Environmental Science Processes & Impacts

ROYAL SOCIETY OF CHEMISTRY

CRITICAL REVIEW

View Article Online
View Journal | View Issue

Cite this: *Environ. Sci.: Processes Impacts*, 2020, **22**, 1444

Strategies for grouping per- and polyfluoroalkyl substances (PFAS) to protect human and environmental health

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Grouping strategies are needed for per- and polyfluoroalkyl substances (PFAS), in part, because it would be time and resource intensive to test and evaluate the more than 4700 PFAS on the global market on a chemical-by-chemical basis. In this paper we review various grouping strategies that could be used to inform actions on these chemicals and outline the motivations, advantages and disadvantages for each. Grouping strategies are subdivided into (1) those based on the intrinsic properties of the PFAS (*e.g.* persistence, bioaccumulation potential, toxicity, mobility, molecular size) and (2) those that inform risk assessment through estimation of cumulative exposure and/or effects. The most precautionary grouping approach of those reviewed within this article suggests phasing out PFAS based on their high persistence alone (the so-called "P-sufficient" approach). The least precautionary grouping approach reviewed advocates only grouping PFAS for risk assessment that have the same toxicological effects, modes and mechanisms of action, and elimination kinetics, which would need to be well documented across different PFAS. It is recognised that, given jurisdictional differences in chemical assessment philosophies and methodologies, no one strategy will be generally acceptable. The guiding question we apply to the reviewed grouping strategies is: grouping for what purpose? The motivation behind the grouping (*e.g.* determining use in products *vs.* setting guideline levels for contaminated environments) may lead to different grouping decisions. This assessment provides the necessary context for grouping strategies such that they can be adopted as they are, or built on further, to protect human and environmental health from potential PFAS-related effects.

Received 3rd April 2020
Accepted 18th May 2020

DOI: 10.1039/d0em00147c

rsc.li/espi

Environmental significance

PFAS comprise more than 4700 individual substances that are used in many, highly diverse applications in society. All PFAS are very persistent (if PFAS with persistent transformation products are considered as persistent substances, as is the case under REACH) and several PFAS are also known to be bioaccumulative and toxic. However, for most PFAS there are insufficient data to facilitate chemical assessments. Generating these missing data on a chemical-by-chemical basis is too resource intensive and it is therefore essential to identify groups of similar PFAS that can be assessed together. Here we discuss various grouping approaches and their advantages and limitations. The structural diversity of PFAS poses a challenge to grouping. However, some kind of grouping approach, or a combination of several different approaches, will be needed for the future assessment and management of PFAS.

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Introduction

Buck *et al.*[1] provided the first class definition of per- and polyfluoroalkyl substances (PFAS) as "the highly fluorinated aliphatic substances that contain 1 or more C atoms on which all the H substituents… have been replaced by F atoms, in such a manner that they contain the perfluoroalkyl moiety C_nF_{2n+1}–" (where n is equal to or greater than 1, *i.e.* the structure must contain at least one CF_3– group). A more recent and broader definition by the Organisation for Economic Co-operation and Development (OECD)/United Nations Environment Programme (UNEP) Global PFC Group[2] defined PFAS as chemicals with at least one perfluorocarbon moiety (–C_nF_{2n}–). PFAS therefore comprise a diverse group of chemistries with the common feature of the fully or "per"-fluorinated carbon chain.

Structurally diverse PFAS are used in a wide variety of commercial products and industrial applications. In the 2018 OECD PFAS list[2] over 4700 CAS numbers were identified for PFAS on the global market. For the majority of PFAS, little or no data on uses, properties and effects are available to determine how these chemicals may impact the health of living organisms.[3–6] Our current understanding of biological impact is based primarily on studies of four PFAS, perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS), and perfluorononanoic acid (PFNA).[7] Epidemiological studies of human populations suggest that PFAS may act as endocrine and metabolic disruptors, increase cholesterol levels, adversely impact the immune system, and cause cancer.[7] These data are supported by studies in laboratory animals showing changes in liver, thyroid, immune and pancreatic function.[7]

But researching individual chemicals is both expensive and time consuming. It can take many years to gather the evidence needed under regulatory regimes to restrict harmful chemicals. It is becoming increasingly apparent that to effectively protect the public and environment from the wide range of possible PFAS-related environmental and human health effects, strategies should be sought to group PFAS for action, *e.g.* for guiding regulatory and voluntary phase-out actions, *etc.*, rather than to address them chemical-by-chemical. For example, in the recent Zurich Statement,[8] the authors recommended "that actions need to address groups of PFAS rather than individual chemicals and that such a grouping approach needs to be scientifically sound." It was further recognized "that a grouping approach requires a better mechanistic understanding of the physicochemical and toxicological properties of PFAS as well as additional data that can be used to support grouping approaches for PFAS."

Between 2000 and 2002,[9] after about 50 years of continuous manufacture, 3M phased out all PFAS products derived from perfluorooctane sulfonyl fluoride (POSF; C-8) and its C-6 and C-10 homologues, which represented the first large-scale grouping of hundreds of PFAS for voluntary phase-out. Shortly thereafter, in 2006, eight major PFAS manufacturers committed to eliminating the global use and emissions of PFOA, its longer-chain homologues, and their precursors by 2015 through the PFOA Stewardship program[10] agreement with the US Environmental Protection Agency (US EPA).

In conjunction with these phase-outs, the fluorochemical industry introduced another grouping approach, namely the concept of "long-chain" and "short-chain" perfluoroalkyl acids (PFAAs),[11] defining long-chain PFAAs as only perfluoroalkyl carboxylic acids (PFCAs) with ≥7 perfluorinated carbons and perfluoroalkane sulfonic acids (PFSAs) with ≥6 perfluorinated carbons. While emerging evidence showed long-chain PFAAs are bioaccumulative and toxic, the PFAS manufacturing industry held that short-chain PFAAs were not, and thus one of the strategies of the PFAS manufacturing industry was to replace long-chain PFAAs with their short-chain homologues.[12] Another substitution strategy is to replace long-chain PFAAs with substances containing perfluoroalkyl ether moieties (*e.g.* per- and polyfluoroalkyl ether carboxylic and sulfonic acids (PFECAs and PFESAs)).[12]

It is now apparent that this industry substitution strategy for long-chain PFAAs requires reconsideration given (1) the widespread environmental contamination (including drinking water sources) by short-chain PFAAs[13] and perfluoroalkyl ether acids[14] due to their high environmental mobility and (2) the listing of both hexafluoropropylene oxide dimer acid (HFPO-DA, sometimes referred to as GenX), a PFOA-replacement introduced by DuPont in 2009 that contains perfluoroalkyl ether moieties, and perfluorobutane sulfonic acid (PFBS), a short-chain PFAA that is the ultimate degradation product of 3M's replacement chemistry (introduced in 2003), as Substances of Very High Concern (SVHCs) under the EU REACH Regulation.[15]

Given the number of substitutions of long-chain PFAAs with other PFAS that are now also considered to be problematic, there is a need for more effective grouping strategies for the regulation of PFAS than the current approach of regulating only long-chain PFAAs and related substances. In the Madrid Statement,[16] more than 200 scientists and regulators suggested that PFAS should be managed as a class, and that production and use should be limited. This grouping of all PFAS for phase-out is based on concerns regarding the high persistence of PFAS, the lack of knowledge on chemical structures, properties, uses, and toxicological profiles of most PFAS currently in use, and the need for informed substitutions of problematic PFAS chemistries.[16] A counterpoint to regulating PFAS as a class, authored by the FluoroCouncil[17] in response to the Madrid Statement, stated (among other things) that PFAS are a structurally diverse group exhibiting "important differences between the health and environmental impacts", and that "fluorotechnology is essential technology for many aspects of modern life".

The Montreal Protocol's concept of essential use has been put forward as an approach for reducing exposure to PFAS, by phasing out all non-essential uses of PFAS.[18] While such a phase-out of PFAS is likely not feasible in the short term, it is not an insurmountable challenge in the longer term. Indeed, within the European Union (EU), there are already discussions underway for a restriction proposal for all non-essential uses of PFAS,[19,20] although it is not yet known how "essential use" will be defined. Innovation, in conjunction with regulation and economic incentives for the development of new technologies,

should in time provide functional alternatives to even current essential uses of PFAS.[18] In cases where the uses of PFAS are seen as "necessary for health, safety or is critical for the functioning of society"[16] but no functional alternatives with favourable hazard properties are currently available, certain uses of PFAS will probably continue, at least in the short term.[18] However, the use of the grouping strategies presented here could provide opportunities for market adjustment, and spark more voluntary efforts to reduce non-essential uses.[18]

The aims of this paper are to discuss (1) current and potential grouping strategies that inform PFAS assessment for various control actions, with advantages and disadvantages for each, (2) highlight motivations for action that could guide use of specific grouping approaches and (3) outline the way forward and remaining challenges in advancing these grouping approaches.

Motivations for grouping

The method used to group PFAS depends on the type of action intended. Grouping PFAS may have benefits, for example: (1) to more efficiently protect human and environmental health, (2) to avoid animal testing through read across,[21] (3) for product labelling and consumer education (*e.g.* for interpretation of a label such as "PFAS free"), or (4) to manage clean-up of contaminated sites.

Most existing grouping approaches have been developed to protect human and environmental health from potential adverse effects resulting from exposure to the multiple PFAS in commerce. Moreover, further motivations for grouping of PFAS are based on their environmental and biological persistence, the high number of individual PFAS, and the lessons learned from recent industrial substitution strategies.

Proactive strategies concerning new or continued use of PFAS may benefit from more precautionary grouping approaches because these decisions will directly impact future exposures and because their implementation – at least avoidance of non-essential uses – will always be less costly than retrospective risk assessment and remediation. On the other hand, decisions for how to group already emitted PFAS for the establishment of drinking water guidelines or environmental cleanup levels will have profound impacts on enforcement including costs and resource needs. It may therefore be necessary, in resource-constrained settings, to more strictly prioritize cleanup levels on the basis of established toxicological risk.

Grouping approaches

Here existing grouping approaches to protecting human and environmental health are subdivided into (1) those based on the intrinsic properties of the PFAS and (2) those that inform risk assessment through estimation of cumulative exposure and/or effects (see Fig. 1). National or international chemical assessments rely on intrinsic properties of the chemical, including its persistence (P), bioaccumulation (B) and toxicity (T). This "PBT approach" can be found for example in the EU REACH Regulation.[22] Under REACH, substances can also be identified as "Substances of Very High Concern" (SVHC) if they are very persistent (vP) and very bioaccumulative (vB) meaning that if these criteria can be met, toxicity does not require consideration.

The approaches that inform risk assessment, on the other hand, consider anticipated exposure when determining whether or not an adverse effect to human health or the environment may occur. For example, the point of departure for establishing acceptable risk could be the no observed adverse effect level (NOAEL) for a critical toxicological endpoint. The NOAEL can then be compared to either the external dose or exposure (*e.g.* concentration in exposure medium) or internal dose or exposure (*e.g.* serum or tissue concentration) to determine the risks.

Risk assessment has typically been performed on a chemical-by-chemical basis, but there is some current focus on developing methods for combined risk assessment through estimation of cumulative exposure (*e.g.* total organofluorine (TOF) or extractable or adsorbable organofluorine (EOF/AOF)) and/or effects (*e.g.* additive).[23] Such combined risk assessment is challenging for multiple PFAS, given that sufficient toxicity data are only available for relatively few (<20) substances.[7] Measurement of exposure can be achieved for more substances, but may be constrained by the lack of knowledge of what/how to measure and also lack of analytical standards.

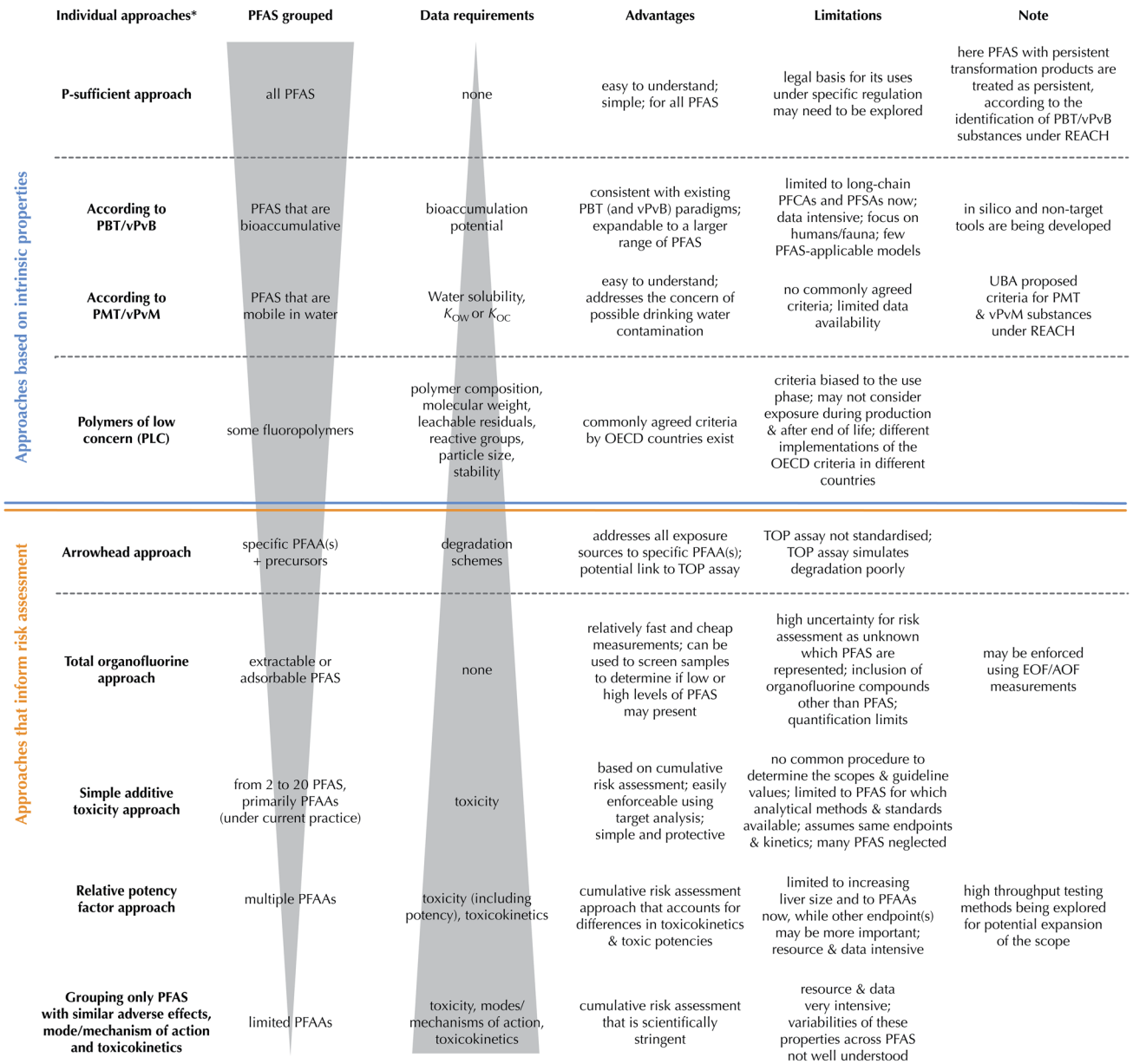
Each individual approach is discussed in more detail in the following sections. It is important to note that the individual grouping approaches were developed for different purposes, have different data needs, and therefore cannot always be directly compared to each other. The selection of the grouping approach needs to account for the specific protection goal, data requirements and enforcement techniques.

Grouping approaches based on intrinsic properties

Grouping according to the "P-sufficient" approach

The continuous release of persistent chemicals will lead to widespread, long-lasting, and increasing contamination, which will inevitably result in increasing probabilities of known and unknown adverse effects on human health and the environment.[24] The perfluoroalkyl (C_nF_{2n+1}–) and perfluoroether (C_nF_{2n+1}–O–C_mF_{2m}–) moieties are highly persistent under environmental conditions.[4] Although some polyfluoroalkyl substances (so called "precursors") may degrade in the environment and biota, they all ultimately (partially) transform into highly stable end products, which are usually the persistent PFAAs.[3] This view is consistent with the REACH Regulation that all chemicals with persistent transformation products should be classified as persistent.[22] Based on this definition, all PFAS are therefore considered to be very persistent in environmental media, and under the proposed "P-sufficient" approach all PFAS would be managed as a single group.

An advantage of this approach is that it is easily implementable to all PFAS for non-experts, *i.e.* non-experts will not need to ask if a (new) PFAS belongs to the group or not. A



	Individual approaches*	PFAS grouped	Data requirements	Advantages	Limitations	Note
Approaches based on intrinsic properties	**P-sufficient approach**	all PFAS	none	easy to understand; simple; for all PFAS	legal basis for its uses under specific regulation may need to be explored	here PFAS with persistent transformation products are treated as persistent, according to the identification of PBT/vPvB substances under REACH
	According to PBT/vPvB	PFAS that are bioaccumulative	bioaccumulation potential	consistent with existing PBT (and vPvB) paradigms; expandable to a larger range of PFAS	limited to long-chain PFCAs and PFSAs now; data intensive; focus on humans/fauna; few PFAS-applicable models	in silico and non-target tools are being developed
	According to PMT/vPvM	PFAS that are mobile in water	Water solubility, K_{OW} or K_{OC}	easy to understand; addresses the concern of possible drinking water contamination	no commonly agreed criteria; limited data availability	UBA proposed criteria for PMT & vPvM substances under REACH
	Polymers of low concern (PLC)	some fluoropolymers	polymer composition, molecular weight, leachable residuals, reactive groups, particle size, stability	commonly agreed criteria by OECD countries exist	criteria biased to the use phase; may not consider exposure during production & after end of life; different implementations of the OECD criteria in different countries	
Approaches that inform risk assessment	**Arrowhead approach**	specific PFAA(s) + precursors	degradation schemes	addresses all exposure sources to specific PFAA(s); potential link to TOP assay	TOP assay not standardised; TOP assay simulates degradation poorly	
	Total organofluorine approach	extractable or adsorbable PFAS	none	relatively fast and cheap measurements; can be used to screen samples to determine if low or high levels of PFAS may present	high uncertainty for risk assessment as unknown which PFAS are represented; inclusion of organofluorine compounds other than PFAS; quantification limits	may be enforced using EOF/AOF measurements
	Simple additive toxicity approach	from 2 to 20 PFAS, primarily PFAAs (under current practice)	toxicity	based on cumulative risk assessment; easily enforceable using target analysis; simple and protective	no common procedure to determine the scopes & guideline values; limited to PFAS for which analytical methods & standards available; assumes same endpoints & kinetics; many PFAS neglected	
	Relative potency factor approach	multiple PFAAs	toxicity (including potency), toxicokinetics	cumulative risk assessment approach that accounts for differences in toxicokinetics & toxic potencies	limited to increasing liver size and to PFAAs now, while other endpoint(s) may be more important; resource & data intensive	high throughput testing methods being explored for potential expansion of the scope
	Grouping only PFAS with similar adverse effects, mode/mechanism of action and toxicokinetics	limited PFAAs	toxicity, modes/ mechanisms of action, toxicokinetics	cumulative risk assessment that is scientifically stringent	resource & data very intensive; variabilities of these properties across PFAS not well understood	

* Note: The individual approaches can also be used in combinations to group PFAS, e.g. the grouping of C_9 to C_{20} PFCAs and their precursors in Canada.

EOF/AOF = extractable/adsorbable organofluorines; K_{OC} = organic carbon-water partition coefficient; K_{OW} = octanol-water partition coefficient; OECD = Organisation for Economic Co-operation and Development; P = persistent; PBT = persistent, bioaccumulative and toxic; PFAA = perfluoroalkyl acid; PFAS = per- and polyfluoroalkyl substances; PFCAs = perfluoroalkyl carboxylic acids; PFSAs = perfluoroalkane sulfonic acids; PMT = persistent, mobile and toxic; REACH = Registration, Evaluation, Authorisation and Restriction of Chemicals; TOP = total oxidisable precursors; UBA = German Environment Agency; vPvB = very persistent and very bioaccumulative; vPvM = very persistent and very mobile

Fig. 1 Grouping approaches for PFAS.

disadvantage of the "P-sufficient approach" is that no legal precedent has been made in any jurisdiction, although the idea of regulating highly persistent chemicals and microplastics is being explored within the EU.[25,26]

Grouping according to the PBT/vPvB approach

As mentioned in the introduction, PFAAs have been grouped into long-chain and short-chain PFAAs, where long-chain PFAAs are considered bioaccumulative in animals and short-chain PFAAs are not.[11] A major disadvantage in the current grouping of long- *versus* short-chain PFAAs to determine if PFAS are bioaccumulative is that the definitions of long- and short-chain PFAAs only apply to PFCAs and PFSAs;[11] however, it has been suggested that there are other PFAS that are bioaccumulative. To more accurately define those PFAS that are bioaccumulative, new grouping approaches would be required; a few suggestions are provided below.

There are already a number of PFAS that are suggested to be bioaccumulative according to observations from bioaccumulation experiments. For example, certain perfluoroalkyl phosphonic and phosphinic acids (PFPAs and PFPIAs) can only be slowly eliminated from rainbow trout[27] and rats,[28] similarly to long-chain PFCAs and PFSAs.[29] There is also evidence that perfluorotripropyl amine is bioaccumulative based on the long elimination half-lives observed in the liver and spleen of rats.[30] Perfluorooctane is also potentially bioaccumulative based on bioconcentration factor (BCF) measurements in European carp (BCF up to 3200 L kg^{-1}) and rice fish (BCF up to 13 600 L kg^{-1}).[31] Finally, chlorinated PFESAs, predominately the so-called 6:2 Cl-PFASA (often called F-53B, CAS no. 73606-19-6), and a novel PFECA, perfluoro-2-[(propoxy)propoxy]-1-propanoate have been shown to bioaccumulate in biota and human serum.[32–35]

Indications of bioaccumulation that need further evaluation are the observations of a number of emerging and novel PFAS in top predators including humans. For example, perfluoro-4-ethylcyclohexane sulfonate has been detected in top predator fish in the Great Lakes[36] and in crucian carp in China.[37] PFPIAs, predominately 6:8 PFPIA (cormorants and pike) and 6:6 PFPIA (dolphins), have been observed in biota in North American inland and coastal waters.[38] PFPAs, predominately perfluorohexyl phosphonate (PFHxPA), have been detected in a Norwegian human cohort.[39]

Fig. 2 illustrates the structures of some PFAS suggested to be bioaccumulative. A common feature of the PFAS in Fig. 2 is that they contain at least six perfluorinated carbons. The head group of PFAAs is also known to influence their bioaccumulation potential; for example, it is well known that PFSAs are more bioaccumulative than PFCAs with the same perfluorinated carbon chain length.[11]

Both computational and empirical methods have been explored to estimate protein binding affinity. *In vitro* methods include, among others, equilibrium dialysis[40] and fluorescence displacement.[41,42] In a recent paper, Yang *et al.*[43] used a non-target screening approach to identify novel PFAS present in aqueous film forming foams (AFFF) that bind to human liver fatty acid binding protein. Computational methods are based on structure–property relationships and could potentially be used to estimate the bioaccumulation potential of novel and emerging PFAS. For example, the protein affinity of certain legacy and novel PFAS was recently estimated using molecular dynamic approaches,[44] and protein affinity is a key determinant of bioaccumulation potential. Such structure–property relationships may also aid in estimating the elimination half-lives

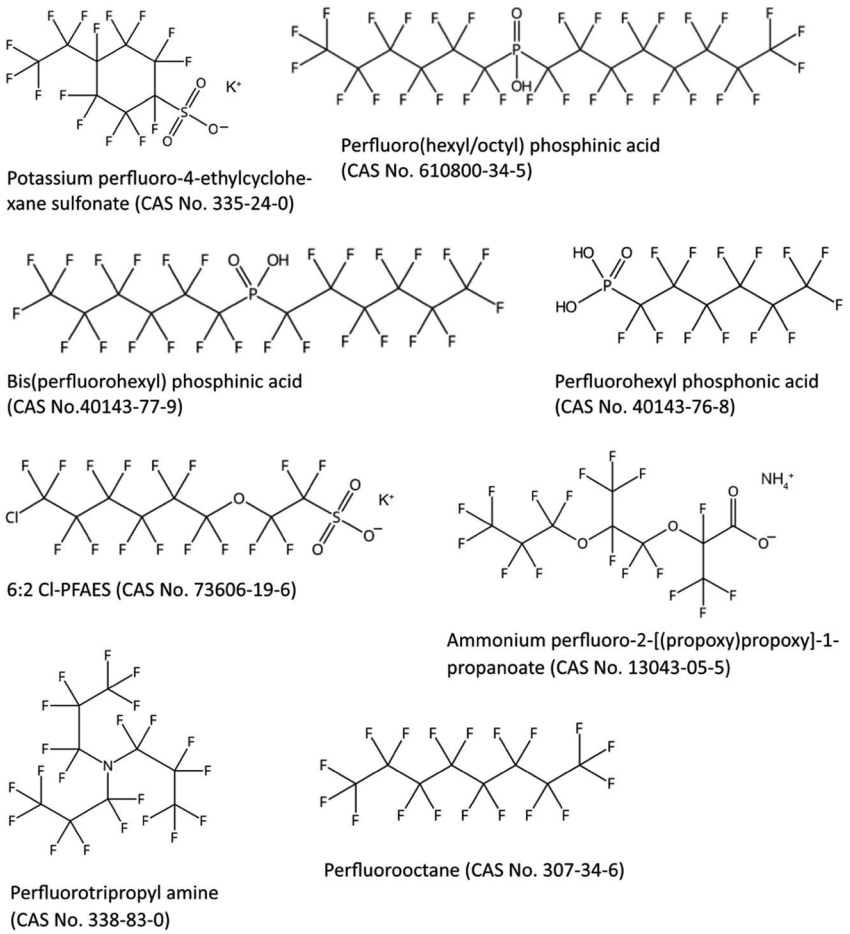


Fig. 2 Chemical structures of various potentially bioaccumulative PFAS (other than the already well-known long-chain PFAAs). Note that this figure only provides a few examples of potentially bioaccumulative PFAS from the wider universe of PFAS.

of PFAS, which is another important factor in determining bioaccumulation potential. Predictive approaches for bioaccumulation potential will be especially important for informing grouping, as they are proactive and resource-efficient in comparison to biomonitoring and laboratory testing (*in vitro* or *in vivo* testing).

Short-chain PFAAs have not been reported to bioaccumulate in animals,[11] but are known to bioaccumulate in above-ground plant tissues (shoots, leaves and fruit).[45–48] An inverse relationship has been observed between perfluoroalkyl chain length and BCFs of PFAAs in above-ground plant tissues for edible crops grown in sludge-amended soils.[47] In regions where the soil is highly contaminated with short-chain PFAAs, human exposure from consumption of crops can become an important pathway.[49]

A fundamental limitation of grouping according to bioaccumulation potential (B) is that for highly persistent chemicals, B may become less relevant if a high exposure is achieved *via* other pathways than uptake and accumulation within the body. It has been argued[50] that B is not a sufficient criterion for protecting against poorly reversible effects because the residence time of highly persistent chemicals in the environment is often much greater than their residence time in humans and biota, which means that levels in organisms will be poorly reversible regardless of the magnitude of B. The limitations of the PBT and vPvB assessment criteria were the motivation for the development of other complementary chemical management approaches such as the "P-sufficient" and the "PMT/vPvM" approaches. On the other hand, the PBT/vPvB approach is a well-established regulatory framework.

Grouping according to the PMT/vPvM approach

The German Environment Agency (UBA) has recently proposed a PMT/vPvM approach for identifying substances that may pose a threat to sources of drinking water.[51] The approach presents and discusses updated guidelines for using the REACH registration process to identify persistent, mobile, and toxic (PMT) substances as well as very persistent and very mobile (vPvM) substances. The motivation for this approach is to pinpoint substances that might require control to protect waters used as sources for drinking water or food production. The PMT approach classifies substances considered persistent in the environment (P), mobile in the aquatic environment (M) and toxic (T). For substances identified as very persistent (vP) and very mobile (vM), it is not necessary to consider toxicity data.[51] Under this concept, the short-chain PFAAs and many other replacements of long-chain PFAAs such as HFPO-DA, which are both vP and vM, would be identified.

A consequence of introducing the PMT/vPvM approach is that, in combination with the existing PBT/vPvB approach under REACH, a wide range of substances that are vP would be covered. Hydrophobic substances with a high octanol–water partition coefficient (K_{OW}) (*e.g.* K_{OW} cutoff of log K_{OW} > 5 under the Stockholm Convention on Persistent Organic Pollutants) would be covered by the vPvB approach, and hydrophilic substances with low K_{OW} (a cutoff of log K_{OW} < 4 under the proposed PMT/vPvM approach) would be covered by the vPvM approach. Therefore, the authors of the "P-sufficient" approach argue that partitioning properties such as K_{OW}, K_{OC} (organic-carbon-water partition coefficient) and the BCF are irrelevant and that PFAS should be managed according to their high persistence alone.[24] Similar to the "P-sufficient approach" the PMT/vPvM approach is still a proposal and not currently broadly implemented under REACH.

Grouping some fluoropolymers as "polymers of low concern"

PFAS are broadly subdivided into low molecular weight substances and fluorinated polymers.[1] There are three subclasses of fluorinated polymers that meet the PFAS structural definition and these are termed: fluoropolymers, perfluoropolyethers and side-chain fluorinated polymers.[1] According to Buck *et al.*,[1] fluoropolymers are a distinct subset of fluorinated polymers made by (co)polymerization of olefinic monomers, at least one of which contains fluorine bound to one or both of the olefinic carbon atoms, to form a carbon-only polymer backbone with fluorine atoms directly attached to it, *e.g.*, polytetrafluoroethylene (PTFE).

It was recently suggested that a subset of fluoropolymers should be considered distinct from other fluorinated polymers based on international criteria for "polymers of low concern" (PLC) due to (among other things) their high molecular weight, narrow molecular weight distribution, negligible oligomer content and organic and inorganic leachables.[52] Classification as PLC may exempt the manufacturers of certain fluoropolymers from certain regulatory notification requirements. Integration of the PLC criteria into a risk management framework may differ from country to country according to individual regulatory mandate.[52] Although a recent framework for polymer risk assessment recommended consideration of impacts throughout the lifecycle of a polymeric product,[53] Henry *et al.*[52] limited their assessment of fluoropolymers to the use phase. However, there are serious concerns regarding the environmental impacts of fluoropolymers during manufacture ("beginning of life") and waste management ("end of life") that need to be addressed. Specifically: (i) some fluoropolymers (*e.g.* PTFE fine powder) are still manufactured in Asia using processing aids containing hazardous long-chain PFAAs (*e.g.* PFOA), which are widely distributed in the Asian environment[54] and can undergo long-range global transport,[55,56] (ii) there are concerns among scientists and regulators regarding the substitute processing aids used (*e.g.* HFPO-DA is now an SVHC under the EU REACH regulation),[15] (iii) a wide range of potentially hazardous byproducts have been observed in the environment near fluoropolymer manufacturing sites,[14,57,58] (iv) environmental emissions of these persistent polymers during use and at end of life are problematic given the current concern regarding persistent microplastics in the environment (even if fluoropolymer plastic waste is of relatively low volume),[59] and (v) the best available technology for treatment of solid wastes is currently incineration, from which emissions of harmful chemicals including certain PFAS could occur if incineration is not operated according to international guidelines.[60] The PLC

criteria should be applied on a product-by-product basis because individual fluoropolymer products (*e.g.* due to different impurity levels) may not meet the PLC criteria.

Grouping approaches that inform risk assessment

Arrowhead approach: grouping PFAAs together with their precursors

The so-called "arrowhead approach" is defined as when a representative PFAS (usually a PFAA) is managed together with its salts and precursors. The approach represents the dominant current approach to grouping PFAS for risk assessment and risk management globally. Industry have used the approach in voluntary phase-out actions (*e.g.* 3M [9]) of PFAS chemistries and it is applied globally in PFAS regulations. For example, precursors to long-chain PFAAs have been grouped together with specific PFAAs in risk management (*e.g.* under REACH,[61,62] in the Stockholm Convention,[63,64] see Table 1, or are currently under discussion, see Table 2) given that these precursor substances will transform to an "arrowhead substance of concern" (*i.e.* the long-chain PFAAs that have PBT properties) in the environment, in biota, or in humans. There is no indication of how many substances, past or present, are covered by definitions such as, "PFOA, its salts and PFOA-related compounds". There are thousands of substances that can theoretically be broken down into PFOA, but it is not clear which of them are or have been used.

Although the arrowhead approach is an efficient way of assessing and regulating large groups of chemicals simultaneously there are some limitations. One limitation is that the approach may overlook the risks from the parent PFAS themselves, or intermediate degradation products that are formed along the pathway to the presumed arrowhead degradation products. For example, a recent study demonstrated that 6:2 fluorotelomer alcohol (6:2 FTOH) is significantly more toxic to rodents than perfluorohexanoic acid (PFHxA).[65] The authors

Table 1 PFAAs and their precursors that have been grouped together

Substances	What is included	Context
PFOA, its salts and PFOA-related compounds[63]	Perfluorooctanoic acid (PFOA), its salts and PFOA-related compounds means the following: (i) perfluorooctanoic acid (PFOA; CAS no. 335-67-1), including any of its branched isomers; (ii) its salts; (iii) PFOA-related compounds which, for the purposes of the convention, are any substances that degrade to PFOA, including any substances (including salts and polymers) having a linear or branched perfluoroheptyl group with the moiety $(C_7F_{15})C$ as one of the structural elements The following compounds are not included as PFOA-related compounds: (i) C_8F_{17}–X, where X = F, Cl, Br; (ii) fluoropolymers that are covered by $CF_3[CF_2]_n$–R′, where R′ = any group, $n > 16$; (iii) perfluoroalkyl carboxylic and phosphonic acids (including their salts, esters, halides and anhydrides) with ≥8 perfluorinated carbons; (iv) perfluoroalkane sulfonic acids (including their salts, esters, halides and anhydrides) with ≥9 perfluorinated carbons; (v) perfluorooctane sulfonic acid (PFOS), its salts and perfluorooctane sulfonyl fluoride (PFOSF), as listed in Annex B to the Convention	Stockholm Convention on Persistent Organic Pollutants (POPs)
PFOA, its salts and PFOA related compounds[62]	Any related substance (including its salts and polymers) having a linear or branched perfluoroheptyl group with the formula C_7F_{15}– directly attached to another carbon atom, as one of the structural elements. Any related substance (including its salts and polymers) having a linear or branched perfluorooctyl group with the formula C_8F_{17}– as one of the structural elements. The following substances are excluded from this designation: C_8F_{17}–X, where X = F, Cl, Br – C_8F_{17}–C(=O)OH, C_8F_{17}–C(=O)O–X′ or C_8F_{17}–CF_2–X′ (where X′ = any group, including salts)	EU REACH restriction (REACH Annex XVII entry 68)
PFOA, its salts and precursors as well as long-chain (C_9–C_{20}) PFCAs, their salts and precursors[66]	PFOA, its salts and precursors as well as long-chain (C9–C20) PFCAs, their salts and precursors	Order Adding Toxic Substances to Schedule 1 of the Canadian Environmental Protection Act, 1999

Table 2 Grouping of PFAAs and their precursors currently under discussion

Substances	Context
Undecafluorohexanoic acid (PFHxA), its salts and related substances[67]	EU REACH restriction proposal
Perfluorononan-1-oic acid (PFNA); nonadecafluorodecanoic acid (PFDA); henicosafluoroundecanoic acid (PFUnDA); tricosafluorododecanoic acid (PFDoDA); pentacosafluorotridecanoic acid (PFTrDA); heptacosafluorotetradecanoic acid (PFTDA) including their salts and precursors[68]	EU REACH restriction proposal
PFHxS, its salts and PFHxS-related compounds as well as polymers and mixtures[64]	Proposed for listing under the Stockholm Convention on Persistent Organic Pollutants
PFHxS, its salts and related substances[69]	EU REACH restriction proposal

concluded that the use of toxicological studies conducted with PFHxA to assess 6:2 FTOH exposure may significantly underestimate human health risk.

Challenges with the above groups are the lack of an exhaustive list of present precursors and analytical methods for individually measuring all relevant precursors to a specific PFAA in a certain medium. Although it was primarily developed as a research tool,[70] the total oxidizable precursor (TOP) assay is a potential solution to quantifying PFAAs and their precursors. The TOP assay has been primarily applied to quantify precursors that can be oxidized to PFAAs in water samples,[70] although it has further been developed and applied to a wider range of sample types, *e.g.* soils,[71] paper and textiles.[72]

Application of the TOP assay usually involves quantifying PFAAs in samples using targeted analysis before and after treatment with powerful oxidizing agents.[70] The difference between the levels of PFAAs before and after treatment is considered to be an indicator of the total concentration of the oxidizable PFAA precursors, because PFCAs and PFSAs that were present in the original sample remain mostly intact under the conditions of the assay. Currently it is not possible to apply the TOP assay to enforce the PFOA restriction under REACH in Table 1 because, for example, PFOA might be formed during TOP assay oxidation from a precursor which is not within the restriction scope.

Levels of PFAAs in drinking water samples could be compared to drinking water guidelines after the samples have been treated with the TOP assay. An advantage of this approach is that precursors would be included that could be transformed in the water or metabolized to PFAAs inside the body after intake. On the other hand, the TOP assay may not simulate environmental transformation and metabolic processes accurately. The assay is an aggressive oxidation process that generates shorter-chain PFAAs than natural environmental oxidation processes, and even degrades polyfluoroalkyl ether acids with –O–CFH– moieties.[73] Furthermore, it may overestimate the contribution of some precursors to PFAA body burdens, and underestimate others and, thus, inaccurately estimate the risks. For example, the TOP assay transforms perfluorooctane sulfonamide (FOSA) to PFOA,[70] whereas FOSA is likely metabolized to PFOS *in vivo* in humans.[74] An enzyme-based assay would be preferable to simulate biological transformations, but is not yet broadly available. Finally, the TOP assay has not to date been standardized so results from different laboratories may be inconsistent.[75]

Total fluorine and extractable/adsorbable organofluorine approaches

Driven by the need for fast and inexpensive analytical methods to determine the presence or absence of PFAS in a given sample and by the lack of analytical standards for most known and unknown PFAS, total fluorine (TF) and extractable/adsorbable organofluorine measurements have been put forward.[72,76–79] These methods could also be used in screening-level exposure assessments, *e.g.* to determine if the level of total extractable/adsorbable organofluorine in a sample is below or above a pre-defined limit, which would trigger further chemical assessment and management measures including more in-depth targeted analysis.

TF comprises the sum of all fluorine as a surrogate for all inorganic and organic fluorinated substances in a sample.[76] TF can be measured through particle-induced gamma(γ)-ray emission (PIGE) spectroscopy, X-ray photoelectron spectroscopy (XPS) and combustion ion chromatography (CIC). PIGE spectroscopy is an ion beam technique used for the analysis of fluorine in solid materials, and liquids after solid-phase extraction.[72] XPS has also recently been used for fluorine mass balance experiments in consumer products.[77] CIC involves combusting samples or extracts, collecting fluoride ions in water and then separating them on an ion exchange column, and has also been applied to consumer products.[78]

Today, TF is used in Denmark with an official indicator value of 0.1 $\mu g\ cm^{-2}$ for food packaging.[80] The indicator value can help industry and regulators assess whether organic fluorinated substances have been added to paper and cardboard. Furthermore, it can inform if PFAS levels are increasing over time. If the indicator level is exceeded, this can justify further analyses needed for risk assessment. The fast application of TF methods and relatively simple evaluation of results (yes and no for presence of fluorine) is appealing. The relatively high detection limits of TF methods and lack of specificity (cannot specify if TF is PFAS) are drawbacks. Assuming a 10 mg sample size, detection limits for TF were recently reported as 0.8 and 38 $\mu g\ g^{-1}$ for CIC and PIGE in paper samples, respectively, which is at least

1000 times higher compared to modern PFAS analysis by liquid chromatograph-tandem mass spectrometry (LC-MS/MS).[78]

Depending on the sample type, a certain fraction of the TF can be extracted using organic solvents (extractable organic fluorine, EOF). Alternatively, the PFAS in aqueous samples can be extracted using a sorbent, which is then analyzed for TF (adsorbable organic fluorine, AOF). The EOF/AOF fraction in a sample can be assumed to contain primarily synthetic organofluorine substances given the low abundance of naturally occurring ones, rarely exceeding more than one fluorine per molecule.[79] By comparing the concentration of EOF/AOF with the total PFAS measured in a sample by targeted analysis, the fractions of known and unknown organofluorine substances can be determined. If the unknown fraction of organofluorine substances is large in a given sample, then this can be probed using non-targeted analytical methods.[14,57,81] As shown in recent literature, the explainable contributions of EOF to the TF in, *e.g.*, cosmetics,[82] seawater,[83] food packaging,[78] contaminated water[83] and human blood[84] may be 0.1–3%, 2%, 5.5%, 30% and 80%, respectively. Fig. 3 illustrates fluorine-containing chemicals covered by available analytical methods.

For estimating the drinking water exposure to total PFAS, EOF/AOF could be potentially used instead of targeted analysis for groups of PFAS. For example, in the EU very likely a 'PFAS total' limit of 500 ng L^{-1} will be provisionally set in a recast of the Drinking Water Directive[85] and EOF/AOF could potentially be used to relatively rapidly determine if a sample is below this 500 ng L^{-1} limit. An advantage of the EOF/AOF approach is that all PFAS would be captured in a single measurement that is relatively inexpensive compared to targeted LC-MS/MS methods for individual PFAS. EOF/AOF measurement approaches may further help to determine if unknown PFAS are released to the environment from production sites and are present in drinking water or a particular product (*e.g.* ski waxes or food contact materials). They are therefore good screening approaches that can be followed up with non- or suspect-targeted analytical methods to identify substances in the unknown PFAS fraction.[14,57,81] A disadvantage, however, would be uncertainties in translating the EOF/AOF measurements into risk-based guidelines. A "worst case" assumption could be that the EOF/AOF concentration is equal to the concentration of the most toxic PFAS known (*e.g.* typically PFOS or PFOA, see Table 1). This approach may be considered precautionary and protective, but on the other hand, humans are exposed to a lot of unknown PFAS with unknown risks, which may be more toxic than the currently known ones. Another disadvantage of this approach in its application to PFAS is that it will likely capture organofluorine substances that are currently not considered as PFAS (*e.g.* fluorinated substances used as pharmaceuticals and pesticides). Finally, a common problem with TF, EOF/AOF and the TOP assay is that these methods require further development before they can be considered sufficiently reliable for regulatory applications. Efforts are underway to assess, further develop and standardize methods as well as to conduct inter-laboratory comparison studies.

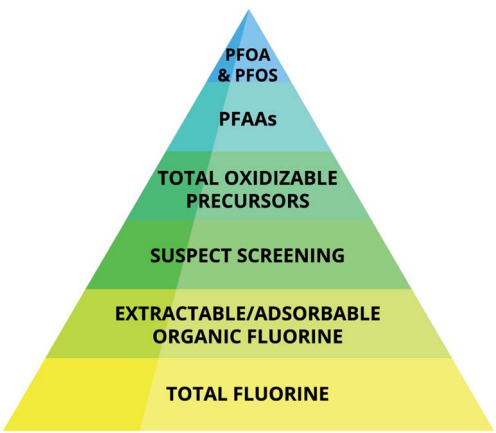


Fig. 3 Schematic of increasing resolution in information detail of analytical methods used for PFAS analyses.

Simple additive toxicity approach: application to drinking water standards

Regulatory agencies worldwide have developed guidelines or advisories for acceptable levels of PFAS in drinking water. Because there are so many PFAS and only limited toxicological and toxicokinetic data for most of them, it is challenging to generate guidelines for individual PFAS, let alone robust grouping strategies. Some regulatory agencies have grouped multiple PFAS together and set one limit for the combined (sum of) concentrations of these chemicals (Table 3). A simple example is the combined drinking water health advisory of 70 ng L^{-1} set by the US EPA for the sum of PFOA and PFOS.[86] The assumptions made in this grouping are that the critical toxicological endpoint is the same for the two substances (*i.e.*, developmental toxicity) and that the margin of safety (MOS, *i.e.* the ratio of NOAEL obtained from animal toxicology studies to the predicted or estimated human exposure level or dose) is similar. In Sweden, 11 different PFAS[87] are grouped with the limit of 90 ng L^{-1} for the sum of these 11 PFAS, above which consumption of drinking water is not recommended.

The simple additive toxicity approach has the advantage that it is easy to understand and environmental or health-based guidelines can be evaluated with current analytical methods. Furthermore, it is thought to be protective for humans and the environment in that the additive toxicity is based on the most toxic PFAS in the group. Scientific shortcomings of the simple additive toxicity approach that sums multiple PFAS are that (1) it assumes an external dose-additive model[88,89] whereas elimination kinetics vary largely among individual PFAS,[90] (2) the identified critical adverse effects, as well as modes and mechanisms of action, may vary for individual PFAS,[7] (3) mixture toxicity may not be simply additive even if the critical adverse effects are the same[88,89] and (4) although multiple PFAS are included in these drinking water standards, many more PFAS are neglected. Some possible solutions to the highlighted issues are discussed in the remaining approaches reviewed, below.

Relative potency factor approach

The Dutch National Institute for Public Health and the Environment (RIVM) recently developed a mixture toxicity approach

Table 3 Existing or proposed grouping approaches based on the sum of various PFAS in drinking water

Entity	Date	Conc. (ng L^{-1})	Sum of which PFAS?	Background
EU[85]	2020 (pending final adoption)	100; 500	100 ng L^{-1} for sum of 20 PFAS (C_4–C_{13} PFSAs and C_4–C_{13} PFCAs)	Politically agreed parameter (not based on risk assessment) based on a precautionary approach
			500 ng L^{-1} for 'PFAS Total' – the total of all PFAS	'PFAS Total' suggested to be enforced through measurement of EOF/AOF
Denmark[91]	2015	100	C_4–C_{10} PFCAs, PFBS, PFHxS, PFOS, PFOSA, and 6:2 FTS	Assumes all 12 PFAS are similarly toxic to PFOS
Sweden[87]	2014	90	C_4–C_{10} PFCAs, PFBS, PFHxS, PFOS and 6:2 FTS	Assumes all 11 PFAS are similarly toxic to PFOS
Australia[92]	2017	70	PFOS and PFHxS combined, if both present	Assumes PFHxS is similarly toxic to PFOS
Canada[93]	2018	200, 600	PFOA and PFOS	When PFOS and PFOA are found together in drinking water, a cumulative toxicity approach is applied[b]
US EPA[a86]	2016	70	PFOA and PFOS	Lifetime health advisory level. Assumes additive toxicity of PFOA and PFOS
Connecticut (USA)[94]	2017	70	PFHpA, PFOA, PFNA, PFHxS and PFOS	Application of US EPA lifetime health advisory level to the sum of five PFAS; assumes toxicity similar to that of PFOS and PFOA
Maine (USA)[95]	2020	70	PFHxS, PFNA, PFHpA, PFOA and PFOS	Application of US EPA lifetime health advisory level to the sum of five PFAS; assumes toxicity similar to that of PFOS and PFOA
Massachusetts (USA)[96]	2018/19	20	PFHpA, PFOA, PFNA, PFDA, PFHxS and PFOS	Proposed maximum contaminant level (MCL) based on similarities in chemical structure and toxicities of six PFAS to PFOS and PFOA. Same approach as US EPA lifetime health advisory level, but includes an additional uncertainty factor to account for evidence of toxicities in experimental animals at lower levels of exposure than those used by US EPA
Vermont (USA)[97]	2019	20	PFHpA, PFOA, PFNA, PFHxS and PFOS	Interim drinking water standard based on similar health risks of five PFAS. Difference to US EPA advisory is due to Vermont's calculation being based on infant consumption rates

[a] Many US States have simply adopted US EPA's recommended Lifetime Health Advisory (LHA) of 70 ppt for PFOA and PFOS in drinking water. Several states have passed or proposed compound-specific MCLs or health advisories, including California, Michigan, Minnesota, New Hampshire, New Jersey, North Carolina, Ohio. Some states have recommendations for ground water that are separate from drinking water. Only sum of PFAS parameters are included. [b] Cumulative toxicity estimated by adding the ratio of the monitoring result for PFOS to its maximum acceptable concentration (MAC) with the ratio of the monitoring result for PFOA to its MAC; if the result is below or equal to one, then the water is considered safe for drinking. According to the Canadian assessment, "science currently does not justify the use of this approach for other PFAS".[93]

for a number of PFAS termed Relative Potency Factors (RPFs).[98] RIVM's RPF approach builds on the assumption that the combined toxicity of two or more substances can be calculated based on the concept of dose addition, whereby the substances have the same effect, but differ only in their toxic potencies. Liver toxicity data were available for a number of PFAS for rats and mice from which RPFs could be derived. PFOA was the reference substance and assigned an RPF of 1.0. RPFs were estimated for 18 other PFAS with values ranging from 0.001 for PFBS up to 10 for PFDA. Environmental concentrations can be

converted into PFOA equivalents by multiplying the RPFs by specific PFAS concentrations. However, questions surrounding potential synergism of toxic effects remain;[99] while observations for many endpoints have been largely additive, there is some evidence from *in vivo* animal studies on specific endpoints and *in vitro* studies, for some higher doses, that PFAS impacts may be synergistic.[100] Thus, a successful grouping strategy may need to be endpoint-specific, in which the additivity of impact for the most sensitive endpoint will need to be carefully considered.[101,102]

The RPFs derived by RIVM were defined using external exposures in rodents, *i.e.* based on the administered dose. Gomis *et al.*[90] demonstrated that the differences in RPF in rats can be largely explained by differences in the elimination rates of PFAS. When potencies of PFAS were compared on an internal dose basis, the differences in potencies disappeared and the various PFAS were equally potent. This suggests that relative external potency is in fact largely a measure of accumulation potential, and that it may be possible to set a single internal dose for a particular endpoint and sum across all PFAS. Further confirmation is needed that this observation holds across a wider variety of PFAS structures, as Gomis *et al.*[90] considered primarily PFAAs. Moreover, the application of simple addition of effective internal dose across many PFAS, in the absence of effects data linked to internal dose, would require more toxicokinetic data than are currently available. Elimination half-lives can vary by PFAS structure (chain length and degree of branching), across species, and by sex. Because of this, grouping for the purpose of wildlife protection should be based on first identifying the most sensitive species and sex. For humans, translation of animal data would require two key pieces of information: first, whether the internal dose effect level is the same, and, second, the toxicokinetic data and associated model required to translate the effective internal dose in the human back to an external dose that can be associated with an exposure medium (*e.g.* drinking water).

Finally, the RPF approach may be difficult to reconcile for substances that have the potential to biotransform; should the parent compound, the metabolite, or both be considered in the calculation? In each case, is there a temporal component that needs to be taken into account, in addition to the toxicokinetic considerations suggested above? For example, cellular assays suggest that reactive intermediate degradation products of fluorotelomer alcohols, such as short-chain saturated and unsaturated fluorotelomer aldehydes, are more toxic than either the parent compound or the terminal PFCA transformation products.[103,104]

The specific RPF approach suggested by RIVM is sound if it can be argued that liver hypertrophy is a sensitive and reliable endpoint for all PFAAs; a problem here is that many regulatory jurisdictions disagree with that assessment. However, a similar additive toxicity approach could potentially be applied for those other endpoints. The RPF approach is currently limited by the database of toxicity data available for PFAS. Expanding this knowledge base would require a large number of animal experiments and associated ethical considerations, time and money.

Grouping only PFAAs with the same adverse effect, modes and mechanisms of action, and toxicokinetics

The most demanding grouping approach would be to only group PFAS that have the same adverse effects, modes and mechanisms of action, and toxicokinetics for risk assessment. The clear disadvantages with an approach of this kind are that (1) very few substances are likely to be grouped together given that there is currently no agreement on a single mode and mechanism of action for even the well-studied PFCAs and PFSAs,[7] (2) modes and mechanisms of action may be tissue or system-specific, requiring a determination of the most sensitive or reliable effect for grouping, (3) detailed effect and kinetic data are needed for each PFAS, such that individual chemicals would still need extensive toxicological profiles and (4) many groups will be required. Such a grouping approach can be considered only a marginal improvement on conducting risk assessments on a chemical-by-chemical basis.

Remaining challenges and the way forward

There are a number of challenges if the PFAS grouping approaches summarized in this article are to be integrated into chemical regulation and company policies, namely; (1) the universe of PFAS[2] has not been fully mapped and divided into subcategories, (2) only for a few PFAS (*e.g.* certain PFAAs and their precursors) is there sufficient information available to conduct detailed hazard and risk assessments, whereas little or no information exists on production volumes, properties and toxic effects for the vast majority of PFAS,[3,8] and (3) no single grouping strategy may be adequate for all decision contexts. Each of these challenges will be discussed in turn below.

Within the universe of PFAS, most research to date has focused on the occurrence and effects of certain PFAAs and their precursors due to the availability of analytical methods and standards for these substances. Expanding beyond this domain has been challenging because the chemical composition of most remaining commercial products is unknown. These factors are slowly becoming less of a barrier for identifying overlooked and unknown PFAS due to the recent advancement of non- and suspect-targeted screening techniques.[14,57,81] However, these screening analytical methods are extremely challenging to apply, even by experts, and the lack of methods and analytical standards for a wider range of PFAS will remain a barrier for regulatory purposes.

Depending on the grouping strategies to be taken by individual regulatory agencies and companies, there will inevitably be efforts in the coming years to generate the missing data for some of the thousands of PFAS. To address these data issues, the US EPA in partnership with the US National Toxicology Program (NTP) has recently selected 150 PFAS (expanded from 75 [10,86,105]) for high-throughput toxicity testing (*e.g. in vitro* assays) for multiple endpoints.[106] Selection criteria for this

subset of 150 PFAS included maximizing information to support read-across within structure-based groupings and capturing the structural diversity of the PFAS landscape. The new toxicity and toxicokinetic data generated from this initiative will support the development of quantitative structure–activity relationships (QSARs) that could facilitate filling data gaps, as well as further grouping and prioritization of the universe of PFAS. There are clearly relationships between PFAS structural elements and properties and behaviour (*e.g.* number of fluorinated carbons in the perfluoroalkyl(ether) chain, protein binding affinities, bioaccumulation potential, elimination rates, bioactivities within the PFAA/perfluoroalkylether acid subclasses),[11,44,90,107] but on the other hand, critical toxic endpoints, as well as modes and mechanisms of action vary within the PFAS and such inconsistencies could limit the applicability of QSARs and thus reliability of computational tools.

Within the EU, there is already discussion to phase out all non-essential uses of PFAS based on concerns of the chemical class as a whole.[19] Within the US, as discussed above, the focus of the US EPA is on developing high-throughput testing methods for PFAS,[106] but otherwise adhering to the traditional risk assessment paradigm. These differences in approaches are inevitable given the differences in chemical management philosophies around the world and motivations to group PFAS. It is expected that many of the approaches reviewed in this paper will be taken in parallel by regulatory agencies in the different countries. In addition, some of the reviewed grouping approaches could even be combined (*e.g.* the newly identified bioaccumulative PFAS could be regulated together with potential precursors).

An advantage of the precautionary grouping approaches based on intrinsic properties is that relatively few data are needed to group PFAS and regulate them. Conversely, traditional testing and regulation of PFAS on a chemical-by-chemical basis would require huge resources and the information required to perform risk assessments would take many years or decades to generate. Arguably, regulation could never catch up given that new PFAS continue to be invented and produced. Regulation is not the only way to reduce the use of harmful PFAS in society. Since PFAS have come under pressure in society, there has been much innovation to produce a new generation of alternative chemical products that aim to provide healthier, safer, and more sustainable solutions.[18,108] It should be possible for manufacturers to make chemical products that provide the function required in modern society while limiting or eliminating hazardous impacts over a chemical product's life-cycle.

Some product manufacturers and retailers continue to take proactive voluntary measures to phase out PFAS from their supply chains especially where they are non-essential or where functional non-fluorinated alternatives are available. Examples of retailers who have phased out PFAS from their supply chains include IKEA,[109] Lindex,[110] and H&M[111] in Sweden, Coop[112] in Denmark, and Vaude[113] and Jack Wolfskin[114] in Germany. In some jurisdictions and even internationally, PFAS are also being phased out from certain use categories, for example, PFAS will be phased out of use in ski waxes in international competitions from the winter season of 2020–2021,[115] multiple global manufacturers moved to phase out PFAS from cosmetics by 2020,[116] Denmark will ban PFAS in food contact materials in 2020,[117] South Australia will transition away from the use of PFAS in fire-fighting foams by 2020[118] and California designated all PFAS used in carpets and rugs as "Chemicals of Concern".[119] However, given the complexity of supply chains and ignorance of the full range of PFAS in society, these phase-outs may in some use cases only be partially successful, and largely focus on a few well known PFAS.

Given that PFAS will continue to be used in society until alternatives are developed, scientists should work to identify the groups and applications of PFAS among those still in use that have unfavorable properties which make them particular threats to human and environmental health. However, there is a justifiable concern that approaches requiring multiple grouping approaches would result in a similarly large usage of resources as a chemical-by-chemical regulatory approach. Investing additional public funds for scientists to identify all troublesome PFAS, their environmental behaviour and effects could delay broader regulatory action on PFAS. A precautionary approach with the aim of phasing out the "non-essential" uses of PFAS[18] would reduce future exposures and the high costs of research, regulation and cleanup of contaminated sites, while having minimal impacts on daily life and the economy.

Conflicts of interest

This paper does not necessarily reflect the opinions or the policies of the German Environment Agency. Ian Cousins has provided expert reports in three separate class actions related to PFAS in the Federal Court of Australia. Jamie DeWitt is serving as a plaintiff's expert witness in several cases related to PFAS. No other authors declare any conflicts of interest.

Acknowledgements

The authors thank the Global PFAS Science Panel (GPSP) and the Tides Foundation for supporting this cooperation (grant 1806-52683). The University of Rhode Island thanks the US National Institute of Environmental Health Sciences (grant P42ES027706). NILU acknowledges the support of the Strategic Institute Program CleanArctic (grant N117031). Dr Juliane Glüge acknowledges the support of the Swiss Federal Office for the Environment (FOEN, grant 1-004496-000). The authors appreciate the contributions of Dr Xenia Trier of the European Environment Agency, Dr Andrew Lindstrom of the U.S. Environmental Protection Agency, and Dr Robin Vestergren of IVL Swedish Environmental Research Institute.

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