Message

From: Giffe Johnson [gjohnson@ncasi.org]
Sent: 4/10/2025 5:51:22 PM
To: Kramer, Jessica L. [kramer.jessical@epa.gov]
Subject: PFAS MCL comments
Attachments: NCASI Comments EPA PFOS PFOA MCL_Final.pdf; EPA PFAS MCL NCASI Comments.pdf

Hi Jessica,

I really appreciated the time you spent at the paper industry meeting yesterday. I wanted to follow up on our discussion on critiquing the science behind the PFAS MCLs. I've attached technical comments we submitted during the rulemaking process. Hopefully, this can be the beginning of continued dialogue about the use of science for policy decision making. Stewart and I are working on gathering some additional subject matter experts to provide you input on these issues. Unfortunately, it looks like Stewart will be out next week and I'll be booked up Tuesday through Thursday; but if you'd like to touch base on a few issues Monday or Friday I'd be happy to. Otherwise, we should definitely set up meeting(s) the week of April 21st to bring in some additional scientists and their perspective.

Let me know if there's any information I can provide to you in the interim.

Thanks!

Giffe

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Attn: Environmental Protection Agency Science Advisory Board
Dr. Sue Shallal, DFO
via email: shallal.suhair@epa.gov

December 22, 2021

Re: Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water; Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanesulfonic Acid (PFOS) in Drinking Water; Analysis of Cardiovascular Disease Risk Reduction as a Result of Reduced PFOA and PFOS Exposure in Drinking Water; and Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of PFAS

NCASI conducts research and technical studies on behalf of forest products companies across the US, and its members represent more than 80% of pulp and paper and two-thirds of wood panels produced nationwide. NCASI has been an active participant at the state and federal levels in technical and scientific aspects of water quality criteria development for many years and, more recently, has collaborated with other researchers to consider approaches to the systematic review of toxicological and epidemiological information when estimating toxicity factors for environmental contaminants.

NCASI appreciates the opportunity to provide technical comments regarding the development of federal drinking water criteria for PFAS. These comments relate specifically to the documents drafted by EPA staff to be considered by the Scientific Advisory Board (SAB) including: *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water*; *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanesulfonic Acid (PFOS) in Drinking Water*; and *Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of PFAS.*

In our comments, we will highlight scientific issues regarding the development of the toxicity values proposed for PFOA and PFOS, the approach for addressing mixtures of PFAS, and issues related to the systematic review approach taken in the development of these documents.

1.0 MCLG Development for PFOS and PFOA

NCASI agrees with the use of systematic review approaches to evaluate causal relationships and dose-response between chemical exposures and potential health outcomes. However, several elements in the systematic review approach relied on in the MCLG development documents for PFOS and PFOA could be improved to ensure

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that the literature used to develop causal conclusions and points of departure for toxicity values are specifically relevant to the needs of these two assessments and that the body of literature selected represents a robust collection of data that can be relied on with high confidence. For instance, the inclusion criteria in the Population, Exposure, Comparator, Outcome (PECO) statement for exposure is the same for both the assessment of general causation as it is for the selection of points of departure (POD). Literature that may be informative for one of these evaluations may not be relevant for the other; in particular, the inclusion criteria allows for 'Any oral exposure to PFOA or PFOS via oral routes'. This broad PECO component will allow many studies to be considered for the selection of a POD that may lack critical data elements for this evaluation, such as an appropriate resolution of measurement of exposure concentrations, appropriate measurements of intake rates, corroborating serum concentrations, and documented temporal/spatial relationships of measured exposures to health outcomes of interest. Observational epidemiology studies are wide ranging in terms of quality and the collection of critical data elements. Without more specific inclusion criteria, there is the potential to consider studies that lack critical data elements for POD selection within a systematic review of this type.

As well, risk of bias criteria could be improved by more prescriptive treatment of studies with specific types of risk of bias elements that could substantially limit the confidence of these studies. For instance, the studies relied upon for selection of a POD include Grandjean et al. (2012, 2017a, 2017b)[1,2,3], which evaluated antibody response to vaccination in the presence of various PFAS exposure concentrations. However, the outcome of antibody response is highly variable at the inter-individual level due to well characterized genetic factors.[4,5] Zimmerman and Curtis, 2019 note a host of factors that potentially impact antibody response from vaccination, "*These include intrinsic host factors (such as age, sex, genetics, and comorbidities), perinatal factors (such as gestational age, birth weight, feeding method, and maternal factors), and extrinsic factors (such as preexisting immunity, microbiota, infections, and antibiotics)*."[6] The studies relied upon in the MCLG documents fail to measure, control, or adjust for most, if not all of these factors that produce variability in the primary endpoint of these studies. Subtle, non-random distribution of these confounding or effect modifying factors could substantially alter the outcomes of these studies and pose a substantial risk of bias. The current risk of bias approach fails to capture this significant threat to study confidence and could be improved to further qualify these studies appropriately.

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[1] Grandjean, P; Andersen, EW; Budtz-Jørgensen, E; Nielsen, F; Mølbak, K; Weihe, P; Heilmann, C. (2012). Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA 307: 391-397.

[2] Grandjean, P; Heilmann, C; Weihe, P; Nielsen, F; Mogensen, UB; Budtz-Jørgensen, E. (2017). Serum Vaccine Antibody Concentrations in Adolescents Exposed to Perfluorinated Compounds. Environ Health Perspect 125: 077018.

[3] Grandjean, P; Heilmann, C; Weihe, P; Nielsen, F; Mogensen, UB; Timmermann, A; Budtz-Jørgensen, E. (2017). Estimated exposures to perfluorinated compounds in infancy predict attenuated vaccine antibody concentrations at age 5-years. J Immunotoxicol 14: 188-195.

[4] Ovsyannikova IG, Dhiman N, Jacobson RM, Poland GA. Human leukocyte antigen polymorphisms: variable humoral immune responses to viral vaccines. Expert Rev Vaccines. 2006 Feb;5(1):33-43. doi: 10.1586/14760584.5.1.33. PMID: 16451106.

[5] Kimman TG, Vandebriel RJ, Hoebee B. Genetic variation in the response to vaccination. Community Genet. 2007;10(4):201-17. doi: 10.1159/000106559. PMID: 17895626.

[6] Zimmermann P, Curtis N. Factors That Influence the Immune Response to Vaccination. Clin Microbiol Rev. 2019 Mar 13;32(2):e00084-18. doi: 10.1128/CMR.00084-18. PMID: 30867162; PMCID: PMC6431125.

It is also important to note, that from a PECO (e.g., defining the outcome) perspective, reduced antibody response from vaccination is not a diagnosable disease outcome. There is no specific criterion for antibody response that can be classified a 'disease or illness' nor is there a threshold where it is understood that an increase in health risk may occur from differential antibody response. The studies considered for a POD selection did not actually identify an increase of the diseases that vaccinations were administered for in any exposure group in the study. Outcomes in systematic reviews for adverse health endpoints should be clearly defined so as to clearly link an exposure response between a specific range of exposures to a specific disease outcome.

The search approach in the review failed to identify an important study that informs the human equivalent dose (HED). When deriving a (HED), it should be understood what the impact of dose is on elimination rate in order to achieve a scientifically defensible value. The kinetics data relied upon by EPA does not capture all the best science available for estimating the half-life of PFAS in humans. Some PFAS are retained in the bloodstream by the kidney, which treats these molecules like fatty acids and uses a similar receptor-based mechanism to prevent their loss from the blood. However, when the concentration of PFAS becomes high enough, this retention system becomes saturated, and the elimination rate of PFAS becomes much higher, shortening the half-life. In animal studies, our observations occur at relatively 'high' concentrations of PFAS compared to observations in humans that are typically much lower. Therefore, the elimination rate we observe in animal studies is faster (because the retention mechanism is saturated) than what occurs in human studies where doses are much lower. However, Elcombe et al. 2013 studied PFAS as a component of a chemotherapeutic regimen for cancer patients and determined that higher doses (more likely to be relevant to human toxicity) of PFAS in humans resulted in faster elimination rates. This study should be captured by the literature search and is important for consideration when developing an HED value.[7]

Potential improvements also exist in the approach to integrate evidence for drawing causal inference and this is particularly notable in the evaluation of PFOA as a carcinogen. The review identifies 8 epidemiological studies that were classified as having 'medium' confidence and one animal model that provided evidence for renal cancer in male rats. However, there is no specified criteria for the integration of these findings, weighted by the risk of bias analysis, to draw a conclusion regarding carcinogenicity. In the absence of a 'high' confidence epidemiological study, an evidence base in the animal toxicology literature should be required to be integrated into the epidemiology evidence base, where the animal toxicology would serve as the primary evidence base and the epidemiology would serve as supporting evidence given the insufficient confidence in that literature. However, only one animal model was identified to support a conclusion of carcinogenicity (among several studies that did not find sufficient evidence of carcinogenicity). Likewise, there is no corroboration of dose-response or specific cancer cell type/site among animal and toxicology studies. A specific evidence integration component in the systematic review protocol would assist in applying these features of the evidence base for drawing conclusions and would perhaps lead to a different conclusion regarding carcinogenicity than is reported in the draft MCLG document for PFOA. NCASI staff have recently coauthored a publication on evidence integration in systematic review that would inform this

[7] Elcombe, C.R., Wolf, C.R., Westwood, A.L., 2013. US Patent Application Publication. Pub. No.: US 2013/0029928. Available at: https://patentimages.storage.googleapis.com/24/ee/73/f58267c7d70dde/WO2011101643A1.pdf

aspect of the systematic review protocol.[8]

Many of these issues could have been addressed by peer review/public comment on the systematic review protocol used in the MCLG development. It is common practice among regulatory agencies to either publish or distribute for comment a proposed protocol that can be revised based on technical feedback as seen in other EPA program areas such as the Integrated Risk Information System (IRIS). Not only does this serve to enhance the transparency of the review process, but also provides additional perspectives on many of the criteria for risk of bias and evidence integration that must be detailed a priori to the actual review. NCASI supports the opportunity to provide technical comments on proposed systematic review protocols.

PFAS Mixtures

NCASI agrees with the general principle that chemicals found to impact the same organ system with the same mechanism of action may be assumed to be additive, proportionate to individual chemical dose response, for the purpose of health protective risk assessment practices. In the tiered approach proposed in the '*EXTERNAL PEER REVIEW DRAFT Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)*', the target organ specific hazard index (TOSHI) relies on this approach. This approach relies on PFAS to have a toxicity value developed (e.g., RfD) for each substance, compared to extant exposure to calculate a hazard quotient, and then the hazard quotients are summed to calculate the hazard index, which is interpreted to be protective of public health when equal to or less than 1.0. However, the draft document would be improved by more clearly defining the data requirements for this approach and the recognition that the class of substances referred to as PFAS are likely to contain unique substances that should not be treated as additive unless organ specificity and mechanism of action specificity criteria are met.

PFAS, as a group, includes thousands of substances with unique physio-chemical properties, unique fate and transport properties, and unique toxicological profiles. Broadly inclusive criteria are unlikely to produce standards or risk assessment approaches with a well characterized margin of safety or that accurately reflects the hazard posed by individual substances within the group. This has been evidenced in the scientific literature, even in studies that have evaluated PFAS of relatively similar chemical structure. As an example, Pizzurro et al. 2019 examined the toxicokinetics of several PFAS compounds and came to the following conclusions:

> *"Overall, our analysis provides one of the first syntheses of available empirical PFAS toxicokinetic data to facilitate interpreting human relevance of findings observed in animal studies and developing health-based criteria for PFAS from such studies. Our analysis highlighted several notable differences among the different PFAS regarding species and substance-specific tissue partitioning, half-life, and transfer to developing offspring via the placenta or lactation, as well as highlighted data gaps for certain substances."*
>
> *"Lastly, the results of this analysis indicate that there are toxicokinetic differences among the different PFAS based on chain length, and these substances should not be regulated as a group*

[8] Julie E. Goodman, Robyn L. Prueitt, Raymond D. Harbison, Giffe T. Johnson. 2020. Systematically evaluating and integrating evidence in National Ambient Air Quality Standards reviews. Global Epidemiology, Volume 2, 2590-1133, https://doi.org/10.1016/j.gloepi.2020.100019.

> *without careful consideration of how the substance-specific toxicokinetics may impact potential toxicity, including differing specific target organ toxicity and overall body burden."*[9]

Also, the draft document refers to several toxicity values derived from the Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level (MRL). The ATSDR is explicit in its guidance on the use of the MRL and clearly indicates the intended use of this value is not to define clean up levels, such as water quality criteria. As noted in the ATSDR Toxicological Profile for Perfluoroalkyls regarding MRLs (underline added):

> *"These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels."*
>
> *"Exposure to a level above the MRL does not mean that adverse health effects will occur."*
>
> *"MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely."*[10]

Use of the MRL to derive water quality criteria results in criteria that are more conservative than needed to protect public health and will not provide additional public health benefit over an approach more consistent with that used by EPA to develop toxicity values. The draft document should specify that toxicity values such as the RfD, which are intended to inform public health policy should be relied on in a mixtures assessment and not screening level toxicity values such as the MRL, which are not designed for this purpose.

Please feel free to contact me regarding any questions associated with these technical comments.

Respectfully,

Giffe Johnson, PhD
Program Manager and Principal Scientist

[9] Pizzurro, Daniella M.; Seeley, Mara; Kerper, Laura E.; Beck, Barbara D. 2019. Interspecies differences in perfluoroalkyl substances (PFAS) toxicokinetics and application to health-based criteria. Regulatory Toxicology and Pharmacology 106 239–250.

[10] Agency for Toxic Substances and Disease Registry (ATSDR). 2018. Toxicological profile for Perfluoroalkyls. (Draft for Public Comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

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TO: Ms. Alexis Lan
Office of Ground Water and Drinking Water
Standards and Risk Management Division
U.S. Environmental Protection Agency
1200 N. Pennsylvania Avenue, N.W.
Washington, D.C. 20460
Docket: EPA-HQ-OW-2022-0114
Submitted through the Federal eRulemaking Portal

May 30, 2023

RE: "Per- and Polyfluoroalkyl Substances National Primary Drinking Water Regulation Rulemaking"

NCASI conducts research and technical studies on behalf of forest products companies across the US, and its members represent more than 80% of pulp and paper and two-thirds of wood panels produced nationwide. NCASI has been an active participant at the state and federal levels in technical and scientific aspects of risk assessment, water quality criteria development for many years and, more recently, has collaborated with other researchers to consider approaches to the systematic review of toxicological and epidemiological information when estimating toxicity factors for environmental contaminants.

NCASI appreciates the opportunity to provide technical comments regarding the "Per- and Polyfluoroalkyl Substances National Primary Drinking Water Regulation". Our technical analysis of the proposed rulemaking has identified a number of scientific issues, including:

- A classification of PFOS as a likely carcinogen without a scientifically defensible evidence base.
- Potential implementation challenges due to laboratory limitations for an MCL of 4 ppt and an action level of 1.3 ppt for PFOA and PFOS.
- The inappropriate application of the Hazard Index approach for additionally listed PFAS under the MCL framework.

1.0 PFOS Carcinogen Classification

In the proposed rulemaking, EPA has determined that PFOS is a likely carcinogen. EPA states "the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor Carcinogenic to Humans." (pg. 18663). As recently as in 2021, as noted in the "*Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water; Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanesulfonic Acid (PFOS) in Drinking Water*", EPA had determined that the PFOS MCLG should be based on a non-carcinogenic endpoint , and it is not clear what new information EPA is considering in order to make this new conclusion. EPA relies on "one high confidence" study before concluding that "available study findings support a plausible correlation between PFOS exposure and carcinogenicity in humans." (pg. 18660).

EPA's determination is put in the context of the scientific uncertainties that exist when evaluating the potential carcinogenicity of PFOS: "The available epidemiology studies reported elevated risk of bladder, prostate, kidney, and breast cancers after chronic PFOS exposure. While there are reports of cancer incidence from epidemiological studies, the study designs, analyses, and mixed results preclude a definitive conclusion about the relationship between PFOS exposure and cancer outcomes in humans."

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There are additional sources of substantive uncertainty cited in EPA's Health Effects Support Document for Perfluorooctane Sulfonate (PFOS) EPA 822-R-16-002 that indicates: "Several human epidemiology studies evaluated the association between PFOS and cancers including bladder, colon, and prostate, but these data present a small number or cases and some are confounded by failure to adjust for smoking. The associations for most epidemiology endpoints are mixed,"; "The genotoxicity data are uniformly negative,"; and "Human epidemiology studies did not find a direct correlation between PFOS exposure and the incidence of carcinogenicity in worker-based populations."

The single animal study relied upon by EPA for the carcinogenicity of PFOS is described as: "The one high confidence animal chronic cancer bioassay study provides evidence of multi-site tumorigenesis in both male and female rats" and "The single chronic cancer bioassay performed in rats is positive for multi-site and -sex tumorigenesis" (pg. 18638)[12] This limited evidence is not sufficient to support the conclusion that "evidence is adequate" as to human carcinogenicity, particularly when considering that these observations of tumorigenesis are in excess of environmentally relevant concentrations of PFOS.

While EPA indicates that that these conclusions were arrived at with a systematic review, it is not clear whether the systematic review protocol was adequately developed to appropriately apply the noted sources of uncertainty into the conclusion of carcinogenic classification. Many of these issues could have been addressed by peer review/public comment on the systematic review protocol used in the MCL development. It is common practice among regulatory agencies to either publish or distribute for comment a proposed protocol that can be revised based on technical feedback as seen in other EPA program areas such as the Integrated Risk Information System (IRIS). Not only does this serve to enhance the transparency of the review process, but also provides additional perspectives on many of the criteria for risk of bias and evidence integration that must be detailed a priori to the actual review. NCASI supports the opportunity to provide technical comments on proposed systematic review protocols.

2.0 Laboratory limitations for Proposed Regulatory Limits and Action Levels

It is not clear that drinking water providers are able to manage a process to the levels of a Practical Quantitation Level (PQL), as EPA has assumed in their evaluation. Due to variability in samples, sampling technique, laboratories, etc., managing a drinking water treatment process for a variety of water treatment facilities (e.g., ranging from small private to large municipal) to the quantification level may be operationally infeasible. Drinking water providers manage risk by not only restricting concentrations to that of the MCLs, but also rely on action levels well below the MCLs, to provide some level of additional operational certainty. Setting MCLs at the PQL does not allow operators to do this.

The proposed rulemaking indicates trigger levels at 1/3 the MCLs, which equates to 1.3 ppt for PFOA/PFOS and a 0.3 HI for other listed PFAS. This means that action levels are not able to be reliably quantified. EPA recognizes the challenges of finding laboratories that can provide accurate quantitation below 4 ppt: "EPA anticipates there would not be sufficient laboratory capacity if the quantitation level were set at a level below 4.0 ppt. The rigorous laboratory certification and quality assurance/quality

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[1] Thomford, P. 2002. 104-Week Dietary Chronic Toxicity and Carcinogenicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS; T–6295) in Rats (pp. 1–216). 3M. Available on the internet at: *https://www.ag.state.mn.us/ Office/Cases/3M/docs/PTX/PTX2805. pdf*

[2] Butenhoff, J.L., Chang, S.C., Olsen, G.W., and Thomford, P.J. 2012. Chronic Dietary Toxicity and Carcinogenicity Study with Potassium Perfluorooctane Sulfonate in Sprague Dawley Rats. *Toxicology,* 293:1– 15. *https://doi.org/10.1016/j.tox.2012. 01.003*

control (QA/QC) procedures could limit the number of laboratories that can achieve lower quantitation levels and many water systems would not be able to secure the services of laboratories that are capable of consistently providing precise and accurate quantitation of concentrations of PFOA and PFOS at levels lower than 4.0 ppt." (pg. 18667).

In addition to the inability to operationalize a risk management plan when action levels exist below the PQL, there may not be adequate laboratory capacity to accommodate the enormous amount of testing across the country that would be required under this proposed rulemaking. The PQLs described by EPA are achieved by cutting edge technology and may not be considered standard instrumentation across commercial laboratories. Additionally, laboratories with PFAS analytical capabilities are already receiving increased demand for NPDES permit compliance testing, as well as for testing for remediation projects. If MCL concentrations are promulgated that are reasonably above the PQL, it will broaden the accessibility of robust analytical evaluation for risk management, which would increase the feasibility of operationalizing risk management of drinking water under PFAS MCLs.

3.0 The Inappropriate Application of the Hazard Index Approach for Listed PFAS

In this rulemaking, EPA proposes a Hazard Index (HI) approach that substantially diverges from the intended justification and implementation of HI in standard human health risk assessment applications:

"An important aspect of the proposed 'general HI' approach is that it is based on the availability of a reference value regardless of the critical effect for each mixture component. Unlike a target organ specific Hazard Index which is typically based on either shared mode-of-action or shared health outcome of mixture components, the general HI is based on a non-cancer reference value (RfD or Minimal Risk Level) for the critical (usually the most sensitive) effect of each component."[3][4](pg. 18656)

An HI approach is only justified, in a toxicological sense, when two or more compounds elicit the same endpoint or act on the same biological mode of action in producing an adverse health effect that forms the basis of the health hazard for those substances. PFAS, as a group, includes thousands of substances with unique physio-chemical properties, unique fate and transport properties, and unique toxicological profiles. Broadly inclusive criteria are unlikely to produce standards or risk assessment approaches with a well characterized margin of safety or that accurately reflects the hazard posed by individual substances within the group. This has been evidenced in the scientific literature, even in studies that have evaluated PFAS of relatively similar chemical structure. As an example, Pizzurro et al. 2019 examined the toxicokinetics of several PFAS compounds and came to the following conclusions:

"Overall, our analysis provides one of the first syntheses of available empirical PFAS toxicokinetic data to facilitate interpreting human relevance of findings observed in animal studies and developing health-based criteria for PFAS from such studies. Our analysis highlighted several notable differences among the different PFAS regarding species and substance-specific tissue partitioning, half-life, and transfer to developing offspring via the placenta or lactation, as well as highlighted data gaps for certain substances....Lastly, the results of this analysis indicate that there are toxicokinetic differences among the different PFAS based on chain length, and these substances should not be regulated as a group

[3] USEPA. 2000a. *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures.* EPA 630-R-00-002. Available on the internet at: *https:// cfpub.epa.gov/ncea/risk/recordisplay. cfm?deid=20533.*

[4] USEPA. 1989. Risk assessment guidance for Superfund. Vol. 1. Human Health Evaluation Manual (Part A). EPA/540/1- 89/002.

without careful consideration of how the substance-specific toxicokinetics may impact potential toxicity, including differing specific target organ toxicity and overall body burden." [5]

None of the listed substances under the HI approach in the proposed rulemaking are have RfDs based on the same critical effect, nor is there a link between a mode of action each substance elicits that is related to all of the critical effects that form the basis of the individual RfDs. The EPA acknowledges the diversity of health outcomes exhibited from exposure to these listed PFAS:

"The adverse health effects observed following oral exposure to such PFAS are significant and diverse..."(pg. 18643)

A HI approach is not appropriate for compounds with different toxic modes of action and it's use in the proposed rulemaking is inconsistent with other EPA programs. EPA states that "the application of the HI approach under a regulatory purview is not novel," and EPA uses CERCLA as an example (pg. 18669). While the HI is not novel, in EPA's 2000 "Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures," EPA lays out three approaches to conducing risk assessments for mixtures, recognizing how the state of the science influences which approaches is appropriate. In the "Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures," an EPA Risk Assessment Forum Technical Panel, August 2000, further states that the "major concerns for the user are whether the available data are on components or whole mixtures, whether the data are composed of either similar components or similar mixtures that can be thought of as acting by similar toxicologic processes, and whether the data may be grouped by emissions source, chemical structure, or biologic activity." EPA, in the proposed rulemaking does not support that these four additional PFAS compounds act by similar toxicologic processes.

The Hazard Index (HI) approach requires confirmation of the fundamental assumption of dose additivity. Systemic toxicants should be confirmed as having the same mode of action prior to dose summation[6]. The four PFAS species included in the proposed HI summation, PFNA, HFPO-DA, PFHxS, and PFBS, are dissimilar and do not seem to have confirmatory data that they adhere to the dose additivity model as they do not share critical effects as the basis for their individual RfDs. The Supplementary Guidance also explains that the "term additivity is used when the effect of the combination of chemicals can be estimated directly from the sum of the scaled exposure levels (dose addition) or of the responses (response addition) of the individual components." EPA's attempt to use additivity is not based on either of the approaches in the 2000 Guidance.

Further, EPA's additivity approach in the proposed rulemaking appears to assume conclusion on issues that EPA is still considering as to PFAS compounds in other programs. In the CERCLA ANPRM issued in April 2023, EPA is specifically soliciting feedback on whether future CERCLA action could group PFAS compounds, including on the basis of modes of toxicological action:

> EPA is considering whether to initiate a future action that would potentially designate groups or categories of PFAS as hazardous substances. A group or category refers to a set

[5] Pizzurro, Daniella M.; Seeley, Mara; Kerper, Laura E.; Beck, Barbara D. 2019. Interspecies differences in perfluoroalkyl substances (PFAS) toxicokinetics and application to health-based criteria. Regulatory Toxicology and Pharmacology 106 239–250.

[6] USEPA 2000 Risk Assessment Guidance for Superfund (RAGS) (https://www.epa.gov/sites/default/files/2015-09/documents/rags_a.pdf

> of PFAS that share one or more similar characteristics. Characteristics of interest could include, but are not limited to, chemical structure (e.g., carbon chain length, functional group), physical and chemical properties, mode of toxicological action, precursors or degradants, or co-occurrence.

EPA also gives an example of the TCSA Significant New User Rule (SNUR) where grouping was based on chemical structure.

> In the TSCA program, EPA has developed Draft Principles for Cumulative Risk Assessment (CRA). In that document, EPA bases additivity on toxicological similarity: "Deciding, based on their toxicological similarity, which chemical substances to include in a cumulative chemical group that subsequently would be evaluated using dose additive models is an important element of a CRA."[7]

These four additional PFAS are not toxicologically similar, so EPA grouping them under the MCL proposed rulemaking is inconsistent with how EPA would group chemicals under TSCA and CERCLA.

In light of the evidence that critical health endpoints for individual PFAS, including those listed under the HI approach in the proposed rulemaking, are unique and diverse the assumption of dose additivity is not valid and therefore the use of the Hazard Index as a risk management approach is not appropriate.

Feel free to contact me regarding these comments.

Respectfully submitted,

Giffe Johnson, PhD
Program Manager, Chemical Management and Health Effects
NCASI

[7] Draft Principles for Cumulative Risk Assessment, EPA Document# EPA-740-P-23-001, Feb. 2023 United States Office of Chemical Safety and Environmental Protection Agency, Pollution Prevention, lines 458-460.