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Review

Zürich II Statement on Per- and Polyfluoroalkyl Substances (PFASs): Scientific and Regulatory Needs

Jamie C. DeWitt,* Juliane Glüge, Ian T. Cousins, Gretta Goldenman, Dorte Herzke, Rainer Lohmann, Mark Miller, Carla A. Ng, Sharyle Patton, Xenia Trier, Lena Vierke, Zhanyun Wang, Sam Adu-Kumi, Simona Balan, Andreas M. Buser, Tony Fletcher, Line Småstuen Haug, Jun Huang, Sarit Kaserzon, Juliana Leonel, Ishmail Sheriff, Ya-Li Shi, Sara Valsecchi, and Martin Scheringer

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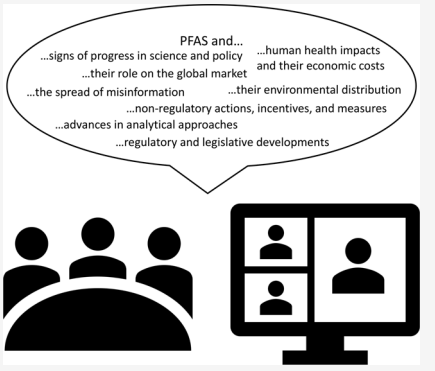
ABSTRACT: Per- and polyfluoroalkyl substances (PFASs) are a class of synthetic organic chemicals of global concern. A group of 36 scientists and regulators from 18 countries held a hybrid workshop in 2022 in Zürich, Switzerland. The workshop, a sequel to a previous Zürich workshop held in 2017, deliberated on progress in the last five years and discussed further needs for cooperative scientific research and regulatory action on PFASs. This review reflects discussion and insights gained during and after this workshop and summarizes key signs of progress in science and policy, ongoing critical issues to be addressed, and possible ways forward. Some key take home messages include: 1) understanding of human health effects continues to develop dramatically, 2) regulatory guidelines continue to drop, 3) better understanding of emissions and contamination levels is needed in more parts of the world, 4) analytical methods, while improving, still only cover around 50 PFASs, and 5) discussions of how to group PFASs for regulation (including subgroupings) have gathered momentum with several jurisdictions proposing restricting a large proportion of PFAS uses. It was concluded that more multi-group exchanges are needed in the future and that there should be a greater diversity of participants at future workshops.



KEYWORDS: *Per- and polyfluoroalkyl substances, PFASs, Zürich Statement, persistence, bilateral workshops, international cooperation*

1. KEY SIGNS OF PROGRESS IN SCIENCE AND POLICY

Per- and polyfluoroalkyl substances (PFASs) are a class of synthetic organic chemicals that have at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), $-CF_3$ or $-CF_2-$.[1] Typical perfluoroalkyl moiety properties in PFASs (e.g., thermal and chemical stability, combined oleophobicity and hydrophobicity) have resulted in extensive use across diverse applications.[2] However, certain PFASs also negatively impact ecosystem and human health, and the vast majority of PFASs are concerning because of high environmental persistence.[3] To consider current cooperative actions between science and policy on PFASs and propose ways forward, 36 scientists and regulators from 18 countries held a hybrid workshop in 2022 in Zürich, Switzerland. They deliberated on progress in the last five years and discussed further needs for cooperative scientific research and regulatory action on PFASs. The present statement reflects the discussion and insights gained during and after this workshop. It focuses on concerns around PFASs in many countries, including increasing human exposure to novel PFASs, human health impacts and their economic costs, PFASs on the global market, analytics, and regulatory developments. It further deliberates ongoing critical issues identified at the workshop and concludes with recommendations for priority regulatory and scientific actions on PFASs.

Aiming to foster synergies between science and policy, the first "Zürich Statement on Future Actions on Per- and Polyfluoroalkyl Substances (PFASs)" summarized respective needs and common goals shared by the scientific and policy communities and recommended cooperative actions on PFASs.[4] In the ensuing five years, scientific understanding of and regulatory action on PFASs have greatly increased. In the United States (US), for example, the US Environmental Protection Agency (US EPA) has proposed significantly lower acceptable levels of exposure for some specific PFASs in drinking water. Moreover, at the time of the writing of this document, the European Union (EU) was working on a restriction proposal for all uses of PFASs,[5] echoing recent calls

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by many scientists to address PFASs as a class due to their high persistence and other concerns.[6,7] However, in most countries, including those in Latin America, Africa, and Asia, there has been little discussion regarding regulatory actions.

Numerous scientific research findings concerning PFASs have been published in the last five years, with an exponential increase in the last ten years (Figure 1), and various actions

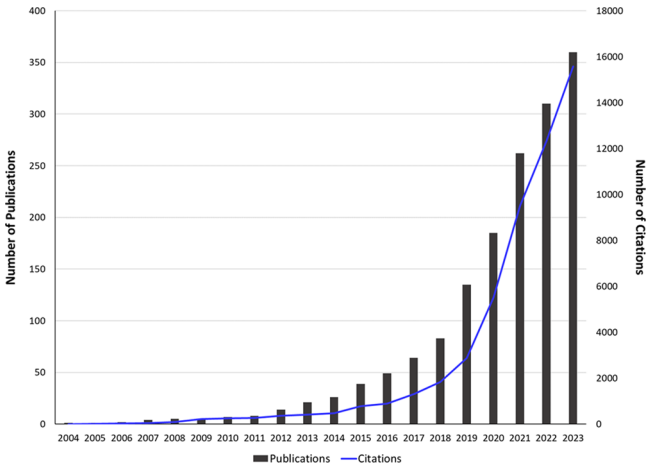

Figure 1. Number of publicly available publications and associated citations indexed in the *Web of Science* for search terms "PFAS and PFOS and PFOA" from 2004 to the end of 2023 (figure created from data collected from the *Web of Science*).

have been taken to address PFASs. Subsections below highlight some key signs of progress. More background knowledge on PFASs can be found in the Helsingør, Madrid, and Zürich Statements.[4,8,9]

1.1. Human Health Impacts. Scientific understanding of human health effects of exposure to PFASs has increased dramatically.[10] Continued improvement is anticipated due to increased public attention, public and private research funding, and regulatory action that stimulates needs for epidemiological and toxicological data.

Table 1 summarizes adverse human health outcomes that multiple organizations recognize as being linked with exposure to PFASs. For example, a special committee of the US National Academies of Sciences, Engineering, and Medicine (NASEM) reviewed epidemiological data for seven individual PFASs and determined *sufficient evidence* for decreased antibody responses, dyslipidemia, decreased infant and fetal growth, and increased risk of kidney cancer associated with exposure to PFASs.[11] The committee also determined *limited suggestive evidence* for increased risk of breast cancer, liver enzyme alterations, increased risk of pregnancy-induced hypertension and preeclampsia, increased risk of testicular cancer, thyroid disease, and dysfunction, and increased risk of ulcerative colitis linked with exposure to PFASs.[11] Many of these adverse end points identified from epidemiological studies are supported by toxicological data from laboratory-based studies. Integration of these diverse data streams generates high confidence for the existence of causal relationships between exposure to certain PFASs and the aforementioned adverse health effects. The NASEM committee finalized their evaluation into recommendations for clinical evaluation of people at risk of increased exposure to PFASs.[11]

Understanding effects of exposure to PFASs on health has also expanded to include health end points that occur at lower exposure concentrations than previously identified.[12] The European Food Safety Authority (EFSA) acknowledged this by identifying 4.4 ng/kg of body weight per week as a tolerable weekly intake for four PFASs (perfluorooctanoic acid [PFOA], perfluorooctanesulfonic acid [PFOS], perfluorohexanesulfonic acid [PFHxS], and perfluorononanoic acid [PFNA]) in food based on decreased antibody responses to vaccinations.[13] In 2023, the Swedish Food Agency introduced a drinking water limit value of 4 ng/L and the Danish Environmental Protection Agency set a drinking water limit value of 2 ng/L, both for the sum of the four PFAS evaluated by EFSA.[14,15] Also in 2023, the US EPA proposed maximum contaminant levels (MCLs) for PFOA and PFOS in drinking water of 4 ng/L each. The underlying health concern driving the MCLs was cancer risk.[16] The low values set by the EFSA, the Swedish and Danish authorities, and the US EPA indicate that current environmental levels are relevant for human health concerns and that risks of adverse health outcomes form the basis of advisories and standards, at least for human ingestion.

1.2. Economic Costs of Health Impacts. The first Zürich Statement called for new approaches to assessing long-term societal costs associated with the very high persistence of many PFASs.[4] This is because many previous socioeconomic assessments for PFASs narrowly focused on costs to industry or government if uses of PFASs were discontinued due to bans or other restrictions, which covers only one aspect of societal costs.[17] To obtain a comprehensive picture, other societal costs of PFASs are needed, such as health-related costs associated with exposure to PFASs.[18]

Recently, annual health-related costs for diseases linked with exposure to some PFASs for the European Economic Area were estimated at EUR 52−84 billion.[19] Based on systematic reviews of evidence for 13 different diseases associated with exposure to some PFASs, another study estimated that annual health-related costs in the US ranged between $5.5 and $62.6 billion.[20] The burden of these societal costs (externalities) falls primarily on local governments and individuals who did not cause the pollution.

These estimates for Europe and the US reflect the costs to society if no actions to curb exposure to PFASs are taken. If measures are taken, e.g., if contaminated areas are remediated, the predicted risks to health might not occur, and the resulting savings (health benefits less the costs of the remediation) are considered benefits of implementing the action. The US EPA benefit-of-action analysis supporting the proposed MCLs for PFOA and PFOS in drinking water used this approach to demonstrate how the most stringent option represents the best overall value.[21]

These economic analyses clearly illustrate the benefits of reducing exposure to PFASs in a timely manner. They also demonstrate the urgent need to phase out nonessential uses of PFASs to prevent further environmental accumulation of a growing suite of PFASs.

1.3. The Global Market. Understanding of the presence of PFASs on the global market has grown, with the US EPA CompTox Chemicals Dashboard including over 14,000 individual substances.[22] This may still be an underestimate of PFASs used in the market or detected in the environment, as a greater number of individual PFASs have been found listed in patents or literature.[23] Regardless of the number of PFASs on the global market, setting priorities and focusing scientific and regulatory action for the hundreds or thousands of individual

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Table 1. Human-Health Effects for which Organizations Have Concluded There Is Epidemiological Evidence for an Association with PFASs[b]

Category	Outcome	ATSDR[104,105]	US EPA[106−109]	EFSA[13]	C8 Science Panel (considered PFOA only)[110]	NASEM (considered PFASs as a group)[11]	Other Statements
				Areas of Consensus			
Carcinogenicity	Kidney Cancer	PFOA[a]	PFOA		PFOA	sufficient evidence	The International Agency for Research on Cancer (IARC) has classified PFOA as carcinogenic to humans (Group 1), based on sufficient evidence for cancer in experimental animals and strong mechanistic evidence in exposed humans. There was "limited" evidence for cancer in humans for renal cell carcinoma. PFOS was classified as possibly carcinogenic to humans (Group 2B) based on limited evidence for cancer in experimental animals and strong mechanistic evidence in exposed humans. There was "inadequate" evidence for cancer in humans.[111]
	Testicular Cancer	PFOA[a]	PFOA		PFOA	limited or suggestive evidence	There was "limited" evidence for cancer in humans for testicular cancer.[111]
Metabolic Disease	Liver Damage (increased liver enzyme levels)	PFOA, PFOS, PFHxS	PFOA	PFOA, PFOS, PFHxS, PFNA		limited or suggestive evidence	
	Increased Serum Cholesterol Levels	PFOA, PFOS, PFNA, PFDA	PFOA, PFOS	PFOS, PFOA, PFNA	PFOA	sufficient evidence	
Immune	Decreased immune response (e.g., antibody response to vaccines)	PFOA, PFOS, PFHxS, PFNA, PFDA	PFOA, PFOS	PFOA, PFOS		sufficient evidence	The National Toxicology Program (NTP) concluded that PFOA and PFOS are presumed to be an immune hazard to humans based on a high level of evidence that PFOA and PFOS suppressed the antibody response from animal studies and a moderate level of evidence from studies in humans.[112]
Endocrine	Thyroid disease		PFOA, PFOS		PFOA	limited or suggestive evidence	
Reproductive and Birth Outcomes	Decreased Birthweight	PFOA, PFOS	PFOA, PFOS	PFOA, PFOS		sufficient evidence	
	Preeclampsia/gestational hypertension	PFOA, PFOS	PFOA		PFOA	limited or suggestive evidence	
				Areas without Consensus			
Carcinogenicity	Breast cancer					limited or suggestive evidence	
Immune	Increased Risk of Asthma Diagnosis						The NTP concluded that, although the strongest evidence for an effect of PFOA on the immune system is for suppression of the antibody response, there is additional, although weaker, evidence that is primarily from epidemiological studies that PFOA reduced infectious disease resistance, increased hypersensitivity-related outcomes, and increased autoimmune disease incidence.[112]
	Increased risk of infection						
	Ulcerative Colitis				PFOA	limited or suggestive evidence	
Metabolic Disease	Gestational diabetes						
	Diabetes						
	Overweight/Obesity						
	HOMA-IR, HOMA-B, adiponectin						
Developmental	Multiple outcomes have been consid-						

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Table 1. continued

Category	Outcome	ATSDR[104,105]	US EPA[106–109]	EFSA[13]	C8 Science Panel (considered PFOA only)[110]	NASEM (considered PFASs as a group)[11]	Other Statements
	ered, such as neurodevelopmental outcomes and growth						
Reproductive and Birth Outcomes	Reduced gestational duration/preterm birth						
	Decreased fertility and fecundity		PFOS				
Cardiovascular	Hypertension						
Skeletal	Decreased bone mineral density						

[a]While the Toxicological Profile for Perfluoroalkyls does not make cancer conclusions, ATSDR lists kidney and testicular cancer as health effects on its Web site. [b]PFOA = Perfluorooctanoic acid, PFOS = Perfluorooctanesulfonic acid, PFHxS = Perfluorohexanesulfonic acid, PFNA = Perfluorononanoic acid, PFDA = Perfluorodecanoic acid.

PFASs is a formidable challenge that calls for grouping[6] or class-based approaches.[7]

When priorities are set, it is important to consider various types of PFASs. The appreciation of the PFAS universe is increasing, going beyond carboxylic and sulfonic acids (PFCAs and PFSAs) and their precursors, as illustrated in OECD (2021).[1] Grasping the size of the PFAS universe is particularly salient when the many discrete/monoconstituent PFASs on the market, including PFASs used in pesticidal and medicinal substances, are considered.[24−26] Meanwhile, considerable knowledge and data gaps persist for identities of those PFASs that are polymers, substances of unknown or variable composition, complex reaction products or biological materials (UVCBs), or reaction byproducts, impurities, and degradation products.[1,27,28]

Another important consideration is production and use volumes of different PFASs (and groups of PFASs). Combined volumes of relevant fluorinated gases, including many hydrofluorocarbons (HFCs), hydrofluoroethers (HFEs), hydrofluoroolefins (HFOs), and hydrochlorofluoroolefins (HCFOs) were estimated at over 1 million tonnes/year.[29] Fluoropolymers, including fluoroelastomers, had the second highest estimated volume after fluorinated gases, at several hundred thousand tonnes/year. Volumes of more commonly studied PFAAs, other perfluoroalkylether acids, and their precursors, including side-chain fluorinated polymers, were estimated at several thousands to several dozens of thousands of tonnes/year.[30] Meanwhile, production volumes of many other groups, including perfluoropolyethers and side-chain fluorinated aromatics, were unknown to authors and likely will change total PFAS production volume estimates if known.[29]

Production of certain PFASs has increasingly moved to Asia in the last two decades, where there is less regulatory scrutiny.[31] Information on production volumes and emissions is as difficult to obtain for Asia as anywhere else.[31] However, high levels of PFASs measured in Chinese rivers[32] are clear evidence of recent steep increases in emissions of certain PFASs in China. However, production of PFOS has stopped in China, which can be considered a success of the Stockholm Convention with its listing in 2009.[33] Although PFOA was also listed in 2019 under the Stockholm Convention and a global ban has entered into force for most countries, the current listing includes many exemptions and is not yet applicable to several countries such as Japan.[34] Public information on locations of sites where PFASs are manufactured in Asia[31,32] can be found with some investigative work, but there is little or no information on production volumes and emissions.

1.4. Analytics. Analytical methods for specific PFASs in water and food have generally improved in sensitivity and selectivity in the past few years, e.g., to meet lower regulatory limit values. However, sensitive and accurate targeted methods that incorporate uses of isotopic-labeled internal standards still cover only about 50+ PFASs, mostly PFCAs and PFSAs with four or more carbons.[35] Some laboratories have developed targeted methods for detecting additional PFASs for which chemical reference standards are available, such as hexafluoropropylene oxide dimer acid (HFPO-DA, sometimes referred to as GenX), ADONA, *n*:2-fluorotelomer sulfonic acids, various other precursors to PFCAs and PFSAs, and some PFASs prevalent in firefighting foams such as betaines.[36] Ultrashort-chain PFCAs and PFSAs that are very water-soluble and mobile, such as trifluoroacetic acid (TFA), are also increasingly measured.[37]

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Sum parameter methods, such as Total Organic Fluorine assays (e.g., adsorbable organic fluorine, extractable organic fluorine), the Total Oxidizable Precursor Assay (TOPA), and the hydrolysis assay,[38,39] are being used more broadly across matrices to quantify the proportion of PFASs not captured by typical targeted analyses.[40] These methods still tend to be hampered by higher detection limits and lack of specificity compared to targeted methods but serve as screening methods, e.g., for identifying hotspots and to determine fluorine mass balances.

As more PFASs are released into the environment, including a greater number of impurities and metabolites, nontargeted analysis (NTA) has become necessary for both nonpolymeric and polymeric PFASs.[41] Suspect screening (SS) and NTA screening methods have become more common with the advent of high-resolution mass spectrometers (e.g., Orbitrap and quadrupole-time-of-flight instruments), and related data analysis software have become more widely available. SS/NTA are used to identify unknown PFASs and are supported by increasing availability of commonly shared lists such as the Norman Network Substance List Exchange[42] or the MassBank of North America[43] that compile chemical identity information on specific compounds.[42] Comparison between NTA and TOPA at an electronic/semiconductor site has shown that only 23% of PFASs in soils were found by TOPA and targeted methods. NTA combined with characteristics for homologous series detected emerging PFASs such as long-chain pentasulfanyl ($-SF_5$) PFSAs (40%), H-containing PFASs, ethers, and diacids.[44]

1.5. Environmental Distribution. In addition to increasing evidence of ubiquitous global distribution of certain PFASs,[45] including in remote regions such as Antarctica and oceans,[46,47] mechanistic understanding of their environmental long-range transport (LRT) is also growing. Many PFASs (including PFAA precursors) are highly environmentally persistent, which suggests that they can undergo LRT either over short or long periods of time depending on their mobility in air or water.[48−52] Concentrations of PFASs in areas close to emission sources may decrease over time after emissions stop due to dilution as a consequence of environmental mobility. Correspondingly, concentrations of PFASs in remote areas and in deep oceans may keep increasing for long periods of time because of inflow via LRT. Such redistribution instead of elimination of PFASs in the environment is concerning, as a recent article demonstrated that even levels of long-chain PFCAs and PFSAs in rainwater in remote regions, while still increasing due to global distribution, have already exceeded recently proposed safe levels of human exposure via drinking water.[45]

While considerable progress has been achieved in understanding variable trends of certain PFASs in the global environment, no study has yet found general decreases for most regions and species. Further, large data gaps still exist for the Global South regions, such as South America, Africa, parts of Asia, and Russia, with little reporting of measurement data and even more so for reporting of time trends. When data on temporal changes of PFASs are compared, various compartments (humans, wildlife, and the physical environment) seem to differ. These divergences likely originate from consumer product exposures for humans, variation in bioaccumulation (including precursor biotransformation) processes in wildlife and humans, and complex transport and deposition capabilities in physical environments.[53−55]

Recent environmental monitoring studies have further expanded to a wider range of PFASs, including the particularly interesting substance, TFA. It is an important terminal transformation product of many PFASs, including many fluorinated gases.[56−58] TFA levels in the environment have increased dramatically in many parts of the world in the last decades[51,59,60] and are expected to continue to grow as industries transition to HFOs.

1.6. Regulatory and Legislative Developments. Regulators in many jurisdictions are increasingly moving toward more comprehensive approaches for addressing PFASs.[61−64] Grouping of PFASs and consideration of their entire life cycles are increasingly important elements of scientific discussion and regulatory action.

To address health and environmental concerns about PFASs, several jurisdictions all from the Global North have developed action plans or strategies, including the EU,[61] Canada,[65] the US,[66] France,[67] Australia, and New Zealand.[68] The legislative initiatives signaled in these action plans are now under way or already in force in many places. Several US states have also taken measures to reduce the use of PFASs, including bans on PFASs in firefighting foams, textiles, food packaging materials, cosmetics, and other consumer products,[69] as well as regulations to promote safer alternatives to PFASs in carpets and aftermarket treatments for textiles and leathers.[70] Furthermore, the US state of Maine has prohibited the sale of any product containing intentionally added PFASs as of 2030, unless such use is specifically designated as currently unavoidable.[71] And, as previously described, the proposed EU restriction would end all uses of PFASs unless specific exemptions are agreed upon.[5] The range of PFAS uses put forward for exemption could, if considerably widened, undermine the effectiveness of this restriction.

The concept of essential use, first applied under the Montreal Protocol, has become a key element in regulatory discussions on how to control impacts of these highly persistent chemicals, although it is not applied in the European PFAS restriction proposal.[61,72] Consensus is also emerging that persistence is a sufficient basis for regulatory action.[73] In this regard, the EU's proposal to restrict microplastics based, among other concerns, on their persistence is an important precedent.[74] Also noteworthy is the EU's move to include criteria for persistence combined with bioaccumulation or mobility in its regulation on the classification, labeling, and packaging of substances and mixtures (CLP Regulation).[75]

2. ONGOING CRITICAL ISSUES TO BE ADDRESSED

2.1. Human Health Impacts and Their Costs. While many linkages have been established between exposure to PFASs and adverse health outcomes, some routes of exposure remain understudied, particularly inhalation. Those who work with PFASs and people living near factories that make or use PFASs may be at risk from health effects arising from the inhalation of PFASs. Workers are among the most highly exposed subpopulations in Europe,[76] especially in chrome-plating facilities and fluoropolymer plants, but publicly available data are lacking for manufacturing sites. Both workers and consumers have reported pulmonary effects after using PFAS-containing sprays for textiles, leather, and wood.[77] Further, cytotoxicity has been reported from PFAS-containing antifog sprays for glasses, suggesting potential health risks for users of these products.[78]

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Also, more is known today about externalities such as health impacts, drinking water and soil contamination, and loss of property value.[18] Additional or improved methods for tracking the impacts of such externalities and for estimating costs at global, national, and local levels are needed. Evaluation of long-term socioeconomic costs will highlight the importance of not delaying action, e.g., how reducing exposures will lead to significant savings in health-related costs. Such cost information will also provide incentives for companies to look for alternatives to the use of PFASs.

The question of "who pays" remains important. While polluters should pay as soon as costs have been estimated, there also is a need for incentives to produce less hazardous products and to use and emit less hazardous substances from processes.

2.2. The Global Market. Industry likely has copious information on production, use, and emissions, but such information is not typically publicly available. Information on production capacities is included in market reports.[31] However, such reports are expensive, and their data quality is unknown.[2] Gathering market information is therefore a substantial challenge. Furthermore, as the market for PFASs is highly fragmented and geographically spread out, it is difficult to obtain comprehensive and consistent data on the historical and ongoing production volumes of most PFASs.

Products containing hazardous substances that cannot easily be identified will also hamper the reuse and recycling of materials. Moreover, addressing problems such as climate change should not worsen the pollution crisis associated with highly persistent chemicals, such as PFASs. Thus, it is wise to avoid and swiftly address the lock-in of PFASs in green technologies. More research and development are needed for practical applications, but safer alternatives do exist and should be used.

2.3. Analytics and Environmental Distribution. New analytical methods are still needed for the majority of PFASs and for certain media (e.g., lipids, soil, emission gases/aerosols) and finished products. For example, analytical methods are lacking for nonpolar polyfluorinated, cationic, and volatile PFASs such as feedstocks used to make fluoropolymers and oligomers, as well as residuals and transformation products emitted from manufacturing and thermal degradation (e.g., during recycling) of fluoropolymers. Methods for larger PFASs (>1000 Da) are seldom established, not because it is impossible to analyze for larger PFASs, but because 1000 Da is the typical mass spectrometry cutoff range for environmental chemicals. Groups of PFASs such as perfluoropolyethers as well as PFAS acrylates, silicones, and imides are therefore not routinely measured.[41] Analysis of sector-specific uses of PFASs, such as for the growing semiconductor/electronic industries, solar panels, and medical uses, also is lacking.

While suspect and NTA screenings are more widely used, for example, in source identification, data treatment remains a very time-consuming step that needs streamlining. Scarce availability of chemical reference standards still limits quantification and identification of large groups of cationic, nonionic, volatiles, and other commercially used PFASs. Environmental researchers still lack access to standards for the use of these PFASs. Recently, Solvay tried to use patent law to block a commercial chemical reference provider from selling small amounts of their chemicals.[79] These examples stress the urgent need to make sufficiently sensitive screening and sum-parameter methods as well as standardization of total organic fluorine methods (e.g., through validation of methods and more interlaboratory studies such as the one from KEMI[80]) available. Such methods will be necessary to support implementation of many forthcoming regulations, particularly for the PFAS restriction proposal in the EU (e.g., for identification of PFASs in products) and for measuring a proxy for total PFASs in drinking water as required by the European Drinking Water Directive.[81]

2.4. Current Challenges for Regulators. It is increasingly recognized that the high persistence of many PFASs could be sufficient for regulating them as a class, since continued production and use will lead to increasing external or internal exposures and thereby increase risk of harm that is poorly reversed.[3] However, many regulatory frameworks currently are not designed in a way to address this issue because they require quantitative instead of qualitative risk assessment.

Some jurisdictions are exploring toxic equivalency factors (TEFs) or relative potency factors (RPFs) as a scientific basis for toxicity analyses and for subgrouping of PFASs.[82] There is concern that the development of TEFs and RPFs requires more extensive hazard data than what currently is needed for regulation of single substances. Subgrouping of PFASs based on TEFs and RPFs could therefore slow, rather than speed up, regulations of a broader span of PFASs.

However, it was discussed whether subgrouping could be useful for setting environmental limit values, which are urgently needed for PFASs in media such as surface and groundwater, air, soil, and sewage sludge. Subgrouping approaches might enable regulators in some regions to set and enforce limits against sources of PFASs contamination, e.g., industrial producers and users.

Cross-regulatory approaches are also needed. For example, while one regulation may allow industrial or urban wastewater emissions of PFASs, such emissions may make compliance with the limit values for surface water quality impossible. Regulatory frameworks should consider emissions throughout the PFAS life cycle, including raw material extraction, production, manufacturing, use, recycling/reuse, and end-of-life. The ability to achieve toxic-free material cycles (e.g., by separate collection of PFAS-contaminated materials) will be particularly problematic due to uncertainty about PFASs in products within global supply chains. Additionally, policy fields outside of environmental and chemicals regulation, such as industry, transportation, and renewable energies, need to be active in developing alternatives to prevent and swiftly address lock-ins of PFAS-dependent technologies, as previously mentioned.

The situation is different in low- and middle-income countries, where regulations on PFASs are still sparse or in earlier stages of development. Many countries still lack effective chemicals regulatory, monitoring, and enforcement systems.[83] For these countries, the Stockholm Convention on POPs is very important.

However, the Stockholm Convention lacks provisions that would enable addressing concerns about the whole class of PFASs. One possible solution would be to change the criteria in the Stockholm Convention to enable the inclusion of highly persistent substances even if their bioaccumulation potential has not yet been proven. This may allow the listing of, e.g., perfluorohexanoic acid (PFHxA) and its precursors, which meet the other POP criteria and warrant global action. In the

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meantime, additional subgroups of PFASs with similar concerns may be listed under the Stockholm Convention, e.g., substances such as HFPO-DA and other perfluoroalkyl-ether acids.

More use could also be made of the OECD/UNEP Global PFC Group, e.g., for sharing regulatory activities and for linking regulators in other countries with resources such as the eChemPortal.[84] Criteria for polymers of low concern should also be reviewed with critical consideration of fluoropolymers.[85,86] Suggestions for polymer assessment criteria have been proposed by Groh et al. (2022).[87]

2.5. Misinformation. Information and awareness around PFASs have expanded dramatically since the first Zürich Statement, likely due to numerous scientific studies and increasing attention from the public and media. Additionally, misinformation on PFASs has also proliferated, perhaps in response to consumer fears (misdirection and greenwashing with respect to PFASs in products) and perhaps partly from impending regulatory actions. The latter has included several industry arguments against treating PFASs as a class, exempting specific types of PFASs (e.g., fluoropolymers or fluorinated gases) from regulation, and sowing doubt about the level of understanding of toxic effects of exposure to PFASs.[88−90] A focus on legacy long-chain PFAAs has delayed knowledge-building on many current-use and widely applied PFASs.[12,91]

Arguments against managing PFASs as a class often focus on physical-chemical differences among PFASs, but these differences primarily impact specific aspects of their environmental fate and transport. The high persistence of many PFASs and/or their degradation products is an inherent problem that makes PFASs stand out from other chemicals.[92]

It has been suggested that variability among health advisory levels for PFASs reflects great scientific uncertainty about toxicity-related end points, including toxicokinetic-toxicodynamic factors and the strength of association with adverse health outcomes.[93,94] However, differences across US states or among national regulatory bodies globally likely reflect multiple influences rather than scientific uncertainty alone.[88] As understanding of PFASs toxicity advances, health advisories are consistently trending toward lower, stricter, limits. Another argument used in cases where health effects from exposure to PFASs are observed is that causation cannot be proven for one person's disease arising from exposure to specific PFASs.[95−97] Proving causation is complex. Instead, strong evidence can be built by integrating information to identify concurrence across different studies and types of studies.

3. POSSIBLE WAYS FORWARD

3.1. Next Steps Needed from the Regulatory Side. Most workshop participants concurred that preventing new PFASs from entering the market and new uses of PFASs from being established should be a priority. It was also noted that it is important to ensure that alternatives to current uses of PFASs follow the principles of green and sustainable chemistry and engineering. It was suggested that avoiding uses of chemicals of concern by applying cutoff criteria for such chemicals in the Safe and Sustainable by Design concept recommended by the EU Joint Research Centre[98] would be a useful step in this regard.

In general, workshop participants agreed that more transparency is needed regarding uses of PFASs in products and industrial processes that are clearly identifiable within the supply chain. The Digital Product Passport that is suggested in the EU legislative proposal "Ecodesign requirements for sustainable products regulation" could be a positive step, as it would require companies to disclose the presence of hazardous chemicals in products.[99] In addition, it was discussed that industry should be obliged to report all uses of PFASs and production volumes and minimize their environmental emissions. It was also discussed that extended producer responsibility will also support measures to "turn off the tap", along with strict application of the polluter-pays principle.

To address the problem of how to identify thousands of PFASs and other chemicals found in the environment today, it was suggested that companies putting chemicals on the market, as individual substances or in products, should be required to supply a standard (representative sample of the chemical) to authorities free of charge and make it publicly available.

Another need that was mentioned was to identify already polluted sites or PFAS contamination "hot spots," alert affected communities to contaminated drinking water or food items, and appropriately address legacy pollution. It was noted that this need is especially important in countries where there is still a huge lack of data for PFASs environmental occurrence and distribution such as countries in Latin America and Africa.

Most agreed also on the point that raising awareness will be critical in encouraging the development of effective policies with better global coverage. Currently very different levels of awareness and concern exist across Europe, North America, Asia, Australia, Africa, and Latin America. Some regions have other pressing needs, such as water scarcity and climate change impacts, and many have limited resources to address these needs. Participants highlighted that a key to continuing and accelerating progress will be to assemble the big picture on PFASs uses, contamination, and impacts—but not to get lost in details and or allow misdirection by misinformation.

3.2. Nonregulatory Actions, Incentives, and Measures. It was discussed that product manufacturers appear to be interested in moving toward more sustainable products in response to consumer demands for safer, healthier, and greener products. "Early-mover" brands have identified market advantages arising from PFAS-free options, particularly in concert with raising consumer awareness of PFAS hazards. Labeling may help consumers make informed choices. However, some concerns were raised that voluntary labeling could lead to greenwashing (e.g., "PFOA-free" as opposed to "PFAS-free"), so it was agreed that transparency is vitally important, including, and maybe even more importantly, throughout global supply chains.

Currently, knowledge across countries and industries differs, and it was suggested that better coordination with experts to find or develop alternatives is needed. Programs for developing more sustainable products and processes conducted in collaboration with industry were thought to be a helpful way forward. An example for such a program is POPFREE,[100] run by the Research Institutes of Sweden. ChemSec also lists companies that have stopped using PFASs,[101] and ZeroPM has developed a database of alternatives to PFAS.[102] It was generally agreed that avoiding the increased use of PFASs in emerging technologies may require transdisciplinary collaboration.

It was discussed that leadership, most likely from the civil society organization community, is needed to coordinate impacted communities as these communities often must act in

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isolation or without a larger network. Most workshop participants agreed that it will be important to facilitate connections among stakeholders directly affected by PFAS exposure to raise awareness about PFASs and inspire changes beyond scientific and regulatory communities. Another effective route mentioned for influencing change, often used by stakeholders at the community level, especially in the US, was litigation.[103]

Lastly, it was agreed that translating information into multiple languages will raise PFASs global awareness. This includes translating from English to other languages and translating scientific or technical text to plain language. This provides opportunities for other organizations and individuals, such as journalists, to contribute.

4. MOVING FORWARD

Workshop participants supported the idea that continued bilateral workshops between academic scientists and regulators provide critical interactions for the growing global dialogue around PFASs. As information about PFASs has grown, the understanding of the complexity of their management also has grown. It was agreed that it is therefore essential that multistakeholder exchanges continue and that more diverse constituents are engaged, including developing and transition countries, non-governmental organizations (NGOs), social and traditional media, and community-based organizations.

AUTHOR INFORMATION

Corresponding Author

Jamie C. DeWitt − *Department of Environmental and Molecular Toxicology, Oregon State University, Corvallis 97331 Oregon, United States;* orcid.org/0000-0002-0440-4059; Email: jamie.dewitt@oregonstate.edu

Authors

Juliane Glüge − *Institute of Biogeochemistry and Pollutant Dynamics, ETH Zürich, Zürich CH-8092, Switzerland*

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

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

Dorte Herzke − *NILU, Tromsø 9296, Norway and Department of Food Safety, Norwegian Institute of Public Health, Oslo 0213, Norway;* orcid.org/0000-0001-9620-3053

Rainer Lohmann − *Graduate School of Oceanography, University of Rhode Island, Narragansett 02882 Rhode Island, United States;* orcid.org/0000-0001-8796-3229

Mark Miller − *National Institute of Environmental Health Sciences, U.S. Public Health Service, Research Triangle Park 27709 North Carolina, United States*

Carla A. Ng − *Department of Civil & Environmental Engineering and Environmental and Occupational Health, University of Pittsburgh, Pittsburgh 15261 Pennsylvania, United States;* orcid.org/0000-0001-5521-7862

Sharyle Patton − *Health and Environment Program Commonweal, Bolinas 94924 California, United States*

Xenia Trier − *Department of Plant and Environmental Sciences, Section for Environmental Chemistry and Physics, University of Copenhagen, Copenhagen 1165, Denmark*

Lena Vierke − *German Environment Agency (UBA), Dessau-Roßlau 06844, Germany*

Zhanyun Wang − *Empa-Swiss Federal Laboratories for Materials Science and Technology, St. Gallen CH-9014, Switzerland*

Sam Adu-Kumi − *EnviroHealth Consulting, Accra GA184, Ghana*

Simona Balan − *California Department of Toxic Substances Control, Safer Consumer Products Program, Berkeley 94710 California, United States;* orcid.org/0000-0003-0438-1616

Andreas M. Buser − *Federal Office for the Environment FOEN, Bern 3003, Switzerland;* orcid.org/0000-0002-0156-8947

Tony Fletcher − *Department of Public Health, Environments & Society, London School of Hygiene & Tropical Medicine, London WC1H 9SH, U.K.;* orcid.org/0000-0003-3385-200X

Line Småstuen Haug − *Department of Food Safety, Norwegian Institute of Public Health, Oslo 0213, Norway*

Jun Huang − *School of Environment, Tsinghua University, Beijing 100084, China;* orcid.org/0000-0001-9207-8953

Sarit Kaserzon − *Queensland Alliance for Environmental Health Sciences, The University of Queensland, Queensland 4102, Australia;* orcid.org/0000-0002-6744-1279

Juliana Leonel − *Department of Oceanography, Universidade Federal de Santa Catarina, Florianopólis 40170110, Brazil*

Ishmail Sheriff − *School of Civil Engineering, Universiti Sains Malaysia, Penang 14300, Malaysia;* orcid.org/0000-0001-5374-6533

Ya-Li Shi − *School of Environment, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, Hangzhou, CN, 310024 and State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China;* orcid.org/0000-0001-9946-1525

Sara Valsecchi − *Water Research Institute-National Research Council, Brugherio 20861, Italy;* orcid.org/0000-0003-2200-3475

Martin Scheringer − *Institute of Biogeochemistry and Pollutant Dynamics, ETH Zürich, Zürich CH-8092, Switzerland; RECETOX, Masaryk University, Brno 62500, Czech Republic;* orcid.org/0000-0002-0809-7826

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.estlett.4c00147

Notes

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ABBREVIATIONS

EFSA	European Food Safety Authority
EU	European Union
HCFOs	hydrochlorofluoroolefins
HFCs	hydrofluorocarbons
HFEs	hydrofluoroethers
HFOs	hydrofluoroolefins
HFPO-DA	hexafluoropropylene oxide dimer acid (also referred to as GenX)
LRT	long-range transport
MCL	maximum contamination level
NASEM	National Academies of Sciences, Engineering, and Medicine
NTA	nontargeted analysis
OECD	Organisation for Economic Co-operation and Development
PFASs	per- and polyfluoroalkyl substances
PFCAs	perfluoroalkyl carboxylic acids
PFHxA	perfluorohexanoic acid
PFHxS	perfluorhexanesulfonic acid
PFNA	perfluorononanoic acid
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid
PFSAs	perfluoroalkanesulfonic acids
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RPFs	relative potency factors
SS	suspect screening
TEFs	toxicological equivalence factors
TFA	trifluoroacetic acid
TOPA	total oxidizable precursor assay
US	United States
US EPA	US Environmental Protection Agency

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