles using Levin's equation (Levin 1953). The population incidence of kidney cancer, 16.9 per 100,000 adults/year, was obtained from the Surveillance, Epidemiology, and End Results Program and multiplied by the AF across the modeled range of population exposures and the US Census population estimates of the annual average number of adults over age 18 years in 2018 to quantify incident cases of kidney cancer attributable to PFOA exposure (Table S3) (Surveillance Research Program Surveillance, Epidemiology, and End Results Program).

Each case of newly diagnosed kidney cancer was associated with direct medical expenses of $33,485 in the first year alone in 2018 (Shih et al. 2019). We multiplied the cost by the PFOA-attributable cases for a total direct cost of first-year medical expenses for newly diagnosed kidney cancer in American adults. We then calculated the indirect 10-year cost of kidney cancer as lost disability-adjusted life years (DALY, 0.288 for each year, valued at $50,000/year) over 10 years, discounting 3% per year for future preference (Neumann et al. 2014). The total 10-year cost for a case of kidney cancer is the sum of first-year medical expenses and accrued indirect costs (DALY loss).

Testicular Cancer

Similarly to kidney cancer, we utilized an ERR from Bartell et al. that demonstrated a 3% increase in risk of testicular cancer per 10 ng/mL of PFOA exposure from a meta-analysis of two studies (Bartell and Vieira 2021). The same methodology was applied as with kidney cancer to determine ORs, convert to RRs using a prevalence of 0.0817% of adult males, and identify a weighted AF (US Cancer Statistics Working Group 2020). The AF was then multiplied by the US population of adult males and baseline incidence of testicular cancer of 5.7 per 100,000 to identify the PFOA-attributable cases of testicular cancer in 2018 (Table S4) (Surveillance Research Program Surveillance, Epidemiology, and End Results Program). The number of PFOA-attributable testicular cancer cases was multiplied by $26,236, the estimated cost of each new case to the US healthcare system in 2018 dollars (Aberger et al. 2014). As with kidney cancer, we calculated the indirect 10-year cost of testicular cancer as lost DALY (0.288 for each year, valued at $50,000/year) over 10 years, discounting 3% per year for future preference, which we then summed with the direct cost of a new case of testicular cancer (Neumann et al. 2014).

Hypothyroidism

Wen et al.'s analysis based on 2007–2010 NHANES data from 1181 adults provided us with an OR of 7.42 (95% CI 1.14–48.12) to estimate the increase in subclinical hypothyroidism per ln-unit increase of PFOA serum concentration (Wen et al. 2013). We conducted a sensitivity analysis using the association between PFOS and increased odds of subclinical hypothyroidism in females from the same study (OR 3.03; 95% CI 1.14–8.07).

For both PFAS, we applied the OR to our exposure percentiles of PFOA/PFOS in adult women then converted to an RR using a prevalence of clinical hypothyroidism of 0.3% (Hollowell et al. 2002). A weighted AF was then calculated and multiplied by the US population of adult women and incidence of subclinical hypothyroidism of 226.2 per 100,000 adults to obtain PFOA-attributable cases of subclinical hypothyroidism (Garmendia Madariaga et al. 2014). This was adjusted downward by 0.3% to account for the baseline prevalence of hypothyroidism (Table S5) (Hollowell et al. 2002).

The annual direct medical cost per case of hypothyroidism is valued at $2555 with associated $171 in indirect costs due to lost productivity in 2015 (Hepp et al. 2021). We converted the sum of these costs into 2018 dollars ($2888) and multiplied by the PFAS-attributable cases for a total annual cost of subclinical hypothyroidism in adult females. Given the variable clinical course of hypothyroidism, we chose to calculate costs for a single year of treatment due to PFAS rather than lifelong costs. As hypothyroidism is a chronic disease, we modeled an indirect 10-year cost as lost DALY (0.019 for each year, valued at $50,000/year) over 10 years, discounting 3% per year for future preference (Neumann et al. 2014).

Adult Obesity

To quantify PFOS-attributable adult obesity, we modeled increases in obesity by shifting the mean BMI for US adults age > 18 years in relation to PFOS exposure in each centile and estimated increases in percentages of the population with BMI > 30 kg/m^2. We applied results from Liu et al.'s study of 520 adults followed for 6–24 months after the cessation of a 2-year clinical trial of energy-restricted diets on weight change that reported those with PFOS levels > 32.1 ng/mL gained 3.2 kg over the 6–24-month study period, those with levels 19.2–32.1 ng/mL gained 3.5 kg, and those with levels < 19.2 ng/mL gained 1.5 kg (Liu et al. 2018a). Weight gain across tertiles was then linearized across the percentiles to estimate a finer distinction between those with varying exposures (Table S6, Table S14, Fig. S1).

After applying NHANES 2017–2018 PFOS levels to calculate attributable annual weight gain, the additional weight was added to mean weight in the unexposed scenario, as calculated from mean BMI (29.78 kg/m^2) and height (1.66 m) and an exposed mean BMI was calculated from the new weight and same height. Increases in obesity (BMI > 30 kg/m^2) in each exposed subpopulation were calculated by subtracting the percent obese in the exposed scenario to the unexposed counterfactual. The increase in obesity was multiplied by the annual number of adults in the US in 2018 as estimated by the US Census and adjusted for a baseline prevalence of obesity (42.4%) to obtain the number of cases of incident obesity among adults over the age of 18 attributable to PFOS (Table S6) (Fryar et al. 2016; Hales et al. 2020).

We estimated the long-term cost of obesity as a sum of the 15-year direct annual medical cost of obesity (e.g., medical expenses) and the indirect cost of quality-adjusted life years (QALY) lost, using a single age group as a model. We selected 35-year olds, as obesity rates increase with age and this age cohort would allow us to model a 15-year period with the assumption that the majority of 35-year-old obese individuals will remain obese and continue to live for at least 15 years. Using the annual direct medical cost of adult obesity as $2741 in 2005 dollars and discounting for future preference (3% annually), we calculated that a 35-year old who became obese as a result of PFAS exposure in 2017–2018 would incur $43,334 in direct medical costs over 15 years (Cawley and Meyerhoefer 2012). This cost was multiplied by the incremental increase in obesity and the total population of 35-year olds in the US. The indirect cost of adult obesity due to PFAS was calculated as QALY lost due to obesity,

with each QALY assigned a value of $50,000 (Eq. 4) (Muennig et al. 2006; Neumann et al. 2014). Results for males and females were calculated separately, as QALY lost to obesity are sex specific (4.4 years for men and 7.2 years for women), and the final indirect costs for each PFAS of both genders were summed (Muennig et al. 2006).

$$\text{Indirect cost} = \frac{\$50,000 \times \text{populationobese} \times \text{QALY}}{\left(1.03^{15}\right)}. \quad (4)$$

Type 2 Diabetes

We extrapolated incident cases of T2D in 2017–2018 due to PFOA exposure in females over age 18 years using the findings of a case–control study of 1586 women nested within the Nurses' Health Study II that found higher odds of T2D associated with each tertile increase in PFOA concentration (Sun et al. 2018). Odds of incident T2D were linearized across tertiles to estimate a finer distinction with varying exposures as described for adult obesity. We converted the ORs to RRs and then applied Levin's equation to calculate AFs from the RRs (Levin 1953). For each exposed subpopulation, the calculated AF was multiplied by the incidence rate of T2D [6.9 per 1000 American adults (CDC 2020)] and the annual population of US women in 2018. To avoid overestimation, we adjusted for baseline prevalence of T2D (13.0%) to obtain a final estimate of PFOA-attributable cases of T2D in adult women (Table S7) (CDC 2020). The lifetime cost of T2D was estimated at $93,183 per individual in 2018 and multiplied by the number of PFOA-attributable cases in 2018 (Zhou et al. 2013).

Gestational Diabetes

We applied findings from a prospective cohort study of 501 women in whom preconception serum PFOA levels were associated with GDM (OR 1.61 per 0.43 SD increase in PFOA concentration; 95% CI 1.14–3.02) (Zhang et al. 2015). We assumed levels of PFOA exposure among women age 18–49 years in 2017–2018 NHANES to be similar to those in pregnant women of the same year and applied a reference level of 0.1 ng/mL below which we assumed no effect. As with prior calculations, we converted ORs to RRs and then applied Levin's equation to calculate AFs from the RRs (Levin 1953). The AF across all centiles was multiplied by the number of births in 2017–2018 and the prevalence rate of GDM (5.60%) to estimate the annual PFOA-attributable cases of incident GDM (assuming that the prevalence of GDM is the same as the incidence, as the natural progression of the disease is < 1 year) (Table S8) (CDC/NCHS 2014).

Each case of GDM was estimated to have an annual medical cost of $12,089 and lifetime cost due to lost productivity for adverse birth outcomes associated with GDM of $56,237 in 2018 dollars (Peterson et al. 2015). These costs were multiplied by the number of PFAS-attributable cases of GDM.

Endometriosis

After determining the percentile groupings of serum PFOA levels in women age 18–49, we utilized ORs for associations between PFOA and endometriosis from the Endometriosis: Natural History, Diagnosis, and Outcomes (ENDO) study, a case–control study of 495 women age 18–44 years that found an association between serum PFOA levels and higher odds of endometriosis (Buck Louis et al. 2012). We calculated ORs for PFOA in each percentile grouping based upon exposure levels in NHANES 2017–2018, applying a reference level of 0.1 ng/mL below which we assumed there was no increase in odds of endometriosis. We converted the ORs to RRs and applied Levin's equation to calculate AFs as with prior outcomes (Levin 1953). The population incidence of endometriosis, 237 per 100,000 women/year, was obtained from the Nurses' Health Study and multiplied by the AF across the modeled range of population exposures and the US Census population estimates of the number of women age 18–49 years in 2018 and then adjusted for baseline prevalence (6.1%) (Fuldeore and Soliman 2017) to quantify incident cases of endometriosis attributable to PFOA exposure (Table S9) (Missmer et al. 2004).

Following the methodology of Attina et al. (2016), we modeled the direct cost of endometriosis as the total healthcare costs over 10 years of treatment, valued at $30,292 in 2018 dollars (Fuldeore et al. 2015). We also calculated the indirect cost of endometriosis by aggregating lost DALY (0.123 for each year with endometriosis, valued at $50,000/year) over 10 years, discounting 3% per year for future preference (Neumann et al. 2014). These costs were multiplied by the newly incident cases of endometriosis attributable to annual PFOA exposure to obtain the annual PFOA-attributable economic burden.

Polycystic Ovarian Syndrome

We quantified incident cases of PCOS in women age 15–45 years attributable to PFOA/PFOS by applying ERRs from a case–control study by Vagi et al. of 52 PCOS patients and 50 controls in Los Angeles to our percentile groupings of PFOA and PFOS exposure (Vagi et al. 2014). Linearized ORs were calculated as described for adult obesity, and ORs for exposure percentile groups were assigned based on the corresponding tertiles of exposure identified in the Vagi et al. study. The ORs for the second and third tertiles versus the first were 1.65 and 6.93 for PFOA ($p_{\text{trend}} = 0.003$) and 3.43 and 5.79 for PFOS ($p_{\text{trend}} = 0.005$), respectively (Vagi et al. 2014). ORs were converted to RRs, which were

then converted to AFs using Levin's equation, (Levin 1953) multiplied by the incidence of PCOS (2 per 1000 women based on a study of PCOS incidence in the United Kingdom) (Ding 2017) and the population of women age 15–45 years in the US (USCBureau 2020), and adjusted for baseline cases of PCOS (6.6%) (Azziz et al. 2004) to calculate the number of PFOA/PFOS-attributable cases of PCOS in 2018 (Table S10).

The annual medical cost of PCOS in the US was estimated as $4.37 billion for 4 million women or $1092 per PCOS case in 2004 dollars (Azziz et al. 2005). This cost estimate includes the annual cost of initial evaluation and treatment of associated menstrual dysfunction, infertility, T2D, and hirsutism. The cost per case was then multiplied by the PFOA/PFOS-attributable cases of PCOS and adjusted to 2018 dollars ($1452 per case) to determine the annual economic burden due to PCOS-related healthcare visits.

Couple Infertility

We quantified PFAS-attributable cases of couple infertility, defined as TTP > 12 months, based on exposure data from 2017 to 2018 NHANES in women of childbearing age (age 18–49 years). To calculate the OR for infertility in each exposure group, we leveraged data from a case–control analysis of 910 women nested within the Norwegian Mother and Child Cohort Study (Whitworth et al. 2012). Although TTP is a couple-based outcome, chemical exposures were measured only in women, a common limitation among TTP studies. We calculated a linearized OR for estimated serum PFOA/PFOS in each exposure group and assigned an OR for infertility based on the corresponding quartile from the Norwegian study. As with prior estimates, we converted the OR to a RR based on a prevalence rate of impaired fecundity (13.1%) (CDC 2018) and subsequently calculated AFs using Levin's equation (CDC 2018; Levin 1953). We multiplied the AFs by the incidence of infertility in 2018 (63.6 per 10,000 women) and the US population of women age 18–49 years and then adjusted for the baseline prevalence of infertility (13.1%) to quantify attributable cases of infertility (Table S11) (Boivin et al. 2007; Stahlman and Fan 2019).

We applied a 56% utilization rate of assisted reproductive technologies (ART) among infertile couples to assess cost (Boivin et al. 2007). The cost of a single fresh cycle of ART was valued at $63,530 in 2018 dollars. This cost is inclusive of direct maternal and infant costs from 27 weeks prior to delivery through the first year of an infant's life and accounts for the increased rate of multiparity and premature births associated with ART (Crawford et al. 2016). This cost was multiplied by the PFOA/PFOS-attributable annual use of ART in 2018 to estimate the total cost.

Breast Cancer

We applied an OR of 1.26 per ng/mL of PFOA and 1.02 per ng/mL of PFOS from a case–control study of 161 Inuit women in Greenland (Wielsoe et al. 2017). We then calculated the ORs for PFOA/PFOS-associated breast cancer for each of our exposure centiles by multiplying the ORs from this study by the levels of exposure from 2017 to 2018 NHANES among women age 18–49, assuming a reference level of 0.1 ng/mL below which we modeled no effect. The OR for each centile was converted to an RR, which was further transformed into an AF. PFOA/PFOS-attributable cases of breast cancer were then determined by multiplying the weighted AFs by the population of women age 18–49 years and the US breast cancer incidence rate (125.1 per 100,000) and then adjusting for a baseline prevalence of 1.2% (Table S12) (US Cancer Statistics Working Group 2020).

The PFOA/PFOS-attributable cases of female breast cancer were multiplied by the healthcare costs for the first 6 months of a new breast cancer diagnosis. While there are varied lifetime cost estimates of having breast cancer depending on the different stages at which patients are diagnosed, $51,498 in 2018 dollars is the minimum estimated cost a patient will incur throughout the first 6 months of diagnosis regardless of prognosis or odds of remission (Lamerato et al. 2006). As with kidney and testicular cancer, we calculated the indirect 10-year cost of breast cancer as lost DALY (0.288 for each year, valued at $50,000/year) over 10 years, discounting 3% per year for future preference (Neumann et al. 2014).

Pneumonia

To determine the PFAS-attributable increase in pneumonia infections among children age < 3 years, we utilized RRs of 1.27 (95% CI 1.12–1.43) and 1.20 (95% CI 1.07–1.34) for PFOA and PFOS, respectively, from an analysis of 1270 maternal-child pairs in the Norwegian Mother and Child Cohort Study (Impinen et al. 2019). We applied the RR to each percentile grouping of maternal serum PFOA/PFOS levels to calculate the increased risk of pneumonia and bronchitis among children age < 3 years as a result of in utero exposure to PFAS. The RR was then transformed to a weighted AF across all centiles using Levin's equation (Levin 1953) and multiplied by the US population of children age < 3 years and a weighted average incidence rate of 49.4 per 10,000 children, as derived from the incidence rates of pneumonia in children < 2 years old and 2–4 years old, to obtain the PFOA/PFOS-attributable cases of pneumonia in children under age 3 (Table S13) (Jain et al. 2015).

The economic burden of pneumonia in children age < 3 years was constructed as a combination of the overall

direct cost of a pneumonia episode (emergency room visit, hospitalization, or outpatient treatment) and the indirect cost defined as lost parental weekly earnings. The average cost across all healthcare settings per case of pneumonia was determined to be $2952 in 2018 dollars (Tong et al. 2018). For the indirect cost, we multiplied the mean weekly earnings of full-time wage and salary workers in 2014 ($113 per diem) by the average length of stay for a pneumonia hospitalization (3.1 days) to obtain an indirect cost of $350 in lost parental earnings per case or $372 in 2018 dollars (US Bureau of Labor Statistics 2021; Williams et al. 2018). We multiplied both costs by the number of PFOA/PFOS-attributable cases to identify total direct and indirect costs.

Results

Risk-of-bias tools yielded consistent evaluations of the quality of articles used as sources for ERRs across the two reviewers. Among the systematic reviews, the Steenland et al. review of associations with LBW was identified as having low risk of bias except for its reliance on a single source for studies (PubMed), failure to identify whether a single author or multiple authors assessed studies for inclusion and extracted data, and lack of risk-of-bias analysis. The Liu et al. review of childhood obesity and Kim et al. review of hypothyroidism were both identified to have low risk across all four domains by both authors. The Bartell et al. meta-analysis was based on data from articles identified in a prior review (Steenland and Winquist 2021) that also relied exclusively on PubMed, failed to identify who reviewed studies for inclusion and extracted data, and lacked a risk-of-bias analysis. Also, their calculations were based on data from only four studies of kidney cancer and two studies of testicular cancer. All four reviews appropriately considered the relevance of the identified research studies to the questions being considered and avoided emphasis on statistical significance, while two of the systematic reviews (Steenland and Bartell) were identified as probably (vs. conclusively) having addressed all concerns in the four domains. The overall risk of bias was identified as low for all four systematic reviews used (Table S15).

Both reviewers evaluated studies as definitely low risk of bias across all domains for subclinical hypothyroidism, T2D in females, childhood obesity, endometriosis, PCOS, and female breast cancer. The Meng et al. study of LBW, Zhang et al. study of GDM, and Impinem et al. study of pneumonia in children were judged by both reviewers to have potential live birth bias as a threat to internal validity, reducing the corresponding domain's assessment to probably low risk of bias. Both reviewers identified the Whitworth et al. study of couple infertility as potentially having conception bias, yielding a probably low risk of bias for internal validity, as well. One reviewer (LK) noted that the Liu et al. study of adult obesity used data collected as part of a randomized controlled trial, meaning the results may not be generalizable, and therefore evaluated the study as probably low risk of bias for internal validity. All of the evaluated studies at minimum had probably low risk of bias across all criteria, as evaluated by both reviewers (Table S16).

We identified PFOA-attributable disease costs in the US in 2018 of $5.52 billion across the five primary disease endpoints based on meta-analytic ERRs. This estimate represented the lower bound of possible costs, with our sensitivity analyses revealing as much as $62.6 billion in overall costs of long-chain PFAS exposure. Attributable fractions for PFAS of disease burden ranged from 0.08% for testicular cancer due to PFOA to 30.7% for LBW due to PFOS (Table 4).

The largest economic contributor to the main estimate of disease costs attributable to PFAS was childhood obesity ($2.65 billion). For childhood obesity, we also modeled a total lifetime direct medical cost of $4.56 billion due to PFOS exposure, which represents the incremental lifetime medical costs of a child becoming obese at age 10 relative to a child with normal BMI. Hypothyroidism in females contributed $1.26 billion in annual cost. This is a composite value of $42.1 million in direct costs of new cases of hypothyroidism and $1.22 billion in indirect costs as DALY lost over 10 years. The total PFOS-attributable cost for hypothyroidism in the sensitivity analysis was $5.18 billion. PFOA-attributable kidney and testicular cancer contributed a total of $4.88 million in direct costs and $187 million in indirect costs as DALY lost over 10 years. LBW due to PFOA exposure added $1.42 billion in healthcare expenditures annually; this estimate was a composite of $305 million due to direct costs of hospitalization associated with a LBW newborn and $1.11 billion attributable to lost IQ points associated with LBW. The cost estimates for PFOS exposure were substantially higher: $2.94 billion due to hospitalization costs and $10.7 billion due to lost IQ.

The highest costs we identified in both the main and sensitivity analyses were PFOS-attributable lifetime costs related to adult obesity, totaling $17.0 billion dollars annually. We estimated the PFOS-associated 15-year direct medical cost of obesity in newly obese 35-year olds as $3.21 billion, with $13.8 billion in QALY lost over the same 15 years. Other metabolic outcomes included T2D, for which the lifetime cost of PFOA-attributable annual incident cases in women was $140 million, and GDM, for which the low estimate totaled $414 million in annual costs due to PFOA exposure: $73.3 million in direct medical costs and $341 million in indirect costs of lost productivity secondary to adverse birth effects of GDM.

Women's gynecologic and reproductive health outcomes were also major contributors to the total calculated for the

sensitivity analysis. Annual incident PFOA-attributable cases of endometriosis accounted for $397 million to $10.2 billion in total costs, with $21.1 to $547 million due to direct medical costs over 10 years and $376 million to $9.76 billion due to DALY lost over the same 10 years. The annual cost of initial evaluation of PCOS and treatment of associated menstrual dysfunction, infertility, T2D, and hirsutism generated at least $10.5 million PFOA-attributable cost estimate, with a higher estimate of $10.9 million. We estimated the cost of PFOA-attributable cases of couples seeking ART per annum to be at minimum $37.6 million ($1.66 billion upper bound) based on the price of a single embryo transfer ART cycle and the increase in medical costs associated with increased multiparity because of ART. For breast cancer due to PFOA exposure, we estimated $159 million in direct medical cost of utilization of healthcare services within the first 6 months of a new breast cancer diagnosis and $3.92 billion in DALY lost over 10 years. Finally, we estimated PFOA-attributable pneumonia in children < 3 years of age to cost the US medical system $1.49 to $22.5 billion annually due to treatment costs and indirect costs of parental absenteeism.

Discussion

PFAS contribute substantially to disease and disability in the US, with at least $5.52 billion and as much as $62.6 billion in associated economic costs. Our study builds on prior papers that have examined the disease burden and costs associated with PFAS exposure by incorporating 13 health outcomes for which evidence is strongest and constructing a range of models to estimate disease burden and economic costs. The findings suggest that the cost of remediation and of substituting PFAS with safer alternatives in consumer products may well be justified by the large economic costs of adverse health outcomes associated with PFAS exposure.

These estimates are highly conservative for multiple reasons. We did not include outcomes reported by the C8 Science Panel that were not confirmed in general population studies, as those associations were identified in a highly exposed population and our focus was on estimating the disease burden and economic costs due to routine exposure. We also did not include endpoints for which not enough consistent evidence has accumulated, such as prematurity, attention-deficit hyperactivity disorder, and lowered IQ in children resulting from prenatal exposure, and prostate cancer in adult men (Kahn et al. 2020). We based our minimum estimate on the costs associated with a single PFAS (PFOA) for each exposure-disease association and did not aggregate costs across multiple members of the PFAS class, when evidence suggests additivity and synergy in this class of > 4700 chemicals (Chohan et al. 2020). We quantified disease burden for only those associations with strongest scientific evidence for probable causation. We aggregated published costs for each of the diseases considered, but our calculations do not capture the real and substantial social costs such as pain and suffering to patients with PFAS-attributable conditions and effects on their loved ones (Cordner et al. 2021).

Our approach has several limitations. Our analysis relies on previously conducted studies to provide ERRs between PFOA/PFOS exposure and the outcomes of interest. These studies may not be generalizable to the current US population due to recent shifts away from the use of PFOA and PFOS in manufacturing; indeed, median serum levels of PFOA and PFOS in the US have declined substantially from 2007–2008 to 2017–2018, although production of—and consequent human exposure to—replacement PFAS, such as GenX, which are at least as toxic as PFOA (United States Environmental Protection Agency 2021), have increased. Despite the vast literature that exists on the endocrine-disrupting effects of PFAS, there have yet to be large cohort studies to evaluate the longitudinal effects of PFAS exposure in humans and decades of epidemiologic data are required before causation may be acknowledged and attributable disease burden calculated with more certainty. However, the risk-of-bias assessments yielded probably to definitely low risk of bias, and the stakes of inaction are high enough to justify action. It is also important to note that there is likely an overlap in some of the indirect costs modeled in our analysis due to high rates of comorbidity of endocrinopathies, e.g., the indirect lifetime costs of adult obesity may overlap with the costs of T2D.

Despite the limitations of our analysis, our models provide an approximation of the scope of the disease burden and associated costs attributable to exposure to these ubiquitous chemicals. As more research investigates the endocrine-disrupting effects of other chemicals in the PFAS class currently prevalent in manufacturing processes, it is likely that the PFAS-attributable disease burden and associated costs will continue to increase, further strengthening the case for regulation of the entire class of chemicals. Further action is urgently needed to limit these exposures from a health equity perspective, as exposure to these chemicals is not distributed equally throughout the US population and there are subsets who bear more of a burden, e.g., those who live near airports, military installations, and industrial plants (Attina et al. 2019).

Conclusion

The present study identifies at least $5.52 billion in annual disease burden and associated social costs of current annual exposure to long-chain PFAS with our sensitivity analyses revealing as much as $62.6 billion. Regulatory action to

limit ongoing PFAS use and remediate contaminated water supplies may produce substantial economic benefits.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12403-022-00496-y.

Acknowledgements Research reported in this publication was supported by the National Institutes of Environmental Health Sciences under award numbers P30ES000260 and P2CES033423. LGK acknowledges additional support from the National Institute of Environmental Health Sciences under award number K99/R00ES030403. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We thank Dr. Linda Birnbaum, Ms. Gretta Goldenman, and Dr. Katherine Pelch for their insights regarding a draft of the manuscript.

Author Contributions LT conceptualized the study with VO. VO performed disease burden modeling and calculated economic costs. VO wrote the first draft, and LGK and LT provided input and final editorial oversight.

Funding This study was funded by the National Institutes of Health (Grant Nos. ES033423, ES000260, ES030403).

Data Availability Data relating to this publication will be provided upon reasonable request.

Declarations

Conflict of interest LT acknowledges honoraria from Houghton Mifflin Harcourt, Audible, Paidos, and Kobunsha; travel support from the Endocrine Society, WHO, UNEP, Japan Environment and Health Ministries, and the American Academy of Pediatrics; as well as scientific advisory board activities for Beautycounter, IS-Global, and Footprint. All other authors declare they have nothing to disclose.

References

Aberger M, Wilson B, Holzbeierlein JM, Griebling TL, Nangia AK (2014) Testicular self-examination and testicular cancer: a cost-utility analysis. Cancer Med 3:1629–1634

Andrews DQ, Naidenko OV (2020) Population-wide exposure to per- and polyfluoroalkyl substances from drinking water in the United States. Environ Sci Technol Lett 7:931–936

Arbuckle TE, Kubwabo C, Walker M, Davis K, Lalonde K, Kosarac I et al (2013) Umbilical cord blood levels of perfluoroalkyl acids and polybrominated flame retardants. Int J Hyg Environ Health 216:184–194

Attina TM, Hauser R, Sathyanarayana S, Hunt PA, Bourguignon JP, Myers JP et al (2016) Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. Lancet Diabetes Endocrinol 4:996–1003

Attina TM, Malits J, Naidu M, Trasande L (2019) Racial/ethnic disparities in disease burden and costs related to exposure to endocrine-disrupting chemicals in the United States: an exploratory analysis. J Clin Epidemiol 108:34–43

Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO (2004) The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 89:2745–2749

Azziz R, Marin C, Hoq L, Badamgarav E, Song P (2005) Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J Clin Endocrinol Metab 90:4650–4658

Bach CC, Bech BH, Brix N, Nohr EA, Bonde JP, Henriksen TB (2015) Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review. Crit Rev Toxicol 45:53–67

Bach CC, Bech BH, Nohr EA, Olsen J, Matthiesen NB, Bonefeld-Jorgensen EC et al (2016a) Perfluoroalkyl acids in maternal serum and indices of fetal growth: the Aarhus Birth Cohort. Environ Health Perspect 124:848–854

Bach CC, Vested A, Jorgensen KT, Bonde JP, Henriksen TB, Toft G (2016b) Perfluoroalkyl and polyfluoroalkyl substances and measures of human fertility: a systematic review. Crit Rev Toxicol 46:735–755

Bartell SM, Vieira VM (2021) Critical review on pfoa, kidney cancer, and testicular cancer. J Air Waste Manag Assoc 71:663–679

Bartell SM, Calafat AM, Lyu C, Kato K, Ryan PB, Steenland K (2010) Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. Environ Health Perspect 118:222–228

Birnbaum LS (2018) Director, National institute of environmental health sciences and national toxicology program, national institutes of health, department of health and human services. Testimony on The Federal Role in the Toxic PFAS Crisis before the Senate Committee on Homeland Security and Governmental Affairs, Subcommittee on Federal Spending. Available at http://www.govinfo.gov

Boivin J, Bunting L, Collins JA, Nygren KG (2007) International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod 22:1506–1512

Buck Louis GM, Peterson CM, Chen Z, Hediger ML, Croughan MS, Sundaram R et al (2012) Perfluorochemicals and endometriosis: the ENDO Study. Epidemiology 23:799–805

C8 Science Panel. C8 probable link reports. http://www.c8sciencepanel.org/prob_link.html

Calafat AM, Wong LY, Kuklenyik Z, Reidy JA, Needham LL (2007) Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. Environ Health Perspect 115:1596–1602

Cawley J, Meyerhoefer C (2012) The medical care costs of obesity: an instrumental variables approach. J Health Econ 31:219–230

CDC (2016) NHANES 2013–2014, laboratory methods and procedure manual. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/manuals.aspx?BeginYear=2013

CDC (2018) Infertility. https://www.cdc.gov/nchs/fastats/infertility.htm

CDC (2020) National diabetes statistics report, 2020: estimates of diabetes and its burden in the United States. Center for Disease Control, Atlanta

CDC (2022a) Tenatus. https://www.Cdc.Gov/tetanus/about/index.Html#:~:Text=today%2c%20tetanus%20is%20uncommon%

20in,all%20the%20recommended%20tetanus%20vaccinations. Accessed 3 Mar 2022a
CDC (2022b) Diphtheria. https://www.Cdc.Gov/diphtheria/about/index.Html. Accessed 3 Mar 2022b
CDC/NCHS (2014) Birth data files. https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm
CDC/NCHS (2018) Birth data files. https://www.cdc.gov/nchs/nvss/birth_methods.htm
Chohan A, Petaway H, Rivera-Diaz V, Day A, Colaianni O, Keramati M (2020) Per and polyfluoroalkyl substances scientific literature review: water exposure, impact on human health, and implications for regulatory reform. Rev Environ Health. https://doi.org/10.1515/reveh-2020-0049
Cordner A, Goldenman G, Birnbaum LS, Brown P, Miller MF, Mueller R et al (2021) The true cost of pfas and the benefits of acting now. Environ Sci Technol 55:9630–9633
Crawford S, Boulet SL, Mneimneh AS, Perkins KM, Jamieson DJ, Zhang Y et al (2016) Costs of achieving live birth from assisted reproductive technology: a comparison of sequential single and double embryo transfer approaches. Fertil Steril 105:444–450
Crone BC, Speth TF, Wahman DG, Smith SJ, Abulikemu G, Kleiner EJ et al (2019) Occurrence of per- and polyfluoroalkyl substances (PFAS) in source water and their treatment in drinking water. Crit Rev Environ Sci Technol 49:2359–2396
Ding T (2017) Epidemiological investigation and economic analysis of polycystic ovary syndrome (PCOS) for women in the UK. University College London, London
Eick SM, Goin DE, Chartres N, Lam J, Woodruff TJ (2020) Assessing risk of bias in human environmental epidemiology studies using three tools: different conclusions from different tools. Syst Rev 9:249
Environmental Protection Agency (2016) Drinking water health advisories for PFOA and PFOS. https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos 2020
Finkelstein EA, Graham WC, Malhotra R (2014) Lifetime direct medical costs of childhood obesity. Pediatrics 133:854–862
Fryar CD, Carroll MD, Ogden CL (2016) Prevalence of overweight, obesity, and extreme obesity among adults aged 20 and over: United states, 1960–1962 through 2013–2014. Center for Disease Control, Atlanta
Fuldeore MJ, Soliman AM (2017) Prevalence and symptomatic burden of diagnosed endometriosis in the United States: national estimates from a cross-sectional survey of 59,411 women. Gynecol Obstet Investig 82:453–461
Fuldeore M, Yang H, Du EX, Soliman AM, Wu EQ, Winkel C (2015) Healthcare utilization and costs in women diagnosed with endometriosis before and after diagnosis: a longitudinal analysis of claims databases. Fertil Steril 103:163–171
Garmendia Madariaga A, Santos Palacios S, Guillen-Grima F, Galofre JC (2014) The incidence and prevalence of thyroid dysfunction in europe: a meta-analysis. J Clin Endocrinol Metab 99:923–931
Goldenman G, Fernandes M, Holland M, Tugran T, Nordin A, Schoumacher C et al (2019) The cost of inaction: a socioeconomic analysis of environmental and health impacts linked to exposure to PFAS. Nordic Council of Ministers, Copenhagen
Gould E (2009) Childhood lead poisoning: conservative estimates of the social and economic benefits of lead hazard control. Environ Health Perspect 117:1162–1167
Grandjean P, Clapp R (2015) Perfluorinated alkyl substances: emerging insights into health risks. New Solut 25:147–163
Grandjean P, Andersen E, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P (2012) Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA 307:391–397
Hales CM, Carroll MD, Fryar CD, Ogden CL (2017) Prevalence of obesity among adults and youth: United States, 2015–2016. NCHS Data Brief 288:1–8
Hales CM, Carroll MD, Fryar CD, Ogden CL (2020) Prevalence of obesity and severe obesity among adults: United states, 2017–2018. NCHS Data Brief 360:1–8
Hepp Z, Lage MJ, Espaillat R, Gossain VV (2021) The direct and indirect economic burden of hypothyroidism in the United States: a retrospective claims database study. J Med Econ 24:440–446
Hill A (1965) The environment and disease: association or causation? Proc R Soc Med 58:295–300
Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA et al (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 87:489–499
Holzer J, Midasch O, Rauchfuss K, Kraft M, Reupert R, Angerer J et al (2008) Biomonitoring of perfluorinated compounds in children and adults exposed to perfluorooctanoate-contaminated drinking water. Environ Health Perspect 116:651–657
Hoylman B (2020) An act to amend the environmental conservation law, in relation to the use of perfluoroalkyl and polyfluoroalkyl substances in food packaging. Available at https://www.nysenate.gov/legislation/bills/2019/S8817
Impinen A, Longnecker MP, Nygaard UC, London SJ, Ferguson KK, Haug LS et al (2019) Maternal levels of perfluoroalkyl substances (PFASS) during pregnancy and childhood allergy and asthma related outcomes and infections in the norwegian mother and child (MoBa) cohort. Environ Int 124:462–472
Institute of Medicine (1981) Costs of environment-related health effects: a plan for continuing study. The National Academies Press, Washington (DC)
Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C et al (2015) Community-acquired pneumonia requiring hospitalization among U.S. Children. N Engl J Med 372:835–845
Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S et al (2014) The navigation guide—evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ Health Perspect 122:1028–1039
Kahn LG, Philippat C, Nakayama SF, Slama R, Trasande L (2020) Endocrine-disrupting chemicals: implications for human health. Lancet Diabetes Endocrinol 8:703–718
Kahn LG, Harley KG, Siegel EL, Zhu Y, Factor-Litvak P, Porucznik CA et al (2021) Persistent organic pollutants and couple fecundability: a systematic review. Hum Reprod Update 27:339–366
Kim MJ, Moon S, Oh BC, Jung D, Ji K, Choi K et al (2018) Association between perfluoroalkyl substances exposure and thyroid function in adults: a meta-analysis. PLoS ONE 13:e0197244
Knol MJ, Le Cessie S, Algra A, Vandenbroucke JP, Groenwold RH (2012) Overestimation of risk ratios by odds ratios in trials and cohort studies: alternatives to logistic regression. CMAJ 184:895–899
Kormos CE, Wilkinson AJ, Davey CJ, Cunningham AJ (2014) Low birth weight and intelligence in adolescence and early adulthood: a meta-analysis. J Public Health (oxf) 36:213–224
Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S et al (2014) The navigation guide—evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. Environ Health Perspect 122:1015–1027
Kowlessar NM, Jiang J, Steiner C (2011) Hospital stays for newborns. Agency for Healthcare Research and Quality, Rockville
Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S et al (2014) The navigation guide—evidence-based medicine meets environmental health: integration of animal and human evidence

for PFOA effects on fetal growth. Environ Health Perspect 122:1040–1051
Lamerato L, Havstad S, Gandhi S, Jones D, Nathanson D (2006) Economic burden associated with breast cancer recurrence: findings from a retrospective analysis of health system data. Cancer 106:1875–1882
Lauritzen HB, Larose TL, Oien T, Sandanger TM, Odland JO, van de Bor M et al (2018) Prenatal exposure to persistent organic pollutants and child overweight/obesity at 5-year follow-up: a prospective cohort study. Environ Health 17:9
Levin ML (1953) The occurrence of lung cancer in man. Acta Unio Int Contra Cancrum 9:531–541
Liu G, Dhana K, Furtado JD, Rood J, Zong G, Liang L et al (2018a) Perfluoroalkyl substances and changes in body weight and resting metabolic rate in response to weight-loss diets: a prospective study. PLoS Med 15:e1002502
Liu P, Yang F, Wang Y, Yuan Z (2018b) Perfluorooctanoic acid (PFOA) exposure in early life increases risk of childhood adiposity: a meta-analysis of prospective cohort studies. Int J Environ Res Public Health. https://doi.org/10.3390/ijerph15102070
Malits J, Blustein J, Trasande L, Attina TM (2018) Perfluorooctanoic acid and low birth weight: estimates of us attributable burden and economic costs from 2003 through 2014. Int J Hyg Environ Health 221:269–275
Max WB, Rice DP, Sung H, Michel M (2004) Valuing human life: estimating the present value of lifetime earnings, 2000. Available at https://escholarship.org/uc/item/82d0550k
Meng Q, Inoue K, Ritz B, Olsen J, Liew Z (2018) Prenatal exposure to perfluoroalkyl substances and birth outcomes; an updated analysis from the Danish National Birth Cohort. Int J Environ Rese Public Health 15(9):1832
Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ (2004) Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol 160:784–796
Muennig P, Lubetkin E, Jia H, Franks P (2006) Gender and the burden of disease attributable to obesity. Am J Public Health 96:1662–1668
Neumann PJ, Cohen JT, Weinstein MC (2014) Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY Threshold. N Engl J Med 371:796–797
Office of Health Assessment and Translation (OHAT) (2022) Handbook for conducting a literature-based health assessment using ohat approach for systematic review and evidence integration. National Institute of Environmental Health Sciences; 2019. https://ntp.Niehs.Nih.Gov/ntp/ohat/pubs/handbookmarch2019_508.Pdf
Olsen GW, Mair DC, Reagen WK, Ellefson ME, Ehresman DJ, Butenhoff JL et al (2007) Preliminary evidence of a decline in perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations in American Red Cross blood donors. Chemosphere 68:105–111
Pelch KE, Reade A, Wolffe TAM, Kwiatkowski CF (2019) PFAS health effects database: protocol for a systematic evidence map. Environ Int 130:104851
Peterson C, Grosse SD, Li R, Sharma AJ, Razzaghi H, Herman WH et al (2015) Preventable health and cost burden of adverse birth outcomes associated with pregestational diabetes in the United States. Am J Obstet Gynecol 212(74):e71-79
Rappazzo KM, Coffman E, Hines EP (2017) Exposure to perfluorinated alkyl substances and health outcomes in children: a systematic review of the epidemiologic literature. Int J Environ Res Public Health 14(7):691
Rogers RD, Reh CM, Breysse P (2021) Advancing per- and polyfluoroalkyl substances (PFAS) research: an overview of ATSDR and NCEH activities and recommendations. J Expo Sci Environ Epidemiol 31:961–971
Schrenk D, Bignami M, Bodin L, Chipman JK, Del Mazo J, Grasl-Kraupp B et al (2020) Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA J Eur Food Saf Auth 18:e06223
Shih YT, Xu Y, Chien CR, Kim B, Shen Y, Li L et al (2019) Rising economic burden of renal cell carcinoma among elderly patients in the USA: part II—an updated analysis of SEER-Medicare Data. Pharmacoeconomics 37:1495–1507
Stahlman S, Fan M (2019) Female infertility, active component service women, U.S. Armed forces, 2013–2018. MSMR 26:20–27
Steenland K, Winquist A (2021) PFAS and cancer, a scoping review of the epidemiologic evidence. Environ Res 194:110690
Steenland K, Barry V, Savitz D (2018) Serum perfluorooctanoic acid and birthweight: an updated meta-analysis with bias analysis. Epidemiology 29:765–776
Steenland K, Fletcher T, Stein CR, Bartell SM, Darrow L, Lopez-Espinosa MJ et al (2020) Review: evolution of evidence on PFOA and health following the assessments of the C8 Science Panel. Environ Int 145:106125
Sun Q, Zong G, Valvi D, Nielsen F, Coull B, Grandjean P (2018) Plasma concentrations of perfluoroalkyl substances and risk of type 2 diabetes: a prospective investigation among U.S. women. Environ Health Perspect 126:037001
Surveillance Research Program NCI (2021) Surveillance, epidemiology, and end results program. Seer*explorer: an interactive website for seer cancer statistics. https://surveillance.cancer.gov/
Tong S, Amand C, Kieffer A, Kyaw MH (2018) Trends in healthcare utilization and costs associated with pneumonia in the United States during 2008–2014. BMC Health Serv Res 18:715
United States Environmental Protection Agency (2021) Human health toxicity assessments for GenX chemicals. https://www.epa.gov/chemical-research/human-health-toxicity-assessments-genx-chemicals. Accessed 2 Nov 2021
US Bureau of Labor Statistics (2020) CPI for all urban consumers (CPI-U). https://data.bls.gov/cgi-bin/surveymost?cu
U.S. Bureau of Labor Statistics (2021) Median usual weekly earnings of full-time wage and salary workers by sex, quarterly averages, seasonally adjusted. https://www.bls.gov/news.release/wkyeng.t01.htm
US Cancer Statistics Working Group (2020) U.S. Cancer statistics data visualizations tool, based on 2019 submission data (1999–2017). https://www.cdc.gov/cancer/dataviz
USC Bureau (2020) U.S. and world population clock. https://www.census.gov/popclock/2020
Vagi SJ, Azziz-Baumgartner E, Sjodin A, Calafat AM, Dumesic D, Gonzalez L et al (2014) Exploring the potential association between brominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phthalates, and bisphenol a in polycystic ovary syndrome: a case–control study. BMC Endocr Disord 14:86
Wan MLY, Co VA, El-Nezami H (2021) Endocrine disrupting chemicals and breast cancer: a systematic review of epidemiological studies. Crit Rev Food Sci Nutr. https://doi.org/10.1080/10408398.2021.1903382
Waterfield G, Rogers M, Grandjean P, Auffhammer M, Sunding D (2020) Reducing exposure to high levels of perfluorinated compounds in drinking water improves reproductive outcomes: evidence from an intervention in Minnesota. Environ Health 19:42
Wen LL, Lin LY, Su TC, Chen PC, Lin CY (2013) Association between serum perfluorinated chemicals and thyroid function in U.S. adults: the national health and nutrition examination survey 2007–2010. J Clin Endocrinol Metab 98:E1456-1464

Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B et al (2016) Robis: a new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol 69:225–234

Whitworth KW, Haug LS, Baird DD, Becher G, Hoppin JA, Skjaerven R et al (2012) Perfluorinated compounds and subfecundity in pregnant women. Epidemiology 23:257–263

Wielsoe M, Kern P, Bonefeld-Jorgensen EC (2017) Serum levels of environmental pollutants is a risk factor for breast cancer in inuit: a case control study. Environ Health 16:56

Williams S, Gousen S, DeFrances C (2018) National hospital care survey demonstration projects: pneumonia inpatient hospitalizations and emergency department visits (National Health Statistics Reports). U.S. Department of Health and Human Services, Washington, D.C.

Xu Y, Fletcher T, Pineda D, Lindh CH, Nilsson C, Glynn A et al (2020) Serum half-lives for short- and long-chain perfluoroalkyl acids after ceasing exposure from drinking water contaminated by firefighting foam. Environ Health Perspect 128:77004

Zhang C, Sundaram R, Maisog J, Calafat AM, Barr DB, Buck Louis GM (2015) A prospective study of prepregnancy serum concentrations of perfluorochemicals and the risk of gestational diabetes. Fertil Steril 103:184–189

Zhou X, Zhang P, Hoerger TJ (2013) Lifetime direct medical costs of treating type 2 diabetes and diabetic complications. Am J Prev Med 45:253–261

Science of The Total Environment
Volume 918, 25 March 2024, 170647

Discussion

Estimated scale of costs to remove PFAS from the environment at current emission rates

Author links open overlay panelAlison L. Ling

https://doi.org/10.1016/j.scitotenv.2024.170647

Highlights

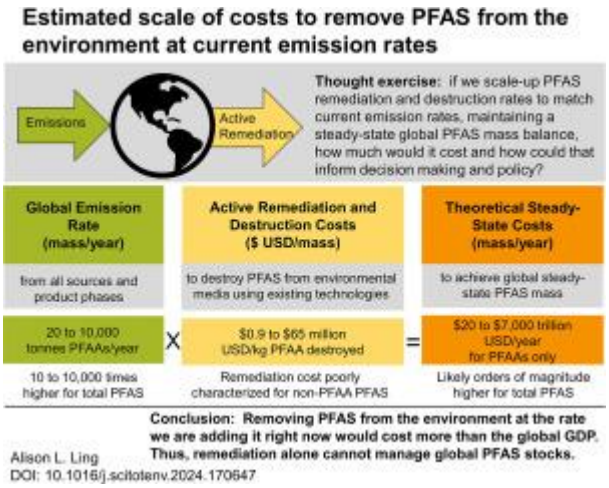
- PFAS remain and cycle in the natural environment until actively destroyed
- Managing environmental stocks of PFAS through treatment alone is unaffordable
- Reduced PFAS emissions is needed to avoid increasing environmental accumulation
- PFAS use restrictions should regulate PFAS as a class and consider “essential uses”

Abstract

This discussion article builds upon existing data to ask whether environmental remediation and treatment is an economically viable solution to manage global environmental stocks of per- and polyfluoroalkyl substances (PFAS) without extensive use restrictions. Their environmental persistence means that PFAS released into the

environment will remain there until actively removed and destroyed. Thus, removing and destroying PFAS from the global environment at the same rate they are currently being added reflects a theoretical steady-state condition where global PFAS stocks remain constant. Current costs to remove perfluoroalkyl acids (PFAAs), a subclass of PFAS, from the environment at the same rate they are being added were estimated here at 20 to 7000 trillion USD per year. If the ratio of total PFAS emissions to PFAAs emissions matches current production ratios, total PFAS release rates and associated treatment costs could be 10 to 10,000 higher than presented above for PFAAs only. Thus, current costs to remove and destroy the total PFAS mass released annually into the environment would likely exceed the global GDP of 106 trillion USD. While this level of treatment is not technically or economically achievable, it highlights the unaffordability of using environmental remediation alone to manage environmental PFAS stocks. Without significant reductions in production and emissions, the mass of PFAS present in the global environment will continue to rise. Treating targeted environmental media will be needed to manage human and environmental health impacts, but we are limited to the level of treatment that is practical and affordable.

Graphical abstract



1. Download: Download high-res image (403KB)
2. Download: Download full-size image

Introduction

PFAS are a broad class of over 10,000 chemicals used in manufacturing processes and consumer products, across many industries, including electronics, automotive, textiles, pulp and paper, metal finishing, and personal care products (Brunn et al., 2023; ECHA, 2023). The definition used by the European Chemicals Agency (ECHA) states that PFAS contain “at least one fully fluorinated methyl or methylene carbon atom” without a halogen attached to it, and excludes certain fully degradable subgroups (ECHA, 2023). The PFAS most frequently studied and targeted by regulations are perfluoroalkyl acids (PFAAs), including legacy compounds perfluorooctanoic acid (PFOA) and

perfluorooctane sulfonic acid (PFOS). As PFAS attract increasing regulatory and public attention, industries have pivoted to replace these legacy PFAS with alternate "replacement" chemicals. Many of these replacements are also PFAS despite the fact that uses in many consumer products have PFAS-free alternatives (Glüge et al., 2022). Environmental fate and health impacts of newer, replacement PFAS are less understood, complicating efforts to characterize the risks and remediation options for PFAS in active use (Ruan et al., 2022; Wang et al., 2017).

PFAS are globally ubiquitous in the environment and continue to be discharged and disseminated via global transport of products and wastes, atmospheric dispersion, surface water transport, and groundwater flow (D'Ambro et al., 2021; Kurwadkar et al., 2022; Stoiber et al., 2020b). They have been reported in soil, water, and air samples across the world (Abunada et al., 2020; Cousins et al., 2022; Rauert et al., 2018; Valsecchi et al., 2013; Xu et al., 2021), and in human blood serum (DeLuca et al., 2021; Sunderland et al., 2019). The environmental fate of PFAS is complicated by transformations that can convert "precursor" PFAS into other PFAS. For example, some fluorinated gases and side-chain fluorinated polymers have been shown to degrade to PFAAs, such as highly persistent and mobile trifluoroacetic acid (TFA) (Brunn et al., 2023; Freeling and Björnsdotter, 2023; OECD, 2022; Sun et al., 2020). So even if PFAAs are not produced commercially in the future, they can still be produced in the environment via degradation of other PFAS, including through environmental photolysis and oxidation (Armitage et al., 2006; Martin et al., 2006; Thackray and Selin, 2017), biological processes (Kolanczyk et al., 2023; Liu and Mejia Avendaño, 2013), and wastewater treatment (Houtz et al., 2016; Thompson et al., 2022).

The ubiquity and increasing environmental stocks of PFAS raise concerns due to reported toxicity impacts to wildlife and humans (Brunn et al., 2023; Espartero et al., 2022; Jones et al., 2022; Sunderland et al., 2019). A recent National Academies review found sufficient evidence for decreased antibody response to vaccines, dyslipidemia (including increased cholesterol), decreased birthweight, and increased risk of kidney cancer (National Academies of Sciences, Engineering, and Medicine, 2022). Household use of PFAS-containing products can expose humans to PFAS through skin exposure or inhalation of household dust and volatilized PFAS in indoor spaces (DeLuca et al., 2021; Kissel et al., 2023; Sunderland et al., 2019). PFAS in groundwater and surface waters can also impact human health through drinking water supplies and agricultural uptake (Andrews and Naidenko, 2020; Stoiber et al., 2020a; Wang et al., 2020).

Regulations regarding PFAS are rapidly evolving. Drinking water in the U.S. is currently subjected to health guidance values in 30 U.S. states (ITRC, 2023), with proposed Federal maximum contaminant limits (MCLs) for specific compounds (U.S. EPA, 2023b). PFOA and PFOS could soon be classified as a hazardous substance in the United States (U.S. EPA, 2022), which would impact production and remediation costs. In addition to these environmental regulations, regulations restricting PFAS production and use are being implemented in the EU and the United States (ECHA, 2023; Minnesota PFAS Ban, 2023; Vermont Legislature, 2021). PFOA, PFOS, and perfluorohexane sulfonic acid (PFHxS) are specifically addressed by the Stockholm Convention on Persistent Organic Pollutants, targeting international use limitations (OECD, 2023).

European PFAS regulations are generally based on chemical characteristics rather than specific compounds (ECHA, 2023; European Drinking Water Directive, 2020). has Specific U.S. states have also passed PFAS use restrictions addressing PFAS as a group rather than on a chemical-by-chemical basis (California Safer Food Packaging and Cookware Act, 2021; Maine Legislature, 2021; Minnesota PFAS Ban, 2023; Vermont Legislature, 2021). However, Federal regulations in the United States have largely focused on individual PFAS such as PFOA and PFOS rather than defining and restricting PFAS as a group (U.S. EPA, 2021, U.S. EPA, 2022; U.S. EPA, 2023b). Regulations addressing PFAS as a class rather than as individual compounds accommodates the potential for environmental transformation of precursors to other PFAS, despite analytical constraints (Kwiatkowski et al., 2020).

The same chemistry that makes PFAS useful – the thermodynamic strength and short length of carbon-fluorine bonds – also makes them difficult to degrade. Very few PFAS in use today readily degrade to non-fluorinated end products by any known environmental process (ITRC, 2022b). Thus, persistent PFAS entering soils, groundwater, surface water, and the atmosphere remain in the environment until actively removed and destroyed. Our society has previously attempted remediation of persistent and toxic contaminants in the environment, including polychlorinated biphenyl (PCBs) and chlorinated pesticides. However, PFAS, especially emerging short-chain compounds, can be both more persistent and more mobile than these legacy contaminants (Hale et al., 2020), enabling ongoing dispersion and cycling in environmental air and water resources with ongoing risk of human exposure.

Recent work argues that environmental persistence alone should be sufficient justification to regulate production of a chemical, because stocks of persistent chemicals added to the environment consistently increase, with increasing potential for known and unknown human health risks (Cousins et al., 2020; Cousins et al., 2019b). These risks are exacerbated by the very high societal cost of removing persistent chemicals from the environment once released (Barr Engineering Co., and Hazen and Sawyer, 2023; Brunn et al., 2023; U.S. Chamber of Commerce, 2022), by degradation of precursor PFAS into other PFAS, and by unknown health effects of replacement PFAS and PFAS mixtures (De Silva et al., 2021). Despite the challenges with environmental persistence, PFAS are still being produced and integrated into consumer products in “non-essential uses,” exacerbating the problem for future generations (Glüge et al., 2022; Ritscher et al., 2018). “Essential use” reflects chemical use that is “necessary for health, safety or is critical to the functioning of society” with “no available technically and economically feasible alternatives,” while “non-essential uses” are primarily market driven (Cousins et al., 2019a).

The problem of persistence also means that active treatment to remove and destroy PFAS from the environment is difficult and expensive. An U.S. EPA-sponsored, 2022 study evaluated the efficacy and readiness of non-combustion-based technologies to mineralize PFAS associated with spent granular activated carbon (GAC) and anion exchange (AIX) media, soils, wastewater biosolids, aqueous film forming foams (AFFF), and landfill leachate. This study found limited technological readiness other than high-temperature incineration, except potentially for applying supercritical water oxidation (SCWO) for AFFF destruction and pyrolysis for biosolids treatment (Berg et al., 2022).

However, high-temperature incineration is expensive and primarily available at hazardous waste incinerators. The U.S. EPA reported typical costs for hazardous waste incineration at 1110 to 1610 USD per tonne of PFAS-containing liquids, sludges, and solids (U.S. EPA, 2020), orders of magnitude higher than the 55 USD per tonne national average for municipal solid waste tipping fees (Environmental Research and Education Foundation, 2023).

Environmental accumulation of PFAS is best understood by considering a mass balance of PFAS stocks in the global environment. The primary sources of PFAS to the environment include production-phase emissions from PFAS production and product manufacturing facilities and use-phase emissions either released to the ambient environment near the point of use or routed through waste management facilities that receive PFAS from industrial, commercial, and municipal sources (Armitage et al., 2006; ECHA, 2023; Ehsan et al., 2023; Evich et al., 2022; Schellenberger et al., 2022; Thompson et al., 2022) (Fig. 1). The ubiquity of PFAS in consumer products, associated diffuse nature of use-phase emissions, and environment mobility all contribute to the ubiquity of PFAS in environmental media worldwide. A mass balance showing current PFAS emission sources and destruction routes is illustrated in Fig. 1.

Current destruction of PFAS from environmental sources in the U.S. is limited to <15 hazardous waste incineration and GAC reactivation facilities, accepting a total of <3 million tonnes of mixed material per year (U.S. EPA, 2019). If that total capacity was dedicated to PFAS-containing wastes, the PFAS content of that waste matched PFAS-laden GAC reported at 10 to 55,000 ng/g (DiStefano et al., 2022), and capacity is scaled to the entire world based on gross domestic product (GDP), then current global PFAS destruction from environmental sources would fall between 0.15 and 820 t/year. In contrast, global PFAS emissions likely exceed 100,000 tons per year (ECHA, 2023; Evich et al., 2022). Thus, the mass rate of PFAS currently entering the environment vastly exceeds the mass rate being removed and destroyed.

A steady-state condition with constant mass of PFAS in the global environment could theoretically be achieved by either increasing the amount of PFAS removed from the environment via active environmental remediation and destruction, reducing input sources of PFAS to the environment via PFAS use restrictions, or both. This paper presents a thought experiment evaluating costs to reach steady-state conditions by increasing environmental remediation and destruction to match current PFAS emission rates, acknowledging that those treatment rates are not actually feasible. This steady-state reference point could inform relative prioritization of environmental remediation and use restriction to manage PFAS in the global environment.

This simplified, theoretical model does not consider the varying turnaround time of different environmental stocks, instead taking a holistic, long-term view of the global environment, where PFAS in medium-term and long-term environmental sinks can be recycled back into other stocks. Medium-term sinks include open ocean water, landfills, and sediment burial, while long-term sinks include deep ocean burial and deep-well injection. A steady-state mass of PFAS in the global environment would not reflect steady-state conditions in all environmental stocks, as medium- and long-term sinks may take on more PFAS mass while media with shorter turnaround times and more

potential for human exposure like the atmosphere and freshwaters may see reduced PFAS mass during global steady-state conditions.

The goal of this study is to contribute to discussion of long-term economic costs and benefits of PFAS use restrictions and environmental regulations. Societal costs will be incurred regardless of the future balance between 1) ongoing PFAS accumulation due to limited action, 2) reduced emissions through PFAS use and emission restrictions, and 3) increased treatment through environmental regulations. The future balance between these actions will dictate the balance of negative effects, including 1) increasing human and environmental impacts from compounding environmental PFAS stocks, 2) economic impacts of use restrictions, and 3) remediation costs and associated externalities. Understanding the relative and ultimate costs of all three options can support development and prioritization of regulatory actions regarding PFAS.

The estimated annual health burden of current PFAS exposures were recently estimated at tens of billions of USD both in the United States and in the European Economic Area (Goldenman et al., 2019; Obsekov et al., 2023). These reflect a portion of societal costs associated with current environmental PFAS stocks and would be expected to increase as global PFAS stocks increase. Likewise, economic impacts of PFAS use restrictions are also starting to be characterized, with the European Chemical Agency estimating qualitative and quantitative cost impacts of recently proposed use restrictions (ECHA, 2023).

However, reported cost estimates for removing and destroying PFAS from environmental media remain limited, especially at scales relevant to the global mass balance. The environmental media most widely treated for PFAS at full-scale is drinking water, where GAC, AIX, or reverse osmosis (RO) have been applied to separate PFAS from the water phase (AWWA, 2019). Reported removal efficiencies are primarily for PFAAs. As a result, full-scale cost estimates for separating PFAS from media other than drinking water or for separating non-PFAA PFASs from any media are not widely available. Furthermore, full-scale PFAS destruction remains limited to high-temperature thermal technologies with high costs (U.S. EPA, 2020), limited capacity (U.S. EPA, 2019), greenhouse gas emissions, and uncertain regulatory status (PFAS, 2022; NY Senate, 2020; US Department of Defense, 2023).

The demonstrated human health impacts of PFAS will require environmental remediation in targeted applications to protect human health. However, resources available to address environmental PFAS are limited. For example, the Bipartisan Infrastructure Law in the U.S. set aside $9 billion USD over five years to treat PFAS in drinking water (The White House, 2023), but meeting proposed drinking water regulations was recently estimated at $55 billion USD and $24 billion USD by separate studies (Black and Veatch, 2023; U.S. EPA, 2023a). Funding sources to remediate landfills, wastewater effluent and biosolids, and contaminated soils and sediments are more uncertain, especially for facilities without an identified, liable polluter. Improved understanding of how much it costs to remove and destroy PFAS from the environment could help inform discussion of potential costs to implement regulatory criteria for drinking water, wastewater, and other media as well as potential societal cost savings from PFAS use restrictions.

This discussion article addresses that need by considering approximate cost estimates to remove PFAS from the environment as fast as they are being added. For the conceptual framework, order-of-magnitude estimates were developed for technology costs per mass PFAS destroyed and current global emission rates of PFAS mass per year, which were then multiplied together for an estimated annual cost to achieve theoretical steady-state conditions.

Environmental Science & Technology

pubs.acs.org/est

Viewpoint

The True Cost of PFAS and the Benefits of Acting Now

Alissa Cordner,* Gretta Goldenman, Linda S. Birnbaum, Phil Brown, Mark F. Miller, Rosie Mueller, Sharyle Patton, Derrick H. Salvatore, and Leonardo Trasande

Cite This: *Environ. Sci. Technol.* 2021, 55, 9630−9633

Read Online

ACCESS | Metrics & More | Article Recommendations

KEYWORDS: *PFAS, social costs, chemicals policy, remediation, prevention*

INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) are a class of over 9000 persistent hazardous chemicals used in industrial processes and consumer goods. They are ubiquitous in the environment and in people, who are exposed to PFAS via contaminated food and water, consumer products, and workplaces.[1] Exposure to several PFAS has been linked to a plethora of health effects in both animal and human studies, even at background levels. They are so environmentally persistent that they have been termed "forever chemicals."

While in many ways PFAS contamination problems reflect broader issues with the chemicals regulatory system in the United States, a key feature of this industry is that only a handful of companies have produced the basic chemical building blocks for PFAS chemicals. These companies have known about the potential toxicity, human exposure, and extreme persistence of PFAS since the 1970s, yet have continued and expanded production.[2]

In the 2000s, in response to mounting pressure from the U.S. Environmental Protection Agency (EPA) about risks to human and environmental health, PFAS manufacturers agreed to phase out U.S. production of perfluorooctanoic acid (PFOA), perfluorooctanesulfonate (PFOS), and some related PFAS. Replacement PFAS, including new chemicals developed by industry, are widely used in more than 200 use categories,[3] despite growing concerns about exposures, persistence, and toxicity.[4]

The PFAS industry claims that the chemicals' use in consumer goods and industrial applications brings wide benefits, valuing the U.S. fluoropolymer segment at $2 billion a year.[5] However, it fails to mention the costs of exposure, which are long-term, wide-ranging, routinely externalized onto

Received: June 1, 2021
Published: July 7, 2021

https://doi.org/10.1021/acs.est.1c03565
Environ. Sci. Technol. 2021, 55, 9630−9633

the public, and disproportionately experienced. Focusing on a narrow, short-term view of PFAS benefits ignores how costs are displaced to communities and governments, despite existence of safer alternatives in most product sectors.

This review of the true costs of PFAS highlights the need to act now to ensure that exposures are capped at current levels by reducing the production and use of PFAS. It calls attention to systematic failures of U.S. chemical regulation, including inadequate premarket review of new compounds, data gaps that prevent and delay the regulation of existing chemicals, and the widespread externalization of social costs of pollution onto the public.

SNAPSHOT OF THE PROBLEM

Shifting the Burden to Public Utilities. Widespread contamination of surface water and groundwater due to industrial releases of PFAS or use of PFAS-containing firefighting foams is now a major problem in the United States and globally. An estimated 200 million U.S. residents, nearly two-thirds of the U.S. population, receive municipally provided drinking water that is contaminated with PFAS.[6]

Methods to reduce levels of PFAS in drinking water include filtration with granular activated charcoal treatment, reverse osmosis, ion exchange, or blending with less contaminated water from other sources, none of which fully eliminate PFAS. Municipalities may also opt to buy water from other distributors, but each method involves significant capital costs for new infrastructure and ongoing maintenance costs. For example, following extensive contamination by a PFAS manufacturer in the Cape Fear River watershed, Brunswick County, North Carolina spent $99 million on a reverse osmosis plant and will incur $2.9 million annually in operations expenses. Orange County, California estimates that the infrastructure needed to lower the levels of PFAS in its drinking water to the state's recommended levels will cost at least $1 billion.

These costs of cleaning up PFAS contamination of water are rarely internalized by chemical manufacturers or other responsible parties. Instead, they are usually displaced onto public utilities, their ratepayers, and state and local governments.

Communities with PFAS-contaminated drinking water also incur expenses related to testing and monitoring the contamination, informing the public, gathering information on treatment alternatives, studying the feasibility of infrastructure investments, and staff time for these projects. Low-income communities may be unable to cover such expenditures and often have few options for cost recovery, especially when the source of the PFAS contamination has not been determined. Additionally, PFAS contamination is likely to disproportionately impact vulnerable communities due to historic racial discrimination in housing and occupational sectors, and inequitable enforcement of environmental regulations that concentrate point sources of pollution proximal to these communities.

PFAS in wastewater can lead to additional expenses for public utilities. Wastewater treatment plants are designed to remove solids and pathogens, not persistent chemicals, and so any PFAS coming into the treatment plant are largely discharged into receiving waters or left as contaminants in sewage sludge. Needed treatment to remove contaminants will result in increased costs, and failure to treat may decrease existing revenue streams. For example, the public utility managing Merrimack, New Hampshire's wastewater currently earns $400,000 annually from processing sludge into compost for public sale as fertilizer. If the utility can no longer sell the sludge due to PFAS contamination, it will instead have to spend $2.4 million annually in landfill charges.

Other Externalized Costs of PFAS. Many other PFAS-related costs are routinely passed on to the public, rather than paid by the responsible polluters. For example, to prevent further contamination of water resources, the stock of fluorinated aqueous film-forming foams (AFFFs) still in place at military bases, airports, industrial sites, and local fire stations needs to be replaced with nonfluorinated foams. This requires collecting the AFFFs and then decontaminating or replacing equipment. The unused AFFFs and the PFAS-laden rinsewater must be contained, and no safe, permanent destruction methods currently exist.

The process of deciding what to do with hot spots of PFAS contamination is labor-intensive, time-consuming, and expensive. Testing of soil and water to determine the extent of contamination typically costs hundreds of dollars per sample, and few cleanup options exist. Landfilling of contaminated soil involves transportation costs and tip fees, and PFAS are only sequestered for the lifespan of the landfill. Incineration may destroy PFAS but only at extremely high temperatures, and has not been shown to work at large scale. Concerns about emissions from PFAS incineration, as well as public outrage at incineration testing in impacted communities, point to both health and political costs of PFAS incineration.

PFAS contamination may also reduce property values of homes and businesses. The discovery of water contamination, or even the perceived risk of potential contamination, can depress property values and stigmatize neighborhoods, potentially leading to lower home values and blocking residents' from selling properties, particularly when contamination achieves a level of public notoriety.[7]

Households and local businesses seeking to avoid exposure to contaminated drinking water may have to purchase bottled water or install and maintain home water filtration systems. In cases where the polluter is known, these costs may be recoverable through costly litigation. More often, however, the precise source of PFAS contamination is unclear, contested, or involves multiple polluters, making litigation or regulatory outcomes uncertain. Additionally, residents living outside of established boundaries or whose water is below specific action levels may not qualify for alternative water supplies, even if distribution systems exist.

Farms in areas with PFAS-contaminated water or soil may be forced to destroy harvests or products, or even to cease operation. As examples, dairy farms in more than one state were forced to dump milk contaminated with PFAS from agricultural applications of sludge and to euthanize their herds, while an organic farm near Colorado's Fort Peterson Air Force Base completely ceased production after learning that their irrigation water was highly contaminated.

Again, the governance and research expenses in such instances are substantial. In addition to technical expertise and staffing related to exposure assessment, human biomonitoring, and cleanup efforts, local and state governments must invest significant resources in public engagement and communications, and in managing PFAS programs and task forces. For example, North Carolina has allocated over $5 million for its PFAS Testing Network to address ongoing questions about PFAS exposure.

https://doi.org/10.1021/acs.est.1c03565
Environ. Sci. Technol. 2021, 55, 9630−9633

State and local governments may also incur significant legal expenses. States including New Hampshire and New Jersey have been sued by PFAS manufacturers opposed to health-protective drinking water regulations. States have occasionally received compensation from the companies responsible for PFAS pollution in their environs, including Minnesota ($850 million), Alabama ($39 million), and Michigan ($168 million).[8] The number of lawsuits and the size of settlements indicates the nation-wide scope of PFAS contamination and the costs of exposure. Legal actions such as these require significant time and resources from state-employed and contracted lawyers, consultants, and other professionals.

Moreover, these legal actions happen after the damage has occurred. Since complete remediation of PFAS in the environment is impossible at this time, exposures will remain for generations to come.

Health Impacts: The Biggest Externality. Exposure to PFAS via contaminated drinking water has been linked to kidney and testicular cancer, ulcerative colitis, pregnancy and fertility problems, liver diseases, thyroid disease, and high cholesterol.[1,9] PFAS exposure is also linked to immunotoxic effects, including decreased response to vaccines and possible increases in COVID-19 severity.[10] Even low-level exposure is associated with serious health consequences. For example, multiple studies have linked prenatal PFAS exposure with low birth weight, a particularly concerning end point that is associated with higher risk of cardiovascular disease, respiratory disease, and diabetes in adulthood, as well as impaired cognitive development and lower lifetime earnings.[11]

The impacts on human health due to PFAS exposure are immense. A recent analysis of impacts from PFAS exposure in Europe identified annual direct healthcare expenditures at €52−84 billion.[12] Equivalent health-related costs for the United States, accounting for population size and exchange rate differences, would be $37−59 billion annually. These costs are not paid by the polluter; they are borne by ordinary people, health care providers, and taxpayers.

Indirect social costs are also extensive, though more difficult to calculate. They include lost wages; lost years of life; reduced quality of life; increased stress, anxiety, and depression; and subsequent impacts on families and communities. Such social costs are quantifiable and can guide policy,[13] but no such analysis currently exists for health impacts from PFAS in the United States.

Finally, other significant health-related costs borne by government institutions and taxpayers include biomonitoring and health monitoring of exposed populations, and government research expenditures aimed at identifying PFAS toxicity and extent of exposures. In a more equitable world, this research would be carried out by the producer before the chemical came onto the market.

DISCUSSION

The health, societal, and economic impacts of contamination from PFAS production and use are multifaceted and broadly distributed. The costs of these impacts are long-term, incompletely understood, and externalized onto individuals, communities, and government at all levels, while profits accrue to corporations shielded from these costs by the protections built into our chemical regulatory laws and practices.[14] The continued use of PFAS will lead to increases in contamination and exposures in the future. But these exposures can be capped if steps are taken now to reduce and eventually phase out production and use of PFAS in all nonessential applications. In the meantime, the responsibility for paying for the legacy contamination should rest on the companies who continue to produce and market these chemicals even though they know about the chemicals' toxicity and extreme persistence.

Under a precautionary system of chemicals production in which companies had to demonstrate the safety of their products before accessing markets, costs could be substantially reduced by avoiding the production of toxic substances, and remaining costs would be internalized by PFAS producers into the price of their products. But in the United States, these costs are largely borne by the public and public institutions.

As this review of PFAS externalities shows, meaningful action must address not just remediation and cleanup of legacy contamination, but must also reduce current production and uses of PFAS, in order to limit the extent of future exposures. Class-based regulation of all PFAS is needed,[15] and California's recent action to regulate PFAS as a class in consumer products demonstrates that class-based restrictions are possible and desirable.[16]

Ubiquitous exposure to many toxic chemicals, not just PFAS, reflects a failure of regulatory systems to adequately reduce risk, and a privileging of short-term industry profits over long-term public health and environmental impacts. While the costs of drinking water treatment and PFAS remediation are substantial, the potential health-related costs of continued exposure to PFAS are much larger and will likely impact vulnerable communities disproportionately. Failing to take timely action to reduce the production and use of PFAS will result in exponentially higher costs to be paid by exposed populations for generations to come.

Understanding the true extent of these costs will clarify the benefits of improved regulatory controls and timely clean-ups. It will enable residents and policy makers to make informed decisions about who should rightfully bear responsibility for impacts and compensation. A strengthened regulatory system is needed, both in terms of enforcement of existing regulations and enactment of stronger, class-based laws to internalize the costs and reduce or eliminate the production of persistent, mobile, bioaccumulative, and toxic compounds. Only a strengthened regulatory system can adequately protect public health and the environment, and end the practice of forcing the public and future generations to bear the financial and health burden of pollution.

AUTHOR INFORMATION

Corresponding Author

Alissa Cordner − *Department of Sociology, Whitman College, Walla Walla, Washington 99362, United States;* orcid.org/0000-0001-5223-2848; Email: cordneaa@whitman.edu

Authors

Gretta Goldenman − *Founder, Milieu Consulting, Brussels 1060, Belgium*

Linda S. Birnbaum − *Scientist Emeritus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709-2233, United States; Scholar in Residence, Duke University, Durham, North Carolina 97708, United States*

Phil Brown − *Department of Sociology and Anthropology and Department of Health Sciences, Northeastern University, Boston, Massachusetts 02115-5005, United States*

https://doi.org/10.1021/acs.est.1c03565
Environ. Sci. Technol. 2021, 55, 9630−9633

Mark F. Miller − *National Institute of Environmental Health Sciences and U.S. Public Health Service, Research Triangle Park, North Carolina 27709-2233, United States*
Rosie Mueller − *Department of Economics, Whitman College, Walla Walla, Washington 99362, United States*
Sharyle Patton − *Health and Environment Program, Bolinas, California 94924, United States*
Derrick H. Salvatore − *Department of Marine and Environmental Sciences, Northeastern University, Boston, Massachusetts 02115-5005, United States*
Leonardo Trasande − *Center for the Investigation of Environmental Hazards, New York University Grossman School of Medicine, New York City, New York 10016-6402, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.est.1c03565

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Andrew Lindstrom for invaluable comments and suggestions. We acknowledge funding from the National Science Foundation (SES-1456897; AC, PB, and DHS), the National Institute of Environmental Health Sciences (P30ES000260; LT); and the Tides Foundation (TF2101−096968; GG, SP, and DHS).

■ REFERENCES

(1) ATSDR (Agency for Toxic Substances and Disease Registry). 2018. Toxicological Profile for Perfluoroalkyls (Draft for Public Comment). https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf (accessed 2021/3/1).
(2) Richter, L.; Cordner, A.; Phil, B. Non-stick science: Sixty years of research and (in)action on fluorinated compounds. *Social Studies of Science* **2018**, *48*, 691−714.
(3) Glüge, J.; Scheringer, M.; Cousins, I. T.; DeWitt, J. C.; Goldenman, G.; Herzke, D.; Lohmann, R.; Ng, C. A.; Trier, X.; Zhanyun, W. An overview of the uses of per-and polyfluoroalkyl substances (PFAS). *Environ. Science: Process. Impacts* **2020**, *22*, 2345−2373.
(4) Wang, Z.; DeWitt, J. C.; Higgins, C. P.; Ian, T. C. A never-ending story of per-and polyfluoroalkyl substances (PFASs). *Environ. Sci. Technol.* **2017**, *51*, 2508−2518.
(5) Wood Environment & Infrastructure Solutions UK Limited. 2020. Socio-Economic Assessment of the US Fluoropolymer Industry -Executive Summary. https://fluoropolymerpartnership.com/wp-content/uploads/2020/03/Socio-Economic-Assessment-of-the-US-Fluoropolymer-Industry-Executive-Summary.pdf (accessed 2021/3/1).
(6) Andrews, D. Q.; Olga, V. N. Population-wide exposure to per-and polyfluoroalkyl substances from drinking water in the United States. *Environ. Sci. Technol. Lett.* **2020**, *7*, 931−936.
(7) Zabel, J. E.; Dennis, G. A hedonic analysis of the impact of LUST sites on house prices. *Resour. Energy Econ.* **2012**, *34*, 549−564.
(8) Gardella, John. 2020. Are the Floodgates Open for PFAS Product Liability Cases? *National Law Review XI* (94), https://www.natlawreview.com/article/pfas-product-liability-cases-are-floodgates-now-open (accessed 2021/3/1).
(9) C8 Science Panel. 2012. C8 Probable Link Reports. http://www.c8sciencepanel.org/prob_link.html (accessed 2021/3/1).
(10) Grandjean, P.; Timmermann, C. A.G.; Kruse, M.; Nielsen, F.; Vinholt, P. J.; Boding, L.; Heilmann, C.; Kåre, M. Severity of COVID-19 at elevated exposure to perfluorinated alkylates. *PLoS One* **2020**, *15*, No. e0244815.
(11) EFSA (European Food Safety Authority) Panel on Contaminants in the Food Chain. Risk to human health related to the presence of perfluoroalkyl substances in food. *EFSA J.* **2020**, *18*, 6223.
(12) Goldenman, G.; Menna, F.; Michael, H.; Tugce, T.; Amanda, N.; Cindy, S.; Alicia, M. *Cost of Inaction: A Socio-economic Analysis of Environmental and Health Impacts Linked to Exposure to PFAS*; Nordic Council of Ministers, Copenhagen, 2019. http://norden.diva-portal.org/smash/record.jsf?pid=diva2%3A1295959&dswid=6315 (accessed 2021/3/1).
(13) IOM (Institute of Medicine). *Cost of Environmental-Related Health Effects: A Plan for Continuing Study*; The National Academies Press: Washington, DC, 1981; DOI: 10.17226/812.
(14) Gold, S. C.; Wendy, E. W. Filling gaps in science exposes gaps in chemicals regulation. *Science* **2020**, *368*, 1066−1068.
(15) Kwiatkowski, C. F.; Andrews, D. Q.; Birnbaum, L. S.; Bruton, T. A.; DeWitte, J. C.; Knappe, D. R.U.; Maffini, M. V.; Miller, M. F.; Pelch, K. E.; Reade, A.; Soehl, A.; Trier, X.; Venier, M.; Wagner, C. C.; Wang, Z.; Arlene, B. Scientific basis for managing PFAS as a chemical class. *Environ. Sci. Technol. Lett.* **2020**, *7*, 532−543.
(16) Bălan, S. A.; Vivek, C. M.; Dennis, F. G.; André, M. A.. **2021**. Regulating PFAS as a chemical class under the California Safer Consumer Products Program. *Environ. Health Perspect. 129*, DOI: 10.1289/EHP7431.

Environmental Science & Technology

pubs.acs.org/est

Addition/Correction

Correction to The True Cost of PFAS and the Benefits of Acting Now

Alissa Cordner,* Gretta Goldenman, Linda S. Birnbaum, Phil Brown, Mark F. Miller, Rosie Mueller, Sharyle Patton, Derrick H. Salvatore, and Leonardo Trasande

Environ. Sci. Technol. **2021**, *55* (14), 9630−9633. DOI: 10.1021/acs.est.1c03565

Cite This: *Environ. Sci. Technol.* 2021, 55, 12739−12739

Read Online

ACCESS | Metrics & More | Article Recommendations

It has come to our attention that we inaccurately described recent water treatment changes and associated costs in North Carolina. Following extensive contamination by a PFAS manufacturer in the Cape Fear River watershed, Brunswick County, North Carolina is spending $167.3 million on a reverse osmosis plant[1] and the Cape Fear Public Utility Authority spent $46 million on granular activated carbon filters (not $99 million as we originally reported), with recurring annual costs of $2.9 million.[2] We regret the error. This does not change the conclusions or arguments of our paper.

AUTHOR INFORMATION

Corresponding Author

Alissa Cordner; orcid.org/0000-0001-5223-2848;
Email: cordneaa@whitman.edu

Authors

Gretta Goldenman
Linda S. Birnbaum
Phil Brown
Mark F. Miller
Rosie Mueller
Sharyle Patton
Derrick H. Salvatore
Leonardo Trasande

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.est.1c04938

REFERENCES

(1) Brunswick County North Carolina. 2021. Northwest Water Treatment Plant Expansion & Reverse Osmosis Treatment Upgrades. https://www.brunswickcountync.gov/nwtp/.

(2) Cape Fear Public Utility Authority, 2019. CFPUA board OK's steps to obtain construction bids, funding for long-term solution to filter PFAS. https://www.cfpua.org/CivicAlerts.aspx?AID=1019&ARC=2084.

Published: September 2, 2021