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A Never-Ending Story of Per- and Polyfluoroalkyl Substances (PFASs)?

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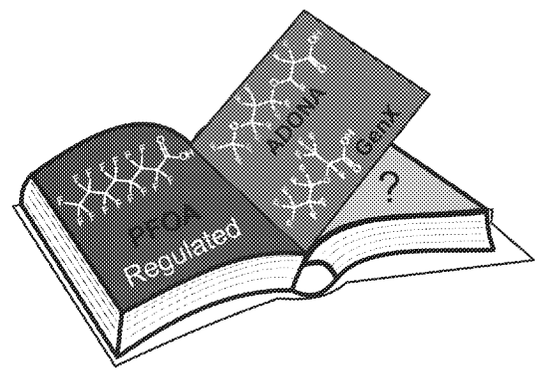
ABSTRACT: More than 3000 per- and polyfluoroalkyl substances (PFASs) are, or have been, on the global market, yet most research and regulation continues to focus on a limited selection of rather well-known long-chain PFASs, particularly perfluorooctanesulfonate (PFOS), perfluorooctanoic acid (PFOA) and their precursors. Continuing to overlook the vast majority of other PFASs is a major concern for society. We provide recommendations for how to proceed with research and cooperation to tackle the vast number of PFASs on the market and in the environment.



INTRODUCTION

Per- and polyfluoroalkyl substances (PFASs, C_nF_{2n+1}–R) refer to a family of chemicals that have been produced since the late 1940s. Due to the strong electronegativity and small atomic size of fluorine, the perfluoroalkyl moiety (C_nF_{2n+1}–) imparts enhanced properties to molecules (e.g., stronger acidity, higher surface activity at very low concentrations, stability, and/or water- and oil-repellency) compared to their hydrocarbon counterparts. Thus, based on desired functionality and production capability, a large number of PFASs have been developed by different companies over time for a wide variety of industrial and consumer applications (e.g., cosmetics, fire-fighting foams, food contact materials, household products, inks, medical devices, oil production, mining, pesticide formulations, and textile, leather, and apparel).[1] Since the late 1990s, multiple long-chain PFASs (perfluoroalkyl carboxylic acids (PFCAs) with ≥7 perfluorinated carbons, perfluoroalkanesulfonic acids (PFSAs) with ≥6 perfluorinated carbons, and their precursors), in particular perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS), have attracted worldwide attention in the scientific and regulatory community and among the public. Numerous efforts and societal resources have been invested to understand, and in some cases to further control, exposure to long-chain PFASs in multiple countries (for examples, see Table 1). Most significantly, after a production history of over half a century, PFOS and its precursors are now listed, and PFOA and related precursors are being evaluated for listing, under the Stockholm Convention on Persistent Organic Chemicals. There have also been a number of national/regional regulatory and voluntary initiatives established to regulate PFOS, PFOA, and/or some other PFASs, mostly in developed countries.[2,3]

These actions should hopefully result in the global elimination of production and use of PFOS, PFOA, and their precursors in the near future, even though it will require a substantive amount of time, effort, and societal resources (e.g., the project "Reduction and Phase-out of PFOS in Priority Sectors in China" supported by the Global Environment Facility (GEF) will cost nearly 170 million USD in the next five years[4]). We are, however, still far from solving all of the issues related to PFASs. Including these well-known long-chain PFASs, a recent report identified 2060 PFASs that are, or have been, on the global market for intentional uses and estimated that there are probably at least 3000 PFASs currently on the global market.[1] Some of the PFAS-containing commercial products may contain other unintentional PFASs as impurities. For example, Place and Field (2012)[5] identified 10 subclasses of PFASs in multiple aqueous film forming foam (AFFF) formulations; however, with limited communication between the public and the manufacturers producing PFASs, it is not immediately clear as to whether these PFASs are intended ingredients, residual intermediates, byproducts formed during production, or degradation products.

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Table 1. Non-Exhaustive Compilation of Reported Initiatives to Understand and Control Exposure to Long-Chain PFASs in Various Countries and Their Costs; Information Is Retrieved from a Simple Web Search with No Pre-Selection[a]

country	site	control measures	costs
Australia	RAAF Base Williamtown	remediation of PFOA and PFOS contamination by treating water and stockpiling contaminated soil at the base (source: http://goo.gl/p9f2rT)	>3 mio. AUD budgeted
	18 sites	conducting detailed environmental investigations at five sites including RAAF Base Williamtown and preliminary sampling programs at another 13 sites by the Defense (source: http://goo.gl/9JxzLQ)	unknown
Germany	Möhne River	collection and carbon filtration of the drainage water at one site, with regular exchange of filters needed (source: http://goo.gl/Rb78Y0)	2 mio. EURO initial + AOM (not reported)
Norway	Oslo airport	cleaning the groundwater and wastewater from the drill areas with the infiltration reservoir using a special treatment plant with activated charcoal (source: https://goo.gl/mCMNu7; http://goo.gl/Rj9y7l)	unknown
Sweden	Stockholm and Gothenburg	four-year investigation of risks and effects of the dispersion of PFAS on aquatic, terrestrial and human populations in the vicinity of Arlanda and Gothenburg Landvetter airports (source: http://goo.gl/Gae4rV)	unknown
United Kingdom	Buncefield	pumping out and treating the polluted groundwater to remove fuel and PFOS (source: http://goo.gl/wb1oyg)[16]	1 mio. GBP/year
	Channel Island, Jersey	remediation of a fire-training site contaminated by PFAS-containing aqueous film forming foams (AFFFs) (source: http://goo.gl/APLKdo)	3.8−4.8 mio. GBP first budgeted
United States	whole country	based on the results from the US EPA's Unregulated Contaminant Monitoring Rule (UCMR3) program, drinking water supplies for 6 million U.S. residents exceed the US EPA's lifetime health advisory (70 ng/L) for PFOS and PFOA individual or combined; no control measures defined yet (source: http://goo.gl/yhQsco)[17]	unknown
	Ohio	pilot scale study by DuPont in 2004 on using GAC filter to treat PFOA/PFOS contaminated water in an one million gallons per day potable water facility (source: presentation slides "Water Treatment of PFOA and PFOS" by Hartten AS on behalf of the DuPont Remediation Group to the US EPA on October 16, 2009)	2.5−3.5 mio. USD initial + 0.1−0.3 mio. USD AOM
	Moose Creek, Alaska	treating water from individual private water wells with a GAC system and/or providing an alternate water supply (water tank) to eliminate the ingestion exposure to PFASs (source: http://goo.gl/diOQTr)	3.5 mio. USD budgeted
	3 sites in Minnesota	cleaning up 3M's Cottage Grove site and two disposal sites including treatment of surface water, groundwater, sediment and soil since 2007 (source: https://goo.gl/VLrqdZ; https://goo.gl/kdaziV; https://goo.gl/cv3nPI; https://goo.gl/XvzPzT; https://goo.gl/QzLaFV)	about 49 mio. USD estimated
	New Jersey	installation of point of entry treatment systems (POETS) for 15 of the private drinking water wells in the vicinity of the West Deptford industrial facility that were contaminated with perfluorononanoic acid (PFNA) levels of ≥20 ng/L (source: http://goo.gl/8KIsz5)	unknown
	Washington County, Minnesota	relocating all waste from the PFAS-contaminated landfill in a new, lined landfill at the current site (source: https://goo.gl/kxzQRm; https://goo.gl/2ybhI9)	27.6 mio. USD initial + 0.2 mio. USD AOM estimated
	Hoosick Falls, New York State	installation of a temporary municipal filtration system and hundreds of private residential water filtration system; working to identify an alternate permanent drinking water source (source: http://goo.gl/yjssV7)	10 mio. USD budgeted

[a]Mio. = million; AUD = Australian Dollar; GBP = British Pound; USD = United States Dollar; GAC = granular activated carbon; AOM = annual operation and maintenance; US EPA = United States Environmental Protection Agency.

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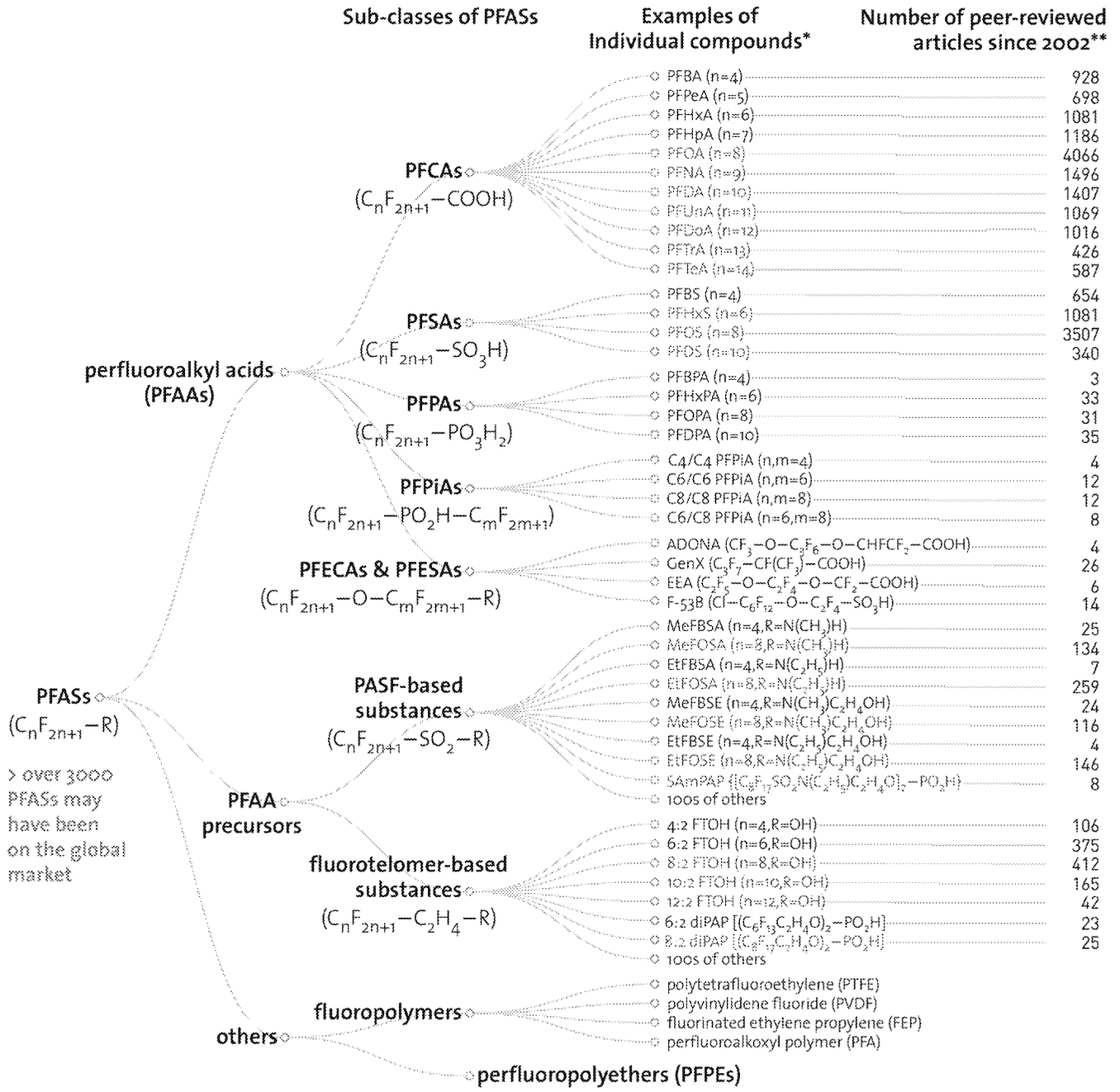

* PFASs in RED are those that have been restricted under national/regional/global regulatory or voluntary frameworks, with or without specific exemptions (for details, see OECD (2015), Risk reduction approaches for PFASs. http://oe.cd/1AN).

** The numbers of articles (related to all aspects of research) were retrieved from SciFinder® on Nov. 1, 2016.

Figure 1. "Family tree" of PFASs, including examples of individual PFASs and the number of peer-reviewed articles on them since 2002 (most of the studies focused on long-chain PFCAs, PFSAs and their major precursors.).

Among the thousands of PFASs still being produced and used, there are many overlooked ones that are structurally similar to PFOS, PFOA, or their precursors, and are produced in high volumes (e.g., >10 tonnes/year; for examples, see references 6–9). Many groups of these overlooked PFASs have been produced since the 1970s or earlier,[6–9] and some of them have recently been chosen or further developed to replace long-chain PFASs (e.g., shorter-chain homologues of PFOS, PFOA and their precursors, perfluoroalkyl phosphinic acids (PFPiAs), and perfluoroether carboxylic and sulfonic acids (PFECAs and PFESAs)).[6–9] For most of these overlooked PFASs, there is little to no information about their fate/transport, exposure, and toxicological effects in the public domain,[6,8,9] or even awareness to study them (see Figure 1), although existing evidence suggests a need for concern.[8,9]

Linking to limited knowledge and awareness, only few specific control measures are known to have been implemented for PFASs other than PFOS, PFOA, and their precursors.[2] For example, some replacements to long-chain PFASs have been registered with regulatory authorities and to varied extents

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evaluated in countries/regions such as the United States[10,11] and European Union.[12,13] Among them, one company agreed to control the release of its replacement to PFOA in fluoropolymer manufacture by at least 99%, as requested by the U.S. Environmental Protection Agency (EPA).[14] In addition, some countries have recently introduced measures to control the release of PFAS-containing fire-fighting foams, which are now typically based on short-chain PFAS chemistries (e.g., in Germany[15]). However, the existing efforts are still inadequate. The current neglect of the vast majority of PFASs including the current common practice of replacing one PFAS with other structurally similar PFASs, is a major concern for society. This is because: [i] assessment of and potential management actions on these additional PFASs will require substantial additional time and resources, as well as research and regulatory efforts, [ii] it is technically and financially challenging to identify and reverse environmental and human exposure to PFASs (for examples, see Table 1), and [iii] the increasing number of new PFASs prolongs and amplifies the previous two challenges.

The objective of this Feature article is to raise awareness among stakeholders of the existence of the wide range of potentially hazardous PFASs in society and to offer guidance for the next steps of research and regulation. We start by outlining why PFASs as a whole, much more than solely PFOS, PFOA, and their precursors, are an intractable, potentially never-ending chemicals management issue that challenges the conventional chemical assessment and management paradigm adopted by society since the 1970s. Then, building on lessons learned from PFOS, PFOA, and their precursors, we provide recommendations for new research and cooperation to tackle the whole group of PFASs. We suggest ways in which research could be targeted and how PFASs could be regulated as a group rather than individually.

WHY ARE PFASs AN INTRACTABLE, POTENTIALLY NEVER-ENDING CHEMICALS MANAGEMENT ISSUE?

The following subsections analyze respective challenges in assessing and managing PFASs as a whole that arise from their properties, the large number of existing substances, and the lack of effective control measures, followed by a brief summary. Some of these individual challenges are not unique to PFASs, but may also be associated with other types of chemicals. However, the combination of all these challenges makes PFASs a unique and intractable issue for the current chemicals management paradigm.

The Properties of PFASs. The perfluoroalkyl ($C_nF_{2n+1}-$) and perfluoroether ($C_nF_{2n+1}-O-C_mF_{2m+1}-$) moieties are highly persistent under natural conditions.[8,18] Even though some PFASs may partially degrade in the environment and biota, they will all ultimately transform into highly stable end products, which are usually the highly persistent perfluoroalkyl or perfluoroalkyl(poly)ether acids (here collectively termed "PFAAs"), for example, PFCAs, PFSAs, PFECAs, and PFESAs.[7−9,18] Thus, when assessing and managing PFAAs, all their precursors (which can be challenging to identify[7,9]) need to be considered as relevant sources and managed as well. The following paragraphs focus on highly persistent PFAAs, although some individual PFAA precursors may also be problematic on their own.

- Due to their high persistence and water solubility, PFAAs will be transported to remote locations from sources through water currents and aerosols (as reviewed in Prevedouros et al. (2006)[19] and Ahrens et al. (2011)[20]). Furthermore, atmospheric transport and deposition of (semi)volatile precursors[21−23] and intensified human activities (e.g., in polar regions[24]) are additional transport pathways for certain PFAAs into remote regions. Past and ongoing production and use of PFASs in individual countries/regions has led to, and will continue to lead to, global distribution of PFAAs in the environment, wildlife, and humans.
- The very high persistence of PFAAs leads to poorly reversible exposure to these substances in the global environment and some local/regional environments including groundwater.[25] Past and ongoing production and use will lead to the accumulation of PFAAs in the global environment, with very slow mixing/sedimentation to the deep oceans and sedimentation/burial in deep sediments as the only known global environmental sinks (as reviewed in Prevedouros et al. (2006)[19]).
- The high solubility and protein-binding characteristics of ionic PFAAs challenge the conventional assessment of bioaccumulation potential that is through either bioconcentration factor in aquatic species (usually fish; BCF_{FISH}) or models based on octanol−water partition coefficients (K_{OW}). For example, PFOA shows low BCF_{FISH} (1.8−27) due to fast elimination through the respiratory system in fish (i.e., gills) that is linked to its high solubility, whereas it can only be slowly eliminated from humans, on the scale of years.[26] Thus, additional "weight-of-evidence" evaluation is needed to understand bioaccumulation mechanisms across trophic levels,[26] which requires a large amount of evidence (e.g., field-derived trophic magnification factors) and can only be done on an individual chemical basis. Even when PFAAs are not characterized as bioaccumulative under the current regulatory frameworks (e.g., short-chain PFAAs), the accumulation of these PFAAs in the environment (as elaborated above) will lead to increasing external exposure. Thus, as concluded by Cousins et al. (2016),[25] bioaccumulation is not a prerequisite for poorly reversible internal exposure to PFAAs.
- Despite variable kinetics and levels of toxicity in biota, a hallmark response of PFAA exposure is hepatotoxicity.[8,9,27−29] An accepted mechanism-of-action for hepatotoxicity associated with some PFAAs is activation of the peroxisome proliferator-activated receptor alpha (PPARα). However, this mechanism does not sufficiently explain all toxicities of all PFAAs, as not all PFAAs produce robust PPARα-mediated responses across species or even among strains of the same species.[28,29] These findings are supported by studies in genetically modified animals that lack PPARα, indicating that hepatotoxicity and likely other toxicities are mediated by additional mechanisms-of-action.[30] Mechanisms for toxicity will undoubtedly be uncovered by the continuous development of nonstandard test methods and epidemiological studies, which increasingly expands the understanding of potential adverse effects related to PFAAs; for details, see individual chapters in DeWitt (2015)[31] and references therein. For example, increasing evidence suggests that exposure to low doses of PFOA or

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PFOS at an early stage of life produces effects that persist in the adult organism.[31] Female mice exposed to PFOA during a critical period of fetal development experienced significant delays in mammary gland development, a measure of pubertal progress.[32] The tests associated with these findings are not part of standard suites of test methods commonly employed and these findings are supported by human epidemiological studies reporting delayed puberty in exposed females.[33,34] Hence, the current lack of an adequate mechanistic understanding of all adverse effects across species and their life stages associated with exposure to individual PFASs may introduce (substantial) uncertainties and difficulties in the selection and testing of the most sensitive toxicological end points. This may be especially critical for susceptible subpopulations (e.g., developing organisms)[31] and end points that often are not captured by current regulatory testing guidelines (e.g., developmental immunotoxicity, types of endocrine disruption, etc.).[31]

The Large Number of PFASs. More than 3000 PFASs are on the global market for intentional uses, and the chemical identities of many are yet unknown.[1] Beyond unknown chemical identities, there is little to no information on the production and use history for most PFASs on the market; this scarcity of data is rather factitious, that is, information may have been generated in some cases, but has not been made publicly available. The vast number of known and unknown PFASs substantially amplifies the resources and technical challenges in data generation/collection to address the following conundrums:

- Recent monitoring studies confirm that humans and the environment are being exposed to a wide range of organofluorine compounds, with increasing ratios of unidentified ones.[35] With improved analytical techniques, some unknown compounds have been identified to be overlooked legacy or novel replacement PFASs.[36−39] There are surely more unknown substances out there. Both new analytical standards for the development of targeted analytical methods and new developments in suspected-/nontarget analytical methods may help to identify individual unknown compounds with known or unknown production in environmental and biota samples.[40] However, both options require highly specialized experts (and high-end instruments, in the case of suspected-/nontarget analytical methods) and will be resource-intensive and time-consuming. Even when all unknown PFASs are identified, challenges will continue in how to prioritize the assessment and management activities pertaining to the large number of PFASs.
- For most PFASs, there is little to no understanding on how much has been, and will be, released and transformed/accumulated in the environment and biota over time. For example, in areas impacted by releases of PFAS-containing AFFFs, not only the past and ongoing changes of the PFAS composition in commercial AFFF formulations, but also natural and remedial efforts at these sites can substantially alter the composition, distribution, and exposure of local PFAS contamination over time.[41] While environmental and biomonitoring of selected PFASs can provide some useful information on ongoing exposure, these generally overlook the copresence of a large number of other PFASs, which can cause substantial underestimation of total PFAS exposure. For example, side-chain fluorinated polymers, and some hydrofluorocarbons and -ethers (HFCs and HFEs) may act as long-term sources of PFAAs due to slow degradation.[7] Hence, it is challenging to fully characterize the scope of contamination and associated exposure at individual sites and globally before determining actions, empirically or through modeling.
- Toxicity has been well studied for only a limited selection of PFASs (reviewed in DeWitt (2015)[31]). Even for these, detailed information about an extensive range of toxicities in test organisms has mostly been provided by industry, supplemented with studies by academic and regulatory scientists in some cases, which is often limited to legally requested end points (e.g., emerging toxicological end points in relation to effects on standard toxicological readouts such as histopathology and carcinogenesis are often not requested in standard test guidelines) and may not always be objective (see a recent debate on the reported toxicity of one PFECA[42]). Thus, an added challenge is ensuring the efficiency, quality and extent of testing, data interpretation, and reporting by different stakeholders.
- Additionally, the concept of mixture toxicity is not adequately considered in the current individual chemical-based paradigm often employed in various countries. Despite known structural similarity among many PFASs, there is nearly a complete lack of empirical knowledge on mixture toxicity for the ongoing simultaneous, chronic, low-level exposure to a large number of known and unknown PFASs. Concurrently, a theoretical exploration of potential toxicological response profiles (additive, synergistic, or antagonistic) for simultaneous exposure to multiple PFASs is hampered by the lack of an adequate understanding of the mechanisms-of-action of individual PFASs as elaborated above. Furthermore, the lack of a comprehensive exposure history at individual sites (as previously discussed) may also cause challenges for conducting conclusive epidemiological studies.

The Lack of Effective Control Measures. A key factor in evaluating and determining management actions is the effectiveness of control measures to eliminate, prevent, reduce, or mitigate the risks. In the case of PFAAs, due to their very high persistence, environmental exposure to them in contaminated regions will only be slowly reversed (i.e., through dilution and burial) if no control measures are taken. The effectiveness of phase-out alone is therefore limited, and complementary remedial measures to reverse environmental and human exposure to PFASs are needed. The following paragraphs summarize various challenges of current control measures in dealing with PFASs, from remedial measures to phase-out and replacement measures.

- For most PFASs, there is no comprehensive understanding of their environmental and human exposure routes due to a lack of information on their life cycles, leading to difficulties in developing proactive, effective strategies for identifying and controlling exposure.
- Once a contaminated site (including drinking water supply) is identified and remediation planned, it is necessary to fully elucidate the extent of PFAS contamination for selection of remediation technologies

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to reduce or eliminate PFAS exposure. While in situ technologies are desirable and hold some promise,[43,44] it may take years to decades until these technologies are adequately mature for PFAS-contaminated sites, technically and financially (for a comparison of remediation technologies, see ref 45). Consequently, energy intensive pump-and-treat technologies are the only tools currently available (e.g., filtration through activated carbon or membranes; for details of advanced treatment technologies for PFASs including advantages and limitations, see references 46−47). These technologies may also be used to treat PFAS-containing wastewater and landfill leachates to reduce or eliminate the amounts of PFASs to be released from the anthroposphere to the environment. However, these technologies require high-temperature incineration of highly contaminated concentrates or sorbent materials, and lengthy treatment times until the site is cleaned up.[45] From a long-term management perspective, this results in substantial resource and financial repercussions (for examples, see Table 1). In addition, some of these advanced treatment technologies have only limited applicability for the removal of short-chain PFAAs such as perfluorobutanesulfonate (PFBS).[48−52] Also, little is known about how these remediation technologies may further impact local ecosystems that may have been influenced by PFAS contamination.[53]

- The control measures above have no influence on diffuse, fugitive, and accidental releases of PFASs during the production, use, and disposal to the indoor and outdoor environment. Reductions in exposure from diffuse sources can only be achieved through phasing out relevant products, for which long lag times in responses in release rates should be expected, depending on the life span of the products manufactured prior to phase out.[7]
- The most common current industrial practice of phasing out one PFAS is to replace it with another (or multiple other) structurally similar PFAS.[6] Such a strategy is easier and less costly than identifying a nonfluorinated substance to be used in the same or similar process (i.e., chemical replacement) or inventing a new process that does not require PFASs (i.e., functionality replacement).[8] For example, one of the criteria used by 3M Company to screen and select its replacement to PFOA in the production process of fluoropolymers (i.e., ADONA)[6] was that the alternative "fulfills all requirements for the polymerization process with minor process adjustments".[54] It is technically legitimate to do so under current regulatory frameworks, but such a replacement strategy will not solve issues in relation to PFASs as a whole group—it will only increase the numbers of PFASs on the market and the difficulties in tracking them. Furthermore, due to considerations such as protection of intellectual property, individual companies tend to have their own replacement PFASs. For example, multiple structurally similar PFECAs have been developed to replace PFOA in fluoropolymer production by different companies.[6] Consequently, there is a proliferation of new PFASs on the market, which will likely continue in the foreseeable future.

Summary of the Challenges. Wildlife and humans are simultaneously exposed to dozens or up to thousands of PFASs, many of which are interlinked and overlooked. Due to a lack of knowledge of their identity, total burden, individual hazards, mechanisms-of-action, and mixture effects, there are large uncertainties related to estimating the associated risks of the whole group of PFASs. It is challenging to reduce the uncertainties, due to the vast number of PFASs involved. More importantly, even once a risk associated with PFASs is identified, it is challenging to mitigate such a risk: due to their high persistence, environmental exposure to existing PFASs is poorly reversible, and there is a lack of effective measures to remove them from the environment and human exposure media, both technically and financially. Furthermore, due to the current common industrial practices, structurally similar PFASs are developed to replace problematic PFASs, and the numbers of such new PFASs may further increase in the future; this may result in similar issues related to the existing PFASs (continuously) recurring in the future. Hence, we recommend prompt global actions to assess the hazards, exposure, and risks associated with the many PFASs on the market, as the basis for effective control measures to limit the production and use of many, if not all, of these substances and their replacement PFASs.

RECOMMENDATIONS FOR NEW RESEARCH AND COOPERATION

Research and monitoring programs are continuously needed for PFOS, PFOA, and their precursors to fill remaining gaps and evaluate the effectiveness of ongoing phase-outs, but the research community should not only focus on just these legacy substances as seen in Figure 1. To solve issues in relation to the whole group of PFASs, additional, intensified research activities are needed, and this should be recognized and supported by society, both politically and financially.

Due to the vast number of PFASs involved, it is neither sensible nor feasible to assess all of them individually within a reasonable time frame. Therefore, to increase efficiency and effectiveness, we recommend the following considerations to be embedded in new research and cooperation. Some of the recommendations are not limited to PFASs and can be extended to other types of chemicals.

Targeting Research Efforts. As resources (time, manpower, material, financial) are limited, we recommend future research on PFASs be more targeted at the most critical issues (e.g., overlooked PFASs, simultaneous exposure and mixture toxicity, safer alternatives) than today's. In particular, we encourage specific goals, objectives and data needs be clearly predetermined and communicated across stakeholders so that discipline-specific research efforts can focus on them first. Depending on the geographical scale (from local, national, regional, to global), the goals and objectives may differ considerably. Here we propose the following set of objectives to be considered for a goal to understand and minimize the exposure and effects by the whole group of PFASs on the global scale:

- As a first step toward understanding the global landscape of PFASs, it may be sensible to establish an inventory of legacy and currently used PFASs, including data on their chemical identity, production and uses, potential exposure media, regulatory status, and alternatives. This inventory can be used to as a pool for selecting testing objects in proposed studies below, and for setting up

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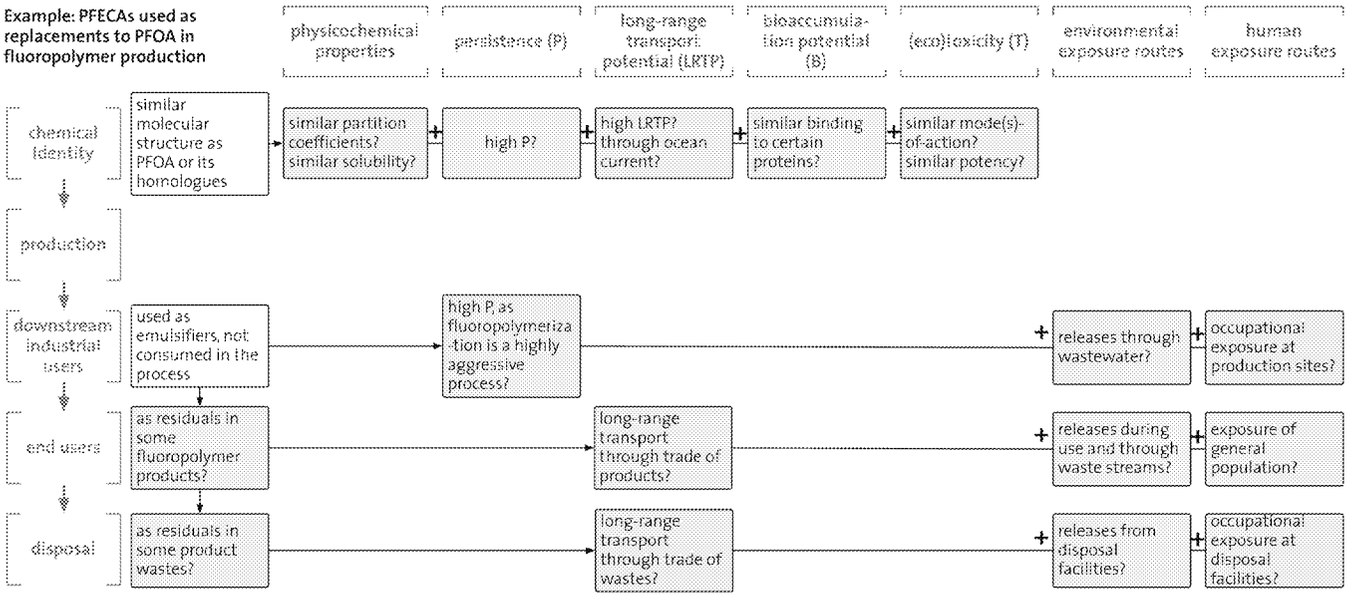

Figure 2. An example of a preliminary matrix used to deduce possible characteristics of PFECAs that are used as replacements to PFOA in fluoropolymer production, based on lessons learned on PFOA. Black boxes with white background contain known facts, whereas black boxes with light orange background contain our deduction. Arrow shows the logical flow, and the "+" sign indicates parallel questions deduced from the same cause.

goals and objectives on the local, national, and regional scales.

- Focus should be given to synthesizing existing knowledge of PFASs and other organic compounds and conducting new quantitative studies to identify and understand all relevant processes and build up (or improve) mechanistic models for the fate and transport of PFASs in the anthroposphere (e.g., wastewater treatment plants, incinerators), environment, and biota. For example, knowledge gained from pharmaceutical research may help to better understand the protein binding and toxicokinetics of some PFASs, and knowledge gained from surfactant research may help to better understand the potential sorption, transport (e.g., on marine aerosols) and bioaccumulation behavior of those PFASs that are fluorosurfactants.
- Another focus should be given to increasing mechanistic understanding of the relationships between molecular structures of tested PFASs and their properties and behavior (e.g., physicochemical properties including adsorption, degradation mechanisms and pathways, protein binding, and associated toxicokinetics, mode(s)-of-action, and mechanism(s)-of-action). This has been done for many types of chemicals, but much less for fluorinated compounds in general. In particular, there is a lack of understanding on how ether linkages in PFECAs and PFESAs influence properties and behavior in comparison to their perfluoroalkyl counterparts. When the necessary mechanistic understanding (e.g., mechanism(s)-of-action or even mode(s)-of-action for specific toxicities or hallmark responses) emerges, it may be possible to develop reliable quantitative structure–property relationships for predicting the properties and behavior of other nontested PFASs. This information can be further used as inputs for the models described above to assess the anthropospheric, environmental, and biotic fate of nontested PFASs, as well as support the development of the best analytical strategies to simultaneously identify/quantify as many PFASs as possible in one sample.
- Further focus should be given to understanding PFASs as a group or as several subgroups, including identifying the drivers of mixture toxicity. This knowledge could then be used in the development of effect-oriented chemical and biological analysis and predictive models to evaluate the total burden of simultaneous exposure to multiple PFASs, as well as the justification of best grouping methodologies for PFASs under the regulatory context (e.g., based on mode(s)-of-action as suggested in the WHO/IPCS framework).[55] As a starting point, we recommend that future studies first evaluate the feasibility and sensibility of grouping subclasses of PFAAs because all of these are very persistent and ubiquitous in the environment. Further subgrouping can be made, such as on the basis of similarity in mode(s)-of-actions/hallmark responses (e.g., hepatotoxicity), as discussed above. Examples of recent regulatory attempt at grouping according to toxicity include the Swedish Drinking Water Guideline based on the sum of 11 PFASs[56] and the US EPA Drinking Water Health Advisories for combined PFOA/PFOS exposure.[57]
- In addition to assessing existing PFASs, substantial efforts should be invested in developing effective control measures, from viable remediation technologies to safe alternatives. For example, the availability of viable remediation technologies might be used as a prerequisite for a new PFAS to be put on the market. Some progress has been made in developing nonfluorinated alternatives for PFASs in durable water repellency for textiles.[58] Future innovation should focus on the development of alternative substances that are truly "benign by design", for example, by following the 12 principles of Green Chemistry,[59] as well as systematic changes in industrial processes, in which PFASs either are no longer needed

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(e.g., in the case of using chromium-(III) instead of chromium-(VI) in decorative plating)[8] or can be fully recovered and reused as raw materials (e.g., by changing the current business model to "chemical leasing" for certain applications).

Targeting future research efforts also requires regular monitoring and evaluation of progress and adjustment of the goals and objectives as needed. Therefore, research synthesis studies should be encouraged to periodically integrate and crystallize existing knowledge and highlight remaining critical knowledge and data gaps. For example, hazard assessment tools (for examples, see OECD Substitution and Alternatives Assessment Toolbox; http://www.oecdsaatoolbox.org) may be used to conduct a comprehensive evaluation of individual PFASs against regulatory end points for human health and environmental hazards. In particular, these tools often may indicate which hazard end point is known with what certainty level, and which helps to prioritize research to fill critical data gaps for decision-making and avoid repetition when quality data are already available. The goal of such systematic frameworks/tools is to keep the "big picture" in perspective: it does not mean that all details should be filled with high certainty, and it may also be used to highlight which details (e.g., hazard end points) are not needed. Furthermore, progress should be made readily available and accessible to all stakeholders, for example, through a dedicated web portal for PFASs and their alternatives.

We further encourage scientists to focus their targeted research with integrated approaches. The goal of integrated approaches is to minimize testing efforts by including not only comprehensive empirical experiments, but also the use of read-across methods to fill in data gaps (when there is good information on how molecular structure is related to properties and behavior), the use of existing models to test hypotheses and for a better empirical study design (e.g., using multimedia fate models to determine relevant media for sampling and monitoring),[60] and integrated thinking. An example of integrated thinking is, that by knowing that certain fluoropolymer manufacturing processes require aggressive free radical reaction conditions, one could deduce that processing aids used therein need to be persistent by design. We encourage that such integrated thinking be developed in a more standardized form, such as using a matrix system with chemical life-cycle on one axis and properties/characteristics on the other axis to describe possible logical links (for an example, see Figure 2). Again, it should be noted that the intention of such a matrix is not to fill in all gaps, but to assist in prioritizing and targeting research activities to those key areas. Using Figure 2 as an example, building on the known fate of PFOA in the fluoropolymer production, it may be postulated that human exposure of replacement PFECAs to PFOA might occur in the form of (1) occupational exposure at fluoropolymer production sites, (2) exposure of populations downstream of production sites, (3) exposure of the general population via products containing PFECA residuals, and (4) occupational exposure at disposal sites of products containing PFECA residuals. Then, considering the sensitivity of analytical methods and the short exposure history (years), human biomonitoring studies of these PFECAs may target workers at production sites and populations downstream of production sites rather than the other two groups.

International, Intersectoral, and Interdisciplinary Cooperation. Even with the targeted research efforts described above, much needs to be done to assess and manage the thousands of PFASs (including the development of safe alternatives) within a reasonable time frame. One could argue that it is unfair and unreasonable to expect taxpayers to bear all the burden of paying for these efforts. Nor should existing and ongoing efforts by all stakeholders (academics, government agencies, industry, and civil society) across countries on PFASs be duplicated or wasted, as with other chemical-related issues that span the globe. Hence, a widened and strengthened international, intersectoral, and interdisciplinary cooperation would be cobeneficial for all stakeholders as exemplified below. We further propose that such cooperation could be supported, coordinated, and facilitated by the existing OECD/UNEP Global PFC Group that is established for addressing PFASs and the transition to safer alternatives under the UN Strategic Approaches to International Chemicals Management (SAICM), a global voluntary, multistakeholder policy framework for managing chemicals sustainably.

- PFAS-specific science-policy workshops with a balanced participation of stakeholders could be initiated to promote dialogue, review the status quo of science and policy, and define common strategies, goals, objectives, and roadmaps that highlight critical data needs and pathways to address them. Topics to be considered could include, but are not limited to, how to assess and manage the whole group of PFASs and set priorities, and potential tools such as a global inventory of existing PFASs, a dedicated public web portal for sharing progress in assessing and managing PFASs and transition to safe alternatives, and a global platform for project idea sharing among stakeholders and joint calls across organizations for new projects.
- Chemical manufacturers are strongly encouraged to readily supply their standards, analytical methods, and other existing information and knowledge (e.g., production and use information, positive and negative testing results) to accelerate research by other stakeholders, for example, through a dedicated public web portal for PFASs and their replacements as proposed above. This may require new thinking/systems that ensure that manufacturers realize the benefits of such an open collaborative approach rather than being concerned about disadvantages (e.g., loss of intellectual property or increased regulation), for example, through the original "no data, no market" principle behind the European Chemicals Regulation, REACH.
- Industry is the only actor that implements solutions to phase out hazardous chemicals. Intersectoral R&D programs are therefore encouraged to stimulate cooperation between academics, industry (chemical manufacturers and/or downstream industrial users), and other interested stakeholders. Such programs could translate up-to-date knowledge into actions that proactively avoid/improve certain processes and/or products and develop new nonfluorinated alternatives. For example, funding may be provided for joint projects between academics and small- and medium-sized enterprises to promote innovation in replacing PFASs.
- Although not specific to PFASs, scientists need to do more to deepen and strengthen effective connections

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between disciplines to ensure that research is less fragmented and to solve challenging multidisciplinary problems, starting from multidisciplinary curricula in education programs.

- Stakeholders in developed countries may share information and lessons learned with their counterparts in developing countries and countries with economies in transition to assist and accelerate their assessment of the whole group of PFASs and transition to safe alternatives.

Whereas the above recommendations will help to better assess and manage the many PFASs on the market in the near to far future, if society wants to be precautionary, it should limit the production and use of most, if not all PFASs, which is a recommendation recently made in the Madrid Statement[18] signed by over 200 scientists. Given the unique properties of PFASs, it can, however, be challenging to identify functional alternatives in some essential use categories. Let us start the dialogue in defining "essential" and "non-essential" uses of PFASs, while simultaneously developing safe alternative substances and processes for those essential uses.

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