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Grouping of PFAS for human health risk assessment: Findings from an independent panel of experts

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ABSTRACT

An expert panel was convened to provide insight and guidance on per- and polyfluoroalkyl substances (PFAS) grouping for the purposes of protecting human health from drinking water exposures, and how risks to PFAS mixtures should be assessed. These questions were addressed through multiple rounds of blind, independent responses to charge questions, and review and comments on co-panelists responses. The experts agreed that the lack of consistent interpretations of human health risk for well-studied PFAS and the lack of information for the vast majority of PFAS present significant challenges for any mixtures risk assessment approach. Most experts agreed that "all PFAS" should not be grouped together, persistence alone is not sufficient for grouping PFAS for the purposes of assessing human health risk, and that the definition of appropriate subgroups can only be defined on a case-by-case manner. Most panelists agreed that it is inappropriate to assume equal toxicity/potency across the diverse class of PFAS. A tiered approach combining multiple lines of evidence was presented as a possible viable means for addressing PFAS that lack analytical and/or toxicological studies. Most PFAS risk assessments will need to employ assumptions that are more likely to overestimate risk than to underestimate risk, given the choice of assumptions regarding dose-response model, uncertainty factors, and exposure information.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a large and diverse group of fluorine containing organic compounds that have been used in industrial and commercial applications since the 1940s. Chemically and physically, PFAS differ widely. Human health risk assessment for PFAS is complicated by a number of factors, including but not limited to: (1) there is not a clear understanding of which PFAS may be relevant for potential human health risk assessment and no consensus definition of what is or not a substance within the PFAS family; (2) there is sparse information on PFAS toxicity and human exposure that precludes an chemical-specific evaluation of the vast majority of PFAS; (3) most human exposures will be to an unknown mixture of PFAS; and (4) results of toxicity tests often lack concordance among assays in animals and observations in humans, and extrapolation from animal data to human relevance (for example, due to species-specific pharmacokinetics and pharmacodynamics and/or mechanisms of action) is highly uncertain.

An appropriate grouping approach for PFAS is the first step necessary for both informing regulatory agencies and assessing risk to the general population from legacy and/or current and future, replacement, PFAS.

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Several component-based approaches for assessing PFAS mixtures have been developed or proposed (for example see discussion by (Goodrum et al., 2021), and (USEPA, 2021a)). These schemes require chemical-specific information or application of "read-across," which involves making assumptions regarding a chemical's toxicity based on extrapolated properties from a structurally similar chemical. However, developing a practicable and technically sound grouping approach for the purposes of performing a human health risk assessment for varying mixtures of individual PFAS remains a challenge. Cousins et al. (2020a) discussed the challenges in developing a meaningful grouping strategy for PFAS and for risk assessment. These challenges include: 1) the current lack of agreement on a common mode of action (MOA) for PFAS; 2) the likelihood that MOAs are species- and/or tissue-specific; 3) the lack of sufficiently detailed knowledge of pharmacokinetics and pharmacodynamics that may vary among individual PFAS; and 4) the prospect that multiple grouping approaches may be required for different purposes or exposure scenarios.

Science peer review through the use of blinded, expert panels can support the advancement of complex scientific challenges (Kirman et al., 2019). Such an expert panel was convened to provide insight and guidance on key questions in PFAS risk assessment. Specifically, given the current state of the science, what are the best approaches:

(1) to grouping PFAS relevant to drinking water exposures for the purposes of protecting human health; and then
(2) for assessing potential hazards from drinking water exposures to the defined PFAS mixture group (potentially comprised of persistent legacy PFAS and modern "replacement chemistries[1]") for risk assessment purposes?

The use of independent expert elicitation was used to compile information to address: how PFAS should be defined for purposes of human health risk assessment and regulatory decision making; how PFAS should be grouped to inform potential mixtures effects; and what information is most technically sound and feasible to inform potential human health risks to exposure to PFAS in drinking water.

2. Background

Existing approaches to predicting the effects of chemical mixtures include dose addition, response addition, and consideration of non-additive effects of mixture components (e.g., synergism, a greater than additive effect – and, antagonism, a less than additive effect). The WHO/IPCS has a tiered framework for combined exposure to multiple chemicals (Meek et al., 2011). Rotter et al. (2018) provided a summary of mixtures risk assessment methods and approaches used in various European regulations and the recent European Food and Safety Authority (EFSA) Scientific Committee has also issued guidance (EFSA, 2019). The USEPA and ATSDR also have guidance on mixtures chemical assessment and site-specific risk assessment approaches (for example (USEPA, 2007), and (ATSDR, 2018)). USEPA recommends dose-additivity as the default option for mixtures for which the modes of action (MOAs) of the various chemical components remain unknown (USEPA, 2007, 2000, 1986). USEPA recently released the "*Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances" (PFAS)* (USEPA, 2021a). Yet these guidance documents and PFAS specific examples are predicated on the availability of well-established chemical specific information, a clear definition of the "mixture" in question, and/or assumptions regarding read-across or extrapolation of potential risk to data-poor PFAS or undefined PFAS mixtures.

Critical gaps in our understanding of PFAS chemistries, mixture compositions and toxicities challenge the application of standard mixtures risk assessment approaches. Even within the various PFAS classes, subclasses and subgroups or subfamilies (Buck et al., 2011), PFAS vary substantially in their physicochemical properties and may include polymers and non-polymers; solids, liquids, and gases; volatile and non-volatile compounds; compounds that are water soluble and water insoluble substances; and so on. The diversity of PFAS chemical structures and their associated physicochemical properties, as well as differences in their uses and releases to the environment, results in a complex conceptual model of exposure and potential human health effects to be assessed in support of reasonable risk management strategies. Some scientists have suggested that any risks from PFAS should be assessed by considering all PFAS as a single chemical class (Kwiatkowski et al., 2020). Others have suggested various groupings for a range of specific purposes based on structural diversity, toxicokinetic properties in both humans and animals, and types of adverse endpoints (Buck et al., 2011; Cousins et al., 2020a; Goodrum et al., 2021; Henry et al., 2018; Patlewicz et al., 2019). Additionally, some regulatory agencies have used "read-across" approaches, whereby the same hazard potential is attributed to other members of a PFAS subfamily without toxicity information, perhaps with modifying factors to account for differences in potential elimination half-life differences (Health Canada, 2019; TCEQ, 2016), and some regulatory agencies used relative potency factors (RPFs) for a subset of PFAS (Bil et al., 2021; Hawaii Department of Health, 2021; Zeilmaker et al., 2018). For other chemical families that are comprised of mixtures of similar compounds (e.g., polychlorinated dibenzodioxins and dibenzofurans (PCDD/PCDF), PCBs, polycyclic aromatic hydrocarbons (PAHs)), they have generally been managed by deriving toxicity equivalent factors (TEFs) or RPFs for the individual isomers/congeners, used for those classes of chemicals with known common MOA (see for example, (USEPA, 2010a; 2010b). Current primary challenges for PFAS risk assessment are the toxicological concordance between the groupings, defining the MOA(s), and how data gaps and overall uncertainties are handled.

When summarizing toxicological effects attributed to PFAS, it is necessary to avoid overgeneralized statements, and instead indicate when statements apply to individual PFAS only (e.g., perfluorooctanoic acid (PFOA) and cancer risk), to specific subgroups, or to PFAS as a general category. The ATSDR Toxicological Profile for Perfluoroalkyls provides a comprehensive review of a few PFAS for which toxicological data are available (ATSDR, 2021). The reported health effects of some PFAS are varied in both humans and animals and the concordance of these effects, both between humans and test species and between different PFAS, is often inconsistent (ATSDR, 2021; Fenton et al., 2021; Steenland et al., 2020; Zodrow et al., 2022). Even between the most well-studied PFAS, perfluorooctane sulfonate (PFOS) and PFOA, a consensus as to what adverse human health effects or disease may be associated with their exposure, has not yet been widely achieved (ATSDR, 2021; Australian National University, 2021; Fenton et al., 2021; Steenland et al., 2020). The understanding of potential human health concerns for PFAS is dynamic and the subject of considerable on-going research. The lack of consistent interpretations of human health risk for well-studied PFAS, and the lack of information for the vast majority of PFAS present significant challenges for any mixtures risk assessment approach.

3. Methods

Scientists with expertise in PFAS and/or mixtures risk assessment were identified from a variety of sources including: (1) SciPinion's internal database of users; (2) searches for authors of recent publications on the topic of interest in online databases (e.g., Pubmed; Google Scholar); (3) searches of profiles on social media databases (i.e.,

[1] Buck et al. (2021) define replacement chemistries as "fluorinated alternatives with more favorable environmental and toxicology profiles, [which] were registered and commercialized, e.g., "short-chain" alternatives such as perfluorobutane sulfonyl products and 6:2 fluorotelomer products, fluorinated ether carboxylic acid polymerization aids, and oligomeric fluoropolyethers".

LinkedIn); (4) general internet searches; and (5) referrals from other scientists. Candidates were invited to apply to this expert panel opportunity via a web app (https://app.scipinion.com). Eleven panelists and one topic expert lead were selected from the available applicants based upon a consideration of objective expertise metrics (e.g., number of publications, years of experience). The 12 experts selected for this project originate from four different countries (Australia, Canada, Sweden, and the United States), with combined expertise of 12 advanced degrees (12 PhDs), approximately 316 years of post-degree experience, and more than 1750 publications (Table 1).

The expert panel represent various stakeholder groups including academia, regulators, and consultants, with expertise in PFAS chemistry, PFAS toxicology, general mixtures risk assessment and toxicokinetics. As shown in Table 2, the experts self-rated their own expertise on a score of 1 (lowest) to 10 (highest) and according to the self-ranking, our panelist expertise is fairly evenly split between PFAS chemistry (mean score of 5.6), PFAS toxicology (mean score of 7.4), general mixtures risk assessment (mean score of 7.8) and general toxicokinetics (mean score of 6.7).

To minimize potential participation and selection bias and to limit potential group-thoughts, the panelists were blinded to the review sponsor, and to each other during the course of the review. All participation in this review was performed online via a web application (https://app.scipinion.com). The review was structured using a modified Delphi format that consisted of five rounds of participation, occurring from approximately August through December of 2021. All 11 panelist participated in each round, with the topic expert lead providing technical review, oversight, and input on each round's questions and format.

- *Round 1* – During Round 1, the panelists worked independently. The panel was tasked with reviewing a summary document (Appendix A) and answering initial charge questions. To minimize potential scope bias, the panelists were also asked to submit a charge question of their own for their fellow panel members to answer in Round 3. Round 1 was approximately three and a half weeks, held from 08/18/2021 through December 09, 2021.
- *Round 2* – During Round 2 the panelists were permitted to interact anonymously (e.g., as "Expert 1", "Expert 2", …" Expert 11"; with numbers assigned randomly to each panelist). The panel was tasked with reviewing each other's answers to Round 1 charge questions (provided as a downloadable pdf report and via online access). They were given the opportunity to interact with one another by submitting comments on each other's answers, and rating (thumbs up or down) each other's comments during the round. Round 2 was approximately two and half weeks, held from December 09, 2021 through January 10, 2021. A total of 79 comments and 48 comment ratings were submitted during this round (Appendix A).
- *Round 3* – During Round 3 the panel was tasked with working independently in answering new charge questions, including those provided by fellow panel members in Round 1. Round 3 was approximately two and half weeks, held from approximately January 10, 2021 through approximately October 19, 2021.
- *Round 4* – As with Round 2, the panelists were permitted to interact anonymously. The panel was tasked with reviewing each other's answers to Round 3 charge questions (provided as a downloadable pdf report and via online access). The panelists commented on each other's answers and rated (thumbs up or down) each other's comments during the round. Round 4 was approximately a week and a half, held from 10/19/2021 through 10/28/2021. A total of 88

Table 2
Self-rated level of expertise by topic area (1 = lowest, 10 = highest).

Panelist	PFAS Chemistry	PFAS Toxicology	Mixtures Risk Assessment	Toxicokinetics
Expert 1	3	8	5	9
Expert 2	9	5	7	7
Expert 3	4	5	9	5
Expert 4	7	8	8	7
Expert 5	4	6	10	8
Expert 6	1	10	6	8
Expert 7	10	6	8	2
Expert 8	6	10	10	8
Expert 9	6	9	7	6
Expert 10	10	4	5	7
Expert 11	3	2	10	7
mean	*5.6*	*7.4*	*7.8*	*6.7*
sd	*2.9*	*2.0*	*1.7*	*2.1*

Table 1
Summary of panel participants for PFAS grouping.

Role	Name	Country	Affiliation	Degree	Area of Expertise	Years Experience (post-degree)	Publications
Topic Lead	Dr. Janet Anderson	United States of America	GSI Environmental Inc	PhD	Risk Assessment, Toxicology	14	19
Panelist	Dr. Ronald Brecher	Canada	Independent Consultant	PhD	Public Health, Toxicology	34	50
Panelist	Dr. Ian Cousins	Sweden	Stockholm University	PhD	Environmental Science, Fate & Transport	23	176
Panelist	Dr. Jamie DeWitt	United States of America	East Carolina University	PhD	Toxicology, Immunotoxicology, Neurotoxicology	17	80
Panelist	Dr. Heidelore Fiedler	Sweden	Örebro University	PhD	Environmental Chemistry, Risk Assessment	36	300
Panelist	Dr. Kurunthachalam Kannan	United States of America	New York University School of Medicine	PhD	Environmental Chemistry, Risk Assessment	27	740
Panelist	Dr. John Lipscomb	United States of America	Lipscomb and Associates	PhD	Risk Assessment, Toxicokinetics	30	89
Panelist	Dr. Paul Price	United States of America	University of Iowa	PhD	Exposure Assessment, Risk Assessment	9	78
Panelist	Dr. Brian Priestly	Australia	Independent Consultant	PhD	Risk Assessment, Toxicokinetics	53	69
Panelist	Dr. Rita Schoeny	United States of America	Rita Schoeny LLC	PhD	Risk Assessment, Regulatory Toxicology	44	89
Panelist	Dr. Jennifer Seed	United States of America	Independent Consultant	PhD	Risk Assessment, Regulatory Toxicology	34	44
Panelist	Dr. Marc-Andre Verner	Canada	Université de Montréal	PhD	Toxicokinetics, Risk Assessment	9	44
			Total:	***PhD (12)***		***330***	***1778***

comments and 38 comment ratings were submitted during this round.

- *Round 5* – During Round 5 the panel was tasked with working independently to revise all previous answers, as needed, and answer final charge questions developed by SciPinion leads and the panel project lead. Panelists had 9 days to complete Round 5, between 10/28/2021 through approximately June 11, 2021.

4. Results

Select input from the expert panel is summarized below. For complete results collected from the panel for all five rounds of participation, the reader is referred to Appendix A.

4.1. PFAS definition and problem formulation

One of the challenges in developing recommendations for PFAS grouping for risk assessment purposes begins with the confusion over the definition of what constitutes a substance within the PFAS family. Table 3 provides example definitions recommended in the literature and amongst regulatory agencies. The expert panel was asked to select a PFAS definition that would serve as a transparent and pragmatic starting place for grouping PFAS and/or assessing mixtures.

The Organisation for Economic Co-operation and Development (OECD) recent guidance "Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance" (OECD, 2021) purposefully provides a very broad revised definition for "PFAS". OECD, however, also states that the term "PFAS" should only be used when actually talking about all of the substances included in the broad definition; otherwise, use of the non-specific term introduces ambiguity and factual errors in statements. The OECD recommends the following:

> "… that users always ask the following two questions when drafting a statement: (1) Am I referring to all PFASs or not? (2) If not, what term (s) would mostly clearly describe the substance(s) that my statement is referring to?"

Experts agreed that a broad definition, such as the OECD 2021 PFAS definition, may be a useful starting place, but that the definition needs to be refined for specific risk assessment goals. The refined definition should include subgroupings and the ability to group PFAS into more defined lists based on the problem formulation and regulatory context. The OECD report also states this: "regulatory definitions (subgroupings) of PFAS will need to be devised for individual regulatory purposes." All panelist agreed that the PFAS definition or "group" needs to be fit for purpose (USEPA, 2014) and may change based on regulatory or public health initiative.

In the absence of a clear problem formulation (i.e., regulatory context, purpose and scope of the assessment, see (USEPA, 2014)), panelists were unable to define or agree on a grouping strategy for PFAS. Different strategies would be needed to support various risk management options such as restrictions in manufacture and use, setting drinking water regulations, and assessing potential human health risks at a contaminated site. It was acknowledged that problem formulations involve regulatory and statutory considerations that often are outside of the scientific realm. The panel noted challenges in grouping PFAS for the purposes of setting a drinking water standard (e.g., a maximum contaminant limit (MCL)). No consensus could be reached on a problem formulation that would sufficiently encompass the necessary scientific and regulatory scope for drinking water regulation support. Experts suggested that specific PFAS would need to be identified, and confirmation of the specific PFAS occurrence in drinking water would need to be conducted. However, technical feasibility and scientific uncertainties were seen as limitations in developing a grouping approach.

Table 3
Example definitions for PFAS.

Author	Definition of PFAS
Buck et al. (2011)	"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 $C_nF_{2n+1}-$ " (Note when n = 1 then F = 3, thus a substance is a PFAS only if it contains at least one CF_3- group.)
OECD (2018)	"including perfluorocarbons, that contain a perfluoroalkyl moiety with three or more carbons (i.e. $-C_nF_{2n}-$, n ≥ 3) or a perfluoroalkylether moiety with two or more carbons (i.e. $-C_nF_{2n}OC_mF_{2m}-$, n and m ≥ 1)."
ITRC (2021) PFAS, Naming Convention Considerations[a]	"PFAS include only fluorinated aliphatic (carbon chain) substances. PFAS do not include fluorinated compounds that contain aromatic (carbon ring) features in their structures (for example, active pharmaceutical ingredients, crop protection agents, or chlorofluorocarbons [refrigerants])."
MI PFAS Action Response Team, 2020 (found within the "Perfluoroethylcyclohexane Sulfonate (PFECHS): Current Knowledge of Physiochemical Properties, Environmental Contamination and Toxicity, Whitepaper"[b])	A chain of two or more adjacent carbon atoms with a charged functional group head attached at one end. For a linear or branched aliphatic tail, this structure can be written as: CnF2n+1-R where "CnF2n+1" defines the length of the perfluoroalkyl chain tail, "n" is ≥ 2, and "R" represents the attached functional group head. The tail may be linear or branched, or contain a cyclic portion, but it always contains adjacent fluorinated carbon atoms in a CnF2n+1 – moiety (with n ≥ 2). The functional group may contain one or more carbon atoms, which are included in the total number of carbons when naming the compound.
OECD (2021)	"fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), i.e. with a few noted exceptions, any chemical with at least a perfluorinated methyl group (–CF3) or a perfluorinated methylene group (–CF2–) is a PFAS."
US EPA 2021 Pre-publication Notice for Rulemaking, TSCA Section 8(a)(7) Reporting Requirements	"R-(CF2)–C(F) (R′)R" wherein none of the R groups can be hydrogens."

[a] https://pfas-1.itrcweb.org/2-pfas-chemistry-and-naming-conventions-history-and-use-of-pfas-and-sources-of-pfas-releases-to-the-environment-overview/Accessed July 21, 2021.

[b] https://www.michigan.gov/documents/pfasresponse/Current_Knowledge_of_Physiochemical_Properties_Environmental_Contamination_and_Toxicity_of_PFECHS_Whitepaper_702591_7.pdf Accessed July 21, 2021.

4.2. USEPA OPPT "working definition" and TSCA toxicity grouping strategy

During panel deliberation, USEPA released the "National PFAS Testing Strategy: Identification of Candidate Per- and Polyfluoroalkyl substances (PFAS) for Testing) (USEPA, 2021b). This document relies upon the prior USEPA TSCA definition for PFAS:

> "a structure that contains the unit R–CF_2-CF(R′)(R′′), where R, R′, and R′′ do not equal "H" and the carbon-carbon bond is saturated (note: branching, heteroatoms, and cyclic structures are included)."

The USEPA working definition eliminates many of the pharmaceutical and agricultural chemicals that would be otherwise defined as a PFAS based on the OECD (2021) definition, due to the formation of trifluoracetic acid as a degradation product. USEPA references trifluoracetic acid as "a well-studied non PFAS", although TFA belongs to the PFAS family according to the OECD definition. USEPA further removes from consideration chemicals for which vapor pressure cannot be calculated, which would presumably remove most, if not all, polymeric PFAS. The agency also excludes free radicals, bare anions, salt forms of the compounds (retaining the counterion), and multicyclic or macrocyclic ringed structures. USEPA states that this definition is helpful because it "provides focus on PFAS of concern based on their persistence and potential for presence in the environment and human exposure." (USEPA, 2021b).

The result is a list of 6504 PFAS, which were then sorted into nine "Primary Structural Categories" as follows (see Fig. 1 from (USEPA, 2021b)):

- PFAS derivatives
- Perfluoroalkyl acids (PFAAs)
- Perfluoro PFAA precursors
- Non-PFAA perfluoroalkyls
- Perfluoroalkane sulfonamide (FASA)-based PFAA precursors
- Fluorotelomer PFAA precursors
- Silicon PFAS
- Side-chain fluorinated aromatic PFAS
- Other aliphatic PFAS
- Other PFAS

USEPA then subdivided the chemicals into "Secondary Structural Categories" based on volatility, defined as greater than 100 mmHg vapor pressure, to address exposure routes. Non-volatiles were then subdivided based on carbon chain length (greater than or equal to 8, versus less than 8). No details were provided by the Agency on the composition of these groupings.

The degree of similarity within each category was then assessed based on "Morgan fingerprints" or small molecular fingerprints within the chemical structure, which may be used to predict chemical characteristics (Morgan, 1965). USEPA has not yet provided further details regarding the "Tertiary Structural Categories" based on the Morgan fingerprints, but their analysis results in a total of 70 terminal categories, 14 of which have existing toxicity data and 56 of which lack toxicity data for at least one PFAS member of the category (USEPA, 2021b).

Most expert panelists agreed that the USEPA TSCA (USEPA, 2021b) definition and approach for grouping PFAS is pragmatic and generally is a good *starting place* for human health risk assessment. However, some panelists were concerned about the exclusion of some PFAS categories in the TSCA definition, and the panel did not reach consensus that USEPA's proposed grouping strategy would be appropriate for defining groups with similar toxicity profiles. Some panelists believed that categorizing PFAS with similar structures was inadequate without consideration of the toxic MOAs, dose-response relationships, and potencies. USEPA did not provide the information necessary for panel members to assess whether PFAS within the same final groups might share toxicological profiles. Panelists noted that the selected representative PFAS may not be a good sentinel chemical for the given subgroup and may or may not be the most toxic member of the subgroup. Several experts suggested that empirical evidence would be needed to validate any assumptions on read-across, and that further subcategories may be derived once additional toxicity and pharmacokinetic information are available. Overall, the majority of panelists considered that USEPA's definition and grouping strategy is a pragmatic approach that represents a testable hypothesis for generating additional information (USEPA's intended purpose) and making conservative initial grouping decisions but would not be sufficient for health-based regulatory approaches.

4.3. Grouping strategies to define mixtures for human health risk assessment

The expert panel was asked whether and how PFAS mixtures in drinking water should be assessed for human health risks – as a single homogenous group or divided into different subgroups. Experts generally agreed that use of a broad definition for PFAS (i.e., "all PFAS") should not be considered as a group for the purposes of risk assessment.

When asked to rank grouping strategies based on scientific merit and feasibility, characteristics such as physical-chemical properties, toxicity and MOA, and exposure were deemed important considerations. Overall production/use was determined to have the lowest scientific merit as a means for grouping unless it was demonstrated to be an appropriate surrogate for potential exposure. One expert noted that risk does not scale predictably with production/use, as risk is related exclusively to hazard and exposure. Additionally, production/use does not consider environmental persistence and bioaccumulation. See Fig. 1 for how the expert panel ranked various ways of grouping PFAS.

4.3.1. MOA/AOP information is crucial to understanding how to group PFAS for risk assessment purposes

The expert panelists credentialed in human health toxicology and risk assessment consistently affirmed that human health risk assessment must be based on the principles of hazard and exposure. These experts agreed that compound-specific MOA or adverse outcome pathway (AOP) information is "the gold standard" critically necessary for grouping of PFAS for the purposes of human health risk assessment. Ideally, PFAS groupings should be based only on common toxic MOAs and/or target organs. Only those PFAS that affect the same target organ/tissue/system should be grouped and assessed for dose additive or response additive approaches. Unfortunately, these data are the least likely to be available for the majority of PFAS. Added complexity noted is that individual PFAS are likely to have different MOA/AOP across tissues/organs.

Grouping compounds with similar physical-chemical properties and structures can be a first step for read across or other approaches. But the assumption that this grouping relates to similar MOA and dose additivity, must be acknowledged as well as the contingent uncertainties. Experts acknowledged that quantitative structure activity relationships (QSAR) have not been well-developed for PFAS although QSAR findings to date seem to indicate that even subtle molecular structural differences can substantially impact predictions of toxicity. High throughput toxicity data are becoming more readily available and additional studies are underway (primarily at the USEPA and U.S. National Toxicology Program) (Houck et al., 2021; Patlewicz et al., 2019). It is anticipated that these data may help inform grouping based on common molecular targets. In the absence of chemical-specific data, the experts agreed that all available tools, including high-throughput data, QSAR, and general read-across may be used to fill data gaps for a risk assessment purpose, but these should include transparent discussion of assumptions, uncertainties, and the level of confidence in the assessment.

4.3.2. Physical-chemical properties and exposure

As shown in Fig. 1, the expert panelists felt that certain physical-chemical properties are potential predictors of both hazard and exposure and could be used to group PFAS when PFAS-specific information were lacking (i.e., lack of toxicity studies, lack of occurrence information or inability to monitor with current analytical standards). It was determined that physical-chemical properties may be used to help approximate the potential for human exposure and/or to screen or prioritize PFAS of potential concern. However, it was noted that these properties are not sufficient in and of themselves for informing either exposure or potential hazardous effects and additional knowledge on toxicological effects and dose-response is necessary for risk assessment. For example, some physical-chemical properties may inform exposure route such as presence of PFAS in drinking water or food versus air; thus, there might

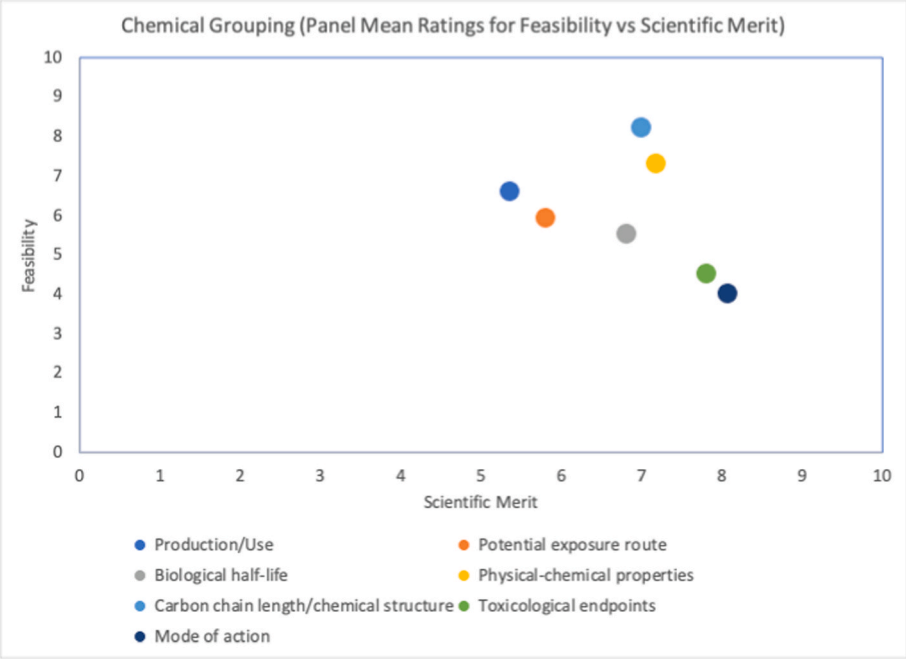

Fig. 1. Mean Ratings for Feasibility versus Scientific Merit, according to panel mean ratings.

be merit in grouping by these potential exposure media, since regulatory risk management actions are often media-specific. Further, PFAS may be de-prioritized based on combinations of physical-chemical properties that make exposure unlikely. This would need to be determined on a case-by-case basis and would be specific to the purpose and scope of the assessment and/or regulatory action. Such information should take into account potential biotransformation and metabolites of the parent compounds. Panelists were unable to and did not support a generalized grouping and/or prioritization without a clear purpose and problem formulation (see above).

4.3.3. Persistence generally not deemed scientifically valid way to group "all PFAS" for the purposes of assessing human health risk

The "p-sufficient" approach to group all PFAS, initially put forth by Cousins et al., in 2019 (Cousins et al., 2019) as a basis for management of chemicals based on high persistence alone, was proposed by two experts, but generally was not supported by the rest of the panel, specifically for drinking water exposures. It was acknowledged that toxicity, bioaccumulation, toxicokinetics, and exposure profiles would vary among PFAS and therefore, those characteristics should be considered when assessing human health risk. Grouping all PFAS together as "persistent" was not supported as practical nor appropriate for assessing human health. Some PFAS are mineralizable (e.g., a CF_3 attached to a heteroatom (O, S, N)) and are not persistent (Cousins et al., 2020b; Singh and Papanastasiou, 2021). The application of "persistence" as a means of grouping PFAS seemed to be best supported when applied to a regulatory context of restricting manufacture and use. One panelist cautioned that even this application of the p-sufficient approach is highly uncertain and may result in the exclusion of "innocuous compounds whose economic importance may be fairly high." Additionally, several experts expressed concerns over the possibility that non-persistent PFAS may have exposure and toxicity that warrant a potential human health concern. Overall – the concept of "persistence" to group PFAS was not accepted by most panelists as surrogate for risk or to set human health-based regulations. The toxicological effects and potential for exposure levels of concern are the "optimal means" for grouping and assessing mixtures of PFAS.

4.4. Methods for assessing potential PFAS mixtures effects

Once the mixture is identified, the key next step is to determine the toxicological similarity of the component compounds, based on MOA, sensitive effect endpoints, dose-response curves, potency estimates, and/or physicochemical similarities. Generally, dose addition is a default assumption that is used when component chemicals share a similar AOP and molecular targets. Commonly, there is a concept of tiered dose-additive approaches for selecting the mathematical way of assessing or combining risk from multiple chemicals, starting with the most common hazard index (HI) approach, to a more complex and data-dependent approach of relative potency, and then to use of a physiologically based pharmacokinetic model for the mixture.

4.4.1. Assumption of dose additivity acceptable as a conservative initial screening step

The expert panel was evenly split as to whether the assumption of dose additivity is justified for PFAS based on the available data and, therefore, whether a quantitative mixtures risk assessment could be conducted.[2] The panelists in favor of assuming dose additivity suggested that this was a conservative and pragmatic approach with some limited support in the scientific literature. Other panelists felt that the toxicological effects and potential MOAs were too uncertain. Most experts agreed that the HI dose additivity assumption for *screening* (i.e., determine if no risk or if further analysis is needed) may be a viable option considering current data gaps. The lack of health effects data and extensive extrapolations that would be required were well acknowledged by the panelists, but with different degrees of comfort; for some, the data gaps result in a high degree of uncertainty that would result in an unreliable estimate of risk and unacceptable low level of confidence in the risk assessment.

A challenge with the HI approach is the need for acceptable daily

[2] It is acknowledged that dose additivity is the default assumption used in chemical mixtures risk assessment by several US Federal Agencies, including the USEPA. Important data that are not available to enable the dose additive approach include data describing the potency of many of the individual PFAS, as well as the dose/concentration of many PFAS.

dose levels for each PFAS component in the assessment group. Read-across methods to derive acceptable daily dose levels for PFAS without sufficient chemical-specific information may be attempted, but is highly uncertain, as discussed above. As noted in guidance documents on the use of HI, the method will likely result in an overestimate of hazard but could be a useful initial screen (see USEPA 2007; EFSA 2019; ATSDR 2018 for more detailed discussion).

4.4.2. Lack of consensus regarding use of TOF as an initial screening step

The use of total organofluorine (TOF) methods was proposed by some panelists as a potential method to "screen" a given exposure scenario (TOF measured in a drinking water source, for example). The expert panel was asked if a screening level risk assessment could be conducted by conservatively assuming the total adsorbable/extractable organic fluorine concentration is equal to the concentration of a known toxic PFAS (e.g., PFOA). No consensus on this approach could be reached. This screen would be based on the assumption that all of the fluorine was in the form of a toxic PFAS reasonably expected to occur in the media/biomonitoring sample. If the total organic fluorine was less than a risk-based threshold concentration for PFOA, for example, one would conclude that any PFAS in the sample would pose no risk. If TOF concentrations were greater than the screening criteria, however, additional risk assessment and evaluation would be necessary. It is unclear what would constitute the higher tiered approach, and several panelists reflected that one would need to proceed with targeted analysis, an available chemical-specific health-based criterion, and the HI method. Some panelists expressed concerns that approach could lead to substantial over-regulation. Furthermore, some experts expressed concerns that use of this method, even for a screen, ignores the fundamental differences in PFAS toxicity profiles.

Using TOF assays was generally supported by the expert panelists for the purpose of screening potential human exposure (not risk). Moreover, it was acknowledged by many panelists that the TOF approach should not be used by regulatory agencies and has very limited usefulness for risk assessment. Limitations include:

- Lack of information to move to next tiered approach if TOF deemed "unacceptable"
- Lack of standardized/harmonized and validated methods[3]
- Lack of availability in commercial laboratories
- Questionable data quality resulting in potentially unreliable data
- Potential for bias due to non-PFAS organic fluorine, associated with incorporating measurements from insoluble organic compounds that contain fluorine, fluorine-based polymers that are not bioavailable, organic fluorine containing pesticides and/or pharmaceuticals
- Potential to result in over-regulation

A similar approach using an extractable organic fluorine method is being evaluated in Sweden (Kärrman et al., 2021), and therefore, additional information and guidance may be forthcoming. As more examples using TOF methods in this manner become available, insights regarding the concerns listed above may be gleaned.

4.4.3. Whole mixtures studies not likely useful or feasible

The experts could not agree that a whole mixtures approach would be practical. It was noted that there are too many "whole mixtures" to feasibly test for toxicity. The composition of any given PFAS whole mixture will be highly variable and likely highly uncertain. The panel did not suggest that additional research or scientific focus should be on whole mixture studies, given the variability and challenges with extrapolating a given whole mixtures to a "sufficiently similar" mixture.

[3] It should be noted that EPA mentioned in the Strategic Roadmap(https://www.epa.gov/system/files/documents/2021-10/pfas-roadmap_final-508.pdf) that they will draft a method for TOF in 2022. Therefore, we can expect some methodological harmonization for TOF soon.

5. Conclusions

Most experts agreed that "all PFAS" should not be grouped together, persistence alone is not sufficient for grouping PFAS for the purposes of assessing human health risk, that subgroups are appropriate, and that the nature and definition of the subgroups can only be defined on a situation-dependent and case-by-case manner. No single grouping strategy was agreed on that would be sufficient for all regulatory or public health risk assessment purposes.

Most panelists agreed that it is inappropriate to assume equal toxicity/potency across the diverse class of PFAS for human health risk assessment. Currently, robust assessment of potential human health risk to a representative mixture of PFAS is not feasible. The concept of using a screening or tiered approach, and for combining multiple lines of evidence was presented by the panelists as a possible viable means for addressing PFAS that lack analytical and/or toxicological studies and for assessing human health risks to a mixture of PFAS.

The expert panelists identified the following data gaps that would need to be filled to conduct a PFAS mixtures risk assessment effectively and efficiently for drinking water exposure:

- Consensus on the relevant critical effects for multiple PFAS
- Mechanisms of toxicity for PFAS such that sub-groups can be constructed with common toxicological endpoints and mechanisms/modes of action
- Potency (dose-response) information for the PFAS of concern
- Data to test the dose additivity assumption
- The role of precursor PFAS and biotransformation pathways
- The contribution of exposure to PFAS from drinking water relative to other routes of exposure

The most critical data gaps identified were (1) exposure, (2) dose-response, and (3) mode of action studies. The panel recommended that future studies focus on these data gaps for individual PFAS. Future steps identified by the panel included the use of exposure information to guide the prioritization of testing PFAS with unknown toxicity profiles. This would also allow prioritization of PFAS sources that are resulting in potentially harmful exposures. Additionally, studies explicitly aimed to define the modes/mechanisms of action of key PFAS are necessary to inform grouping strategies with the assumption of additive risk. Finally, the panel concluded that while whole mixtures for PFAS are likely highly variable, whole mixture studies compared to index compounds could provide valuable information on relative risk.

The expert panel generally supported the following proposed tiered approach for development of PFAS drinking water standards for PFAS grouping.

Step 1. Define a PFAS assessment group based on potential (or measured) presence in drinking water (based on analytical data or assumed presence, but not production/use, and excluding PFAS that do not have the physical characteristic that will allow them to contaminate surface or ground water supplies)
Step 2. Define subgroups of PFAS based on shared similar physical-chemical properties, and carbon chain length/chemical structures (e.g., functional groups)
Step 3. Assess potential risk (hazard and exposure) for each subgroup, based on best available data on each component and on assumed dose additivity using established mixtures methods, such as HI. Uncertainties, subjectivity, and limitations need to be clearly documented.
Step 4. Determine scientific feasibility for assessing potential mixtures interactions between subgroups. The panelists recognize that the default assumption of dose additivity between subgroups may be

necessary, as information regarding interactions between subgroups may not be available nor feasible.

The majority of panelists considered that this was a pragmatic solution and interim approach that would need to be more refined as more data emerges on toxicological effects and mode of action for a broader range of PFAS. Concerns that emerged include the practicality of defining which PFAS might be present in drinking water given analytical challenges, the uncertainty related to grouping PFAS based on shared similar physical-chemical properties rather than common toxicological profiles and mode(s) of action, assumptions regarding assessing potential risk on a subgroup basis rather than based on chemical toxicity, and lack of information to assess potential mixture interactions between subgroups.

Given the current state of knowledge and data gaps, most PFAS risk assessments will need to employ substantial assumptions and defaults; these and the resulting uncertainties will require thorough and clear discussion. Most of the applied assumptions (e.g., dose-additivity, equal potency) are more likely to overestimate risk than to underestimate risk (i.e., will err on the side of caution). Some panelists expressed concerns that these assumptions are often multiplicative and can lead to overestimates of both potency and exposure, and therefore, over-regulation. Overall, the lack of knowledge about exposure, dose/body-burden-response relationships, relevant health effects, mode(s) of action, and potential interactions, does not allow for a science-based grouping of PFAS for the purposes of human health risk assessment.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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