Message

From: KEVIN DOWLING [kdowling@mmm.com]
Sent: 5/13/2025 5:28:36 PM
To: Kramer, Jessica L. [kramer.jessical@epa.gov]
CC: Elise Maheu [emaheu@mmm.com]; Todd Weiss [tweiss@crshq.com]; Mat Lapinski [mlapinski@crshq.com]
Subject: RE: Meeting request: 3M Chief Technology Officer
Attachments: PFOA PFOS information.docx; Bibliography for PFOA PFOS discussion.docx; 2023-05-30 - 3M Comments on EPA NPDWR.pdf; Appendix B to 3M Comments on EPA Proposed National Primary Drinking Water Standard.pdf

Hi Jesscia,

Following up on this request, we'd love to bring in some folks from our scientific team next week to walk through the attached information we shared with ACC and I believe they transmitted to you.

Please let us know if there are any times that work for you next week on Wednesday 5/21 or Friday 5/23? We would like to bring some experts from 3M who can brief you on the attached information. Some of our scientists will be in town for a meeting with the DOD on Thursday so will be in town.

Thanks, and looking forward to it,

-Kevin

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Kevin Dowling
Head of Government Affairs, United States
Global Government Affairs
3M Company, 1425 K Street NW Suite 300 | Washington, DC 20005 | United States
Time: UTC -5:00 / EST
Mobile: +1 202.963.9089 kdowling@mmm.com

From: KEVIN DOWLING <kdowling@mmm.com>
Sent: Thursday, May 1, 2025 1:35 PM

To: kramer.JessicaL@epa.gov
Cc: Elise Maheu <emaheu@mmm.com>; Todd Weiss <tweiss@crshq.com>; Mat Lapinski <mlapinski@crshq.com>
Subject: Re: Meeting request: 3M Chief Technology Officer

Hi Jessica,

Checking back on this request for you and John Banovetz our EVP/CTO to connect as follow up from the water quality summit. Does May 14th or 15th work for you in DC?

Thanks, and looking forward to it,

Kevin

Kevin Dowling
Head of Government Affairs, United States
Global Government Affairs
3M Company, 1425 K Street NW Suite 300 | Washington, DC 20005 | United States
Time: UTC -5:00 / EST
Mobile: +1 202.963.9089 kdowling@mmm.com

From: KEVIN DOWLING <kdowling@mmm.com>
Sent: Wednesday, April 23, 2025 1:03 PM
To: kramer.JessicaL@epa.gov <kramer.JessicaL@epa.gov>
Cc: Elise Maheu <emaheu@mmm.com>; Todd Weiss <tweiss@crshq.com>; Mat Lapinski <mlapinski@crshq.com>
Subject: RE: Meeting request: 3M Chief Technology Officer

Hi Jessica,

Bumping this up. Can we find a time for you to connect with our CTO John Banovetz next week or in early May?

Looking forward to it,

Kevin

3M Science. Applied to Life.™

Kevin Dowling
Head of Government Affairs, United States
Global Government Affairs
3M Company, 1425 K Street NW Suite 300 | Washington, DC 20005 | United States
Time: UTC -5:00 / EST
Mobile: +1 202.963.9089 kdowling@mmm.com

From: KEVIN DOWLING <kdowling@mmm.com>
Sent: Thursday, April 10, 2025 6:08 PM
To: kramer.JessicaL@epa.gov
Cc: Elise Maheu <emaheu@mmm.com>; Todd Weiss <tweiss@crshq.com>; Mat Lapinski <mlapinski@crshq.com>
Subject: Meeting request: 3M Chief Technology Officer

Hi Jessica:
It was great hearing you @ the Chamber water quality summit last week and we really appreciated your offer to connect with stakeholders. Reaching out to set up a meeting between you and your team with your fellow panelist from last week Dr. John Banovetz, 3M's EVP & Chief Technology Officer, Environmental Responsibility. My colleague Elise Maheu is cc'd and will follow up with some times and we can make whenever / wherever works for you in the coming weeks.

Also, I am sorry I didn't get a chance to say hello last week. I am a Team Zeldin alumn from his House office and my family is in his former district. I am envious that you get to work with Eric and Sarah, I miss them!

Really looking forward to connecting soon. Talk to you soon and thanks,

-Kevin Dowling

Kevin Dowling
Head of Government Affairs, United States
Global Government Affairs
3M Company, 1425 K Street NW Suite 300 | Washington, DC 20005 | United States
Time: UTC -5:00 / EST
Mobile: +1 202.963.9089 kdowling@mmm.com

PFOA Carcinogenicity Designation

- EPA improperly relied on evidence of liver, pancreas acinar cell, and Leydig cell tumors in rats exposed to PFOA and a few selective and unrepresentative citations to associations observed between PFOA concentrations and kidney and testicular cancer in humans, placing particular emphasis on a nested case-control study of renal cell carcinoma conducted by the National Cancer Institute involving the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. Shearer et al. (2021).

- As explained in 3M's May 30, 2023 comments to EPA on PFAS National Primary Drinking Water Regulation; Docket No. EPA-HQ-TRI-OW-2022-0114 ("3M's 2023 Comments," attached hereto), EPA incorrectly excluded several occupational exposure studies from their analyses (Steenland and Woskie et al. (2012); Raleigh et al. (2014); Barry et al. (2013)), which collectively demonstrate limited or no association with kidney cancers among workers with 10- to 1000-fold greater exposure to PFOA than seen in the general population.

    - These studies should have been considered by EPA as strong evidence against carcinogenicity. Indeed, Steenland et al. (2022) concluded that the kidney cancer data from Barry et al. (2013), which included both occupational and community-exposed subjects, was statistically inconsistent with Shearer et al. (2021), which included lower-exposed general population subjects. And an effort to combine the two datasets showed that serum levels above approximately 13 ug/L did not present any additional significant risk of kidney cancer – a finding that undermines the generalizability of Shearer et al. (2021). Importantly, occupational cohorts such as followed in Raleigh et al. (2014) included workers with geometric mean serum levels of PFOA as high as 6,800 µg/L. Olsen et al. (2000).
    - Yet, EPA used Shearer et al. (2021), which had very little contrast in exposures among study participants (<4-27 µg/L), to derive a cancer slope factor (CSF) for PFOA of 0.00352 per µg/L PFOA in serum. Applying that slope factor to the occupational exposures in a cohort such as Raleigh would predict an enormous increase in kidney cancer among workers. In contrast, Raleigh et al. (2014) found no association between kidney cancer incidence risk and PFOA exposures among the highest two quartiles of workers, either individually or combined, compared with the referent non-occupationally exposed worker population. Q3 HR = 0.98 (95% CI: 0.33-2.92); Q4 HR = 0.73 (95% CI: 0.21-2.48); Q3 & Q4 Combined HR = 0.85 (95% CI: 0.36-2.06). Likewise, Barry et al. (2013) found no increased risk among the occupationally exposed cohort members who had median estimated annual PFOA serum levels of 174.4 ug/L (range: 5.2-3683 ug/L): HR (no lag) = 0.95 (95% CI: 0.59-1.52); HR (10-year lag) = 0.99 (95% CI: 0.67-1.46).

- As explained more fully in 3M's 2023 Comments, EPA's derivation of the PFOA CSF from Shearer et al. (2021) also appears to be flawed (failed to properly include the mid-points of the exposure categories in the derivation) and EPA used inconsistent methods for deriving candidate CFSs from different studies. EPA offers no explanation for these discrepancies, which appear to be arbitrary.

- As explained in 3M's 2023 Comments, EPA did not properly assess Shearer et al. (2021) for flaws that undermine its reliability, including use of a single serum measurement, inadequate control for confounding by key risk factors such as smoking, body mass index, and history of hypertension, and the potential for reverse causation given that serum PFOA measurements (the exposure variable) can be impacted by kidney function (which can be impacted by the cancer outcome being studied). As noted by Burgoon et al. (2023), "[w]hile Shearer et al. (2021) adjusted their results for estimated glomerular filtration rate (eGFR), adjusting for eGFR alone would not adequately control for potential confounding due to the extensive role of renal transporters in the clearance of PFOA."

- EPA also did not consider the impact of the case/control design of Shearer et al. (2021) on the reliability of the results. As explained in 3M's 2023 comments, the lowest exposure category in Shearer et al. (2021), which served as the reference group for the study, had fewer cases (47) than controls (81), which could have biased the statistical comparisons with the other exposure categories.

- EPA's assessment also improperly failed to account for Rhee et al. (2023) and Purdue et al. (2023), which were published after EPA promulgated its proposed rule for notice and comment but before EPA published its final rule. Rhee et al. (2023) was conducted by the same researchers at the National Cancer Institute that conducted Shearer et al. (2021) and used a similar design with general population subjects. But it involved a larger and more diverse study population derived from the Multiethnic Cohort. Contradicting Shearer et al.'s findings, it reported a non-significant *decrease* in renal cell carcinoma risk with doubling of PFOA serum level: $OR_{continuous} = 0.89$ (95% CI: 0.67, 1.18). Purdue involved a nested case-control design of U.S. Air Force servicemen and it found no associations between PFOA and testicular germ cells tumors either before or after adjustment for other PFAS exposures. Without further comment, in documentation accompanying the final rule EPA inexplicably indicates these study warrant "no change" in its cancer assessment. USEPA (2024).

- EPA's reliance on rodent chronic toxicity studies demonstrating liver, Leydig cell, and pancreas acinar cell tumors as supporting its human carcinogenicity designation for

PFOA is also unsupported. It is well known that these types of tumors in rats are associate with peroxisomal proliferation, a response of limited relevance to human exposures. Burgoon et al. (2023); Corton et al. (2018); Klaunig et al. (2012); ATSDR (2021). As explained further in 3M's 2023 Comments, EPA researchers have previously acknowledged that the peroxisomal proliferation mechanism observed in rodents is not relevant to humans in a peer-reviewed article entitled "The PPARα-dependent rodent liver tumor response is **not** relevant to humans" (Corton et al. (2018) (emphasis added)). The agency failed to acknowledge its own scientists' findings. As further evidence of the irrelevance of these rat findings, fibrate drugs, which are also peroxisome proliferators, are widely prescribed for managing blood lipids. In rodents, similar to PFOA, they produce these same triad of tumors. Cook et al. (1999); Biegel et al. (2001). Yet they have not been shown to result in cancer in humans. Bonvas et al. (2012).

- The animal and mechanistic evidence relied on by EPA to support its PFOA carcinogenicity classification also fail to justify its myopic reliance on the kidney cancer association observed in Shearer et al. (2021) for its cancer slope factor derivation. Burgoon et al. (2023) note that if PFOA were a genuine kidney carcinogen, "one might expect that the massive doses of PFOA used in the rodent (and monkey) bioassays would have also induced kidney tumors. Yet, they did not." Excess renal tumors were seen in the three available PFOA chronic rat studies (NTP (2020); Butenhoff et al. (2012a); Biegel et al. (2001)).

PFOS Carcinogenicity Designation

- EPA improperly relied on the observation of liver tumors and pancreas tumors in PFOS-exposed rats (Thomford (2002); Butenhoff et al. (2012b)), and selective and unrepresentative citations to associations observed between PFOS and cancer outcomes in humans to conclude that PFOS satisfied its classification criteria for "likely to be carcinogenic to humans."

- The epidemiological literature regarding PFOS does not support EPA's designation. As described more fully in 3M's 2023 Comments, the majority of the studies identified by EPA as relevant for assessing whether PFOS is carcinogenic found no increased risk, or in one case, even a reduced risk of cancer from PFOS exposure.

    - In particular, the EPA's failure to give proper consideration to Eriksen et al. (2009), a study with the same methodology as Shearer et al. (2021) on which EPA heavily relies for its PFOA assessment, is arbitrary and unsupported. Notably, while EPA relies on liver and pancreas tumor findings in rats to support its PFOS classification, Ericksen et al. (2009) did not find a significantly significant

association by quartile of PFOS exposure or trend across quartiles for either cancer type.

- Further, while EPA references a significant association with liver cancer reported in Goodrich et al. (2022) above an arbitrarily 54.9 µg/L PFOS serum cut off, numerous other studies, including occupational cohorts with much higher exposure contrasts, do not report significant associations with PFOS. Olsen et al. (2004); Grice et al. (2007); Eriksen et al. (2009); Alexander et al. (2024); Moon et al. (2024); Li et al. (2022).

- Notably, in its most recent hazard assessment of the carcinogenicity of PFOS, IARC found the human epidemiological evidence supporting inadequate to support an association with any type of cancer. IARC (2025).

- As explained further in 3M's 2023 Comments, similar to its assessment of PFOA rat studies, EPA did not consider the biological plausibility and human relevance of the rat liver and pancreas tumor findings in Thomford (2002)/Butenhoff et al. (2012b). Receptor-mediated liver tumors in rats, whether mediated by activation of the chimeric antigen receptor (CAR) or PPARα receptor, are not relevant to humans. Corton et al. (2018); Hall et al. (2012). Nor are the other potential modes identified by EPA – hepatocyte nuclear factor 4 alpha (HNF4α) suppression, cytotoxicity, genotoxicity, oxidative stress, and immunosuppression – biologically plausible in humans. With respect to the pancreas tumor findings, it has been well-documented that there are substantial differences in pancreatic islet cells between rodents and humans in terms of anatomy, cellular components, gene expressions, and functional aspect of insulin secretion. Brissova et al. (2015); Steiner et al. (2010). EPA did not take these differences into account in considering human relevance.

- As further explained in 3M's 2023 Comments, EPA also improperly used two different models to interpret the liver tumor findings, which violates its own *Guidelines for Carcinogenic Risk Assessment.* USEPA (2005)

- EPA also improperly recalculated the statistical significance of pancreas tumor trends in Thomford (2002)/Butenhoff et al. (2012) by using a non-standard approach of eliminating animals who were sacrificed before the appearance of the first pancreas tumor from the analysis. EPA clearly did this to manufacture a significant outcome *post hoc* to justify their pre-determined classification decision. As explained in 3M's 2023 Comments, traditional statistical methods used by the authors adequately accounted for survival.

- The science does not support EPA's classification of PFOS based on its alleged "structural similarity" to PFOA. As outlined in 3M's 2023 Comments, the structural differences between PFOA and PFOS – carboxylic vs. sulfonic acid functional groups – impart significantly different physical-chemical properties to these compounds, which explains their different technical applications as well as differences in biological disposition and receptor site dynamics. Notably, while the PFOA and PFOS chronic toxicology studies in rats both show increased incidences of liver tumors, other sites differ. Further, EPA did not follow its own best practices for applying read across, including failing to follow its seven key workflow steps for evaluating read across or otherwise use its Generalized Read Across Tool.

EPA's Setting of PFOA/PFOS MCLgs To Zero

- EPA improperly set the MCLgs for both PFOA and PFOS to zero. In reaching this decision, EPA assumed a linear-no threshold model of carcinogenicity based on default assumptions of EPA's Guidelines for Carcinogenic Risk Assessment (USEPA (2005)), rather than analysis of the weight of evidence. As detailed in 3M's 2023 Comments, however, the weight of evidence does not support a mutagenic/genotoxic mode of action for either PFOA or PFOS. And the receptor-mediated and cytotoxic modes of action postulated by EPA display non-linear, threshold effects – effects that have not been shown to occur at human relevant exposure levels. See, *e.g.*, Evans et al. (2022); Hall et al. (2012); Beggs (2016). To the extent that EPA relies on these modes of action to support its PFOA and PFOS carcinogenicity classification, it should not assume PFOA/PFOS have no threshold for carcinogenic effects. It is inappropriate for EPA to set a MCLg at zero based on carcinogenicity when a substance does not have a linear mode of carcinogenic action. *Chemistry Council v. EPA*, 206 F.3d 1285, 1287 (D.C. Cir. 2000).

Non-Cancer Endpoints

- EPA identified four critical endpoints from non-cancer outcomes for which it derived reference doses (RfDs) for PFOA and PFOS: developmental effects (decreased birthweight); cardiovascular effects (total cholesterol); liver effects (alanine transaminase (ALT)); immune effects (vaccine antibody response). EPA's approach to assessing the overall weight of evidence for non-cancer health effects of PFOA and PFOS is not consistent with its guidance, and EPA's methods were neither transparent nor reproduceable.

- In addition, as explained in 3M's 2023 Comments, across all of these endpoints EPA relied on studies that used outdated and uncorrected NHANES data and EPA did nothing to verify the accuracy of the data or account for these discrepancies.

- ***Developmental Effects (Decreased Birth Weight)***

  - Overall, the available evidence relating to developmental outcomes was limited and inconsistent for any effects from PFOA or PFOS exposure. As explained in 3M's 2023 Comments, EPA failed to properly consider and account for potential bias in the birth outcomes evaluated in the studies due to pregnancy hemodynamics and PFOA/PFOS sample timing; mixed evidence for gestation duration, measured as gestational age or preterm birth; inconsistent evidence with rapid growth measures, including postnatal height and adiposity up to age 2; little evidence for increased fetal loss; no evidence for increased birth defects; and limited dose-response evidence in birth weight deficit studies.

  - In particular, EPA failed to demonstrate that the studies it relied on for the critical effect of decreases in birth weight were free from bias. As explained in 3M's 2023 Comments, studies show that serum volume increases by about 50% and glomerular filtration rate (GFR) on the same order (40-50%) during pregnancy (Salas et al. (2006); Cheung and Lafayette (2013)). These increases lead to a commiserate decrease in maternal serum PFAS concentration during pregnancy (Monroy et al. 2008; Steenland et al. 2018; Kato et al. 2014) and the magnitude of serum volume and eGFR increases can be correlated with birth weight. This makes the timing of serum sampling in birthweight studies critical in evaluating any association with PFOA/PFOS serum levels. Two meta-analyses by Dzierlenga et al. (2020) and Steenland et al. (2018) found that when PFOA and PFOS were measured in early pregnancy, there was little to no association with decreased birth weight, suggesting that the timing of serum measurement is critical for accurate interpretation of study results. Even though the study EPA relied on for its RfD derivation involved sampling in the first trimester (Wikstrom et al. (2020)), its findings were inconsistent with others with similar sample timing, and it did not attempt to adjust for estimate GFR (unlike other studies). EPA did not demonstrate that Wikstrom et al. 2020 was free from pharmacokinetic bias.

  - As discussed in 3M's 2023 Comments, EPA failed to show that decreases in birthweight observed in studies, even if due to PFOA/PFOS exposure and not pregnancy hemodynamics and PFOA/PFOS sample timing, represent adverse effects or lead to any other clinically meaningful health outcomes.

- ***Cardiovascular Effects (Cholesterol)***

  - EPA did not justify its selection of studies to evaluate for cardiovascular disease RfD derivation. As described in 3M's 2023 Comments, EPA considered only three studies

(Dong et al. 2019; Lin et al. 2019; Steenland et al. 2009), but there were numerous additional medium (Averina et al. 2021; Christensen et al. 2019; Domazet et al. 2016; Donat-Vargas et al. 2019; Fan et al. 2020; Han et al. 2021; Jain and Ducatman 2018; Jain 2019; Kang et al. 2018; Kobayashi et al. 2022; Lin et al. 2009, 2019, 2020; Liu et al. 2018, 2020; Mora et al. 2018; Papadopoulou et al. 2021; Skuladottir et al. 2015; Spratlen et al. 2020; Tian et al. 2021; Zare Jeddi et al. 2021; Eriksen et al. 2013; Fisher et al. 2013; Geiger et al. 2014; Nelson et al. 2010; Sakr et al. 2007; Timmermann et al. 2014; Winquist and Steenland 2014) and high confidence (Gardener et al. 2021; Li et al. 2021) studies it did not consider.

- The cardiovascular disease endpoint was not an appropriate critical effect choice. As noted in 3M's 2023 Comments, EPA acknowledges that the evidence for most cardiovascular-related endpoints such as changes in blood pressure, hypertension, coronary heart disease, and stroke is inconsistent. See also ATSDR (2021); Steenland et al. (2020).

- EPA did not properly consider confounding in selecting the studies evaluating total cholesterol for PFOS/PFOA RfD derivation. As explained in 3M's 2023 comments, dietary habits, family history, and even exercise can have effects on cardiovascular outcomes, including cholesterol measurements. Vincent et al. (2019); Allen et al. (2016); Mensink et al. (2003); Lin et al. (2019). Because of potential confounding due to enterohepatic circulation of both PFOA/PFOS and bile acids *in vivo*, the European Food Safety Authority (EFSA) decided not to use cholesterol as a critical effect for derivation of its tolerable weekly intake values for PFOA and PFOS. EFSA (2020).

- **Liver Effects (alanine transaminase (ALT))**

  - For both PFOA and PFOS, EPA selected increases in ALT as a critical effect for derivation of RfDs. However, as described in 3M's 2023 Comments, EPA failed to characterize the biological relevance of changes in ALT or other liver biomarkers in the context of quantitative clinical outcomes. As EFSA (2020) pointed out, while there is evidence for elevated ALT due to PFOA exposure, the adversity of this effect is uncertain because of the low magnitude of increases and no associations with liver disease.

  - As explained in 3M's 2024 Comments, EPA's reliance on animal studies involving rodents as support for liver affects is also misplaced, as these liver effects involve mechanisms of action with questionable relevance to humans, such as pathways moderated by peroxisome proliferator-activated receptor-alpha ("PPARα").

- EPA also used inappropriate studies to derive its RfD values. As explained in 3M's 2023 Comments, EPA derived its candidate PFOS RfD for elevated ALT from Nian et al. (2019), which was a cross-sectional study from China that reported a 4.1 percent change (95% CI: 0.6, 7.7) in ALT for every 1 ng-mL increase in PFOS. But the change became non-significant when participants taking medications were excluded. And confounding variables, such as alcohol, smoking and diet, were not adequately controlled.

- ***Immune Effects (Vaccine Antibody Response)***

  - EPA determined that there was moderate evidence for an association between PFOA/PFOS exposure and immunosuppressive effects in human studies relying on decreases in antibody responses to various vaccination types observed in children in several studies. However, as described in 3M's 2023 Comments, there were significant uncertainties in the potential immune effects of PFOA and PFOS across studies, including: (1) inconsistent findings of decreased vaccine response in adult populations; (2) Inconsistent and/or imprecise findings of increased infectious disease; (3) mixed findings of hypersensitivity, including allergy, asthma, and eczema; and (4) mixed findings for autoimmune disease.

  - Even with respect to antibody response to diphtheria and tetanus vaccines in children, the results have been inconsistent. As explained in 3M's 2023 comments, the associations between vaccine response for tetanus or diphtheria with PFOA or PFOS exposures in cohorts from the Faroe Islands were not consistent either by age or by vaccine type across several studies (Grandjean et al. (2012); Grandjean et al. (2017a,b); Mogensen et al. (2015); Shih et al. (2021)). The alternate candidate study selected by EPA involving Greenlandic children also had critical limitations that should have been identified as part of a proper systematic review. Timmerman et al. (2021).

  - Deficiencies in the epidemiological evidence relating to vaccine antibody response make it an inappropriate critical endpoint for use in EPA's PFOA/PFOS risk assessment. As described in 3M's 2023 Comments, ToxStrategies conducted an independent assessment of studies examining vaccine response and PFOA exposure using the same IRIS framework for systematic review and critical appraisal of studies used by the EPA in the draft toxicity assessment for PFOA. See 3M's 2023 Comments, Appendix A.

- After identification and critical appraisal of studies examining vaccine response and PFOA exposure in the independent assessment, all studies received an overall rating of "deficient" or "critically deficient." Each study had deficiencies in participant selection, timing of exposure and outcome measures, or confounding, which resulted in a body of evidence that was of low quality with a high risk of bias.

- Based on these findings, vaccine response was not considered appropriate as a critical endpoint for PFOA exposure, and no studies qualified for POD development. Garvey et al. (2023) also conducted an independent review of the evidence and concluded that: "the Faroe Islands cohort data should not be used as the primary basis for deriving PFAS risk assessment values. The panel agreed that vaccine antibody titer is not useful as a stand-alone metric for risk assessment. Instead, PFOA and PFOS toxicity values should rely on multiple high-quality studies, which are currently not available for immune suppression."

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3M Center
St. Paul, MN 55144-1000
651 733 1110

May 30, 2023

Submitted electronically via Regulations.gov

Mr. Alexis Lan
Office of Ground Water and Drinking Water
U.S. Environmental Protection Agency
1200 Pennsylvania Ave., NW
Washington, DC 20460

Re: 3M Comments on PFAS National Primary Drinking Water Regulation; Docket No. EPA-HQ-TRI-OW-2022-0114

Dear Mr. Lan:

The 3M Company (3M) appreciates the opportunity to provide comments on the U. S. Environmental Protection Agency's (EPA) March 23, 2023 proposed rule (the Proposed Rule) to establish National Primary Drinking Water Standards (NPDWRs) for certain per- and polyfluoroalkyl substances (PFAS). 3M has included two appendices containing extensive technical information supporting and in addition to the comments below for EPA's consideration during this public comment period.

3M supports proactive management of PFAS and the goal of using science-based regulatory standards, based on a complete review of the best available scientific information, to provide communities with high-quality drinking water. More than 20 years ago, in 2000, 3M announced its exit from the manufacture of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), two of the PFAS that are the subject of the proposed NPDWRs. Late in 2022, 3M announced that it would cease all PFAS manufacturing by the end of 2025 and work to eliminate the use of PFAS across its product portfolio by the end of 2025. As it works toward its exit from all PFAS chemistries, and even following that exit, 3M will remain committed to working together with all stakeholders to develop reasonable, science-based actions that address PFAS in the environment in view of the continued uses of PFAS in critical industries across our modern economy.

To that end, the proposed NPDWRs are not a science-based response to the presence of the specified PFAS in drinking water. The proposed standards do not reflect the findings of important scientific literature that should help inform the establishment of drinking water standards for PFAS, nor do they sufficiently address the pointed criticisms and recommendations of EPA's own Science Advisory Board (SAB), which is tasked with ensuring the Agency's actions are supported by sound science. EPA should reconsider its proposal and work with all stakeholders to ensure that the full range of scientific evidence is appropriately considered and incorporated into the regulatory process.

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St. Paul, MN 55144-1000
651 733 1110

In short, a science-based approach to this issue would have resulted in a proposal to improve water quality that met statutory requirements. Regrettably, that is not what happened here because, as we explain below, the process that EPA used to develop its NPDWRs was deeply flawed and has resulted in proposed NPDWRs that exceed the agency's authority and can only be characterized as arbitrary and capricious. 3M encourages EPA to revise its proposed standards to reflect the collective body of best available science, which has not been reflected in the rulemaking process to date. This will help ensure that water treatment technologies are deployed where doing so will provide meaningful benefits. 3M remains ready and eager to partner with EPA in that effort.

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3M Center
St. Paul, MN 55144-1000
651 733 1110

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St. Paul, MN 55144-1000
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I. EXECUTIVE SUMMARY

As discussed below, EPA's proposed NPDWRs violate the Safe Drinking Water Act (SDWA) because they are not based on the "best available, peer-reviewed science,"[1] and because EPA did not follow statutorily defined procedures and, in many cases, its own well-established guidance in promulgating them. EPA did not appropriately establish and follow processes designed to help ensure its rulemaking reflects the weight of the evidence-based conclusions about potential consequences of exposure to the PFAS at issue, and the levels at which such consequences could be observed. The processes for collecting and evaluating scientific research are not matters of interpretation or preferred approach. They are foundational scientific practices and guidance, including, in many cases, the Agency's own guidance. Here, EPA has significantly deviated from those foundational practices. This has resulted in a proposal for incredibly low regulatory limits for PFOA, PFOS, and the Hazard Index (HI) substances (perfluorohexanesulfonic acid [PFHxS], perfluorobutane sulfonic acid [PFBS], perfluorononanoic acid [PFNA], and hexafluoropropylene oxide dimer acid [HPFO-DA]) in drinking water without showing that any benefits of such low limits are justified by their significant costs. The agency's flawed process has resulted in proposed NPDWRs that are arbitrary and capricious as they do not achieve the goal of appropriately balancing the costs of compliance against the expected benefits.

EPA Did Not Establish and Follow Required Procedures Designed to Ensure SDWA Compliance and Promote Regulation Based on the Best Available Science

EPA did not follow established best practices, including its own long-standing guidance, to conduct a systematic review of the relevant scientific literature. A proper systematic review is important to ensure that the Agency's conclusions are driven by science and are transparent to the public. Although EPA has long-standing guidance on how to conduct a systematic review, it did not follow it. Here, EPA's own SAB, in its *Review of EPA's Analyses to Support EPA's National Primary Drinking Water Rulemaking for PFAS*, "identified multiple inconsistencies and deficiencies in both the description and execution of the systematic review process utilized in the evaluation of both PFOA and PFOS." (USEPA SAB 2022, p. 3.)[2] SAB also noted that EPA did not publish a pre-defined review protocol, did not have transparent criteria for study inclusion and exclusion, omitted studies that should have been considered, and improperly categorized studies, resulting in a review with "major deficiencies." (USEPA SAB 2022, p. 3.) These issues were so significant that at least one SAB member indicated EPA's systematic review did not "represent the state of practice."

As discussed herein, EPA did not meaningfully implement SAB's feedback. This resulted in an after-the-fact systematic review protocol that is contrary to the SAB's feedback and the Agency's own guidance. *See e.g., ORD Staff Handbook for Developing IRIS*

[1] 42 U.S.C.A. § 300g-1(b)(3)(A).

[2] A complete list of references is available at the end of this document and each of the appendices. Each reference list is specific to the document it accompanies and may have different lettering or other designations when referring to the same document. Those designations may also be different than those in the EPA docket. Refer to the reference list for complete document identification.

Assessments, (USEPA ORD 2022, pp. xiv-xvii) ("The transparency and scientific rigor of the IRIS process is enhanced through the application of systematic review . . . The IRIS process applies a systematic review approach from the literature identification stage through the selection of studies for dose-response assessment"); USEPA SAB 2022 p. 3 ("***Before*** initiating a systematic review process, it is essential to clearly define the study question to be addressed and to develop a protocol.") (emphasis added).

The absence of a rigorous, prescribed systematic review has had a serious impact on the rulemaking process. For example, the lack of a pre-defined review protocol led to outsized weight being placed on studies that have highly material deficiencies while underweighting higher-quality studies that do not support the proposed limits. Further, EPA reliance on cancer endpoints as the basis for a maximum contaminant level goal (MCLG) of zero for PFOA and PFOS is not consistent with the evidence EPA presents nor with its own guidance. Similarly, EPA did not establish review processes designed to ensure that the weight of evidence supports its new classification of PFOS as "likely" to be carcinogenic to humans.

EPA's derivation of its alternate, non-cancer reference doses (RfDs) for PFOA and PFOS are similarly in need of reconsideration and revision. In calculating the RfDs, EPA did not follow its own guidance documents including EPA's *ORD Staff Handbook for Developing IRIS Assessments* (USEPA ORD 2022). These procedures are important for transparency and reproducibility in study evaluation. An appropriate evaluation of the existing literature, consistent with EPA guidance, would have found many of the studies that EPA relied on to calculate the extremely low RfDs for these PFAS were low quality and at high risk of bias, therefore leading EPA to reach different conclusions.

The Proposed Rule is also based on profound uncertainty and assumptions, which EPA did not properly quantify and explain in its rulemaking documents. EPA defines "uncertainty" as "a lack of knowledge about factors affecting exposure or risk" (USEPA 2019, p. 1-7).. "Uncertainty factors" are "used in noncancer risk assessments when insufficient data are available to support the use of chemical-specific and species-specific extrapolation factors" (OEHHA 2008). Because uncertainty factors are used to address a lack of data, the higher the total uncertainty factors, the lower the confidence in the accuracy of the analysis. For its evaluations of HFPO-DA and PFHxS, EPA has assigned "uncertainty factors" totaling 3,000—the maximum that could be considered as the basis of a reference value according to EPA's IRIS Handbook. Had the uncertainty factors been any higher, EPA's own guidance would have precluded it from setting a reference value for those substances. In adopting a total uncertainty factor of 3,000, EPA implicitly acknowledges that its proposed RfDs for those substances are, at best, on the very edge of acceptability. This is important because "uncertainty factors" only account for specific sources of uncertainty in the Proposed Rule. They do not account for significant additional uncertainties, including uncertainties resulting from EPA's poor systematic review, inconsistent and non-transparent study quality evaluations, lack of an independent verification of underlying analyses of the selected points of departure, and the absence of peer review of the proposed hazard index MCLG. Accordingly, EPA's uncertainty factor of 3,000—already at the margins of acceptability—significantly understates the actual uncertainties inherent in EPA's proposal for those substances.

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EPA Did Not Follow SDWA Best Practices in Calculating the Benefits of the Proposed Regulations

The SDWA requires EPA to show that the benefits of its proposed regulations justify the costs. EPA did not comply with that requirement in several important respects.

As an initial matter, EPA's analysis of estimated benefits related to its proposed standards for PFOA and PFOS violates the SDWA's requirement that it analyze separately the benefits of each proposed regulatory standard because EPA improperly conflated its benefits analysis for the two separate regulations. *See* SDWA §1412(b)(3)(C)(i)(I) (stating that EPA "shall" publish and seek public comment on certain considerations including anticipated benefits of regulation at alternative levels for "a maximum contaminant level that is being considered."). For example, EPA's estimated impact on total cholesterol from reducing PFOS is nearly two orders of magnitude less than the reduction in total cholesterol that EPA calculated for PFOA, but EPA combined those levels in its benefits analysis. It did not analyze separately the benefits for PFOA and PFOS individually, as required by the SDWA.

EPA also has not provided enough information in the record to allow the public to understand how EPA conducted its benefits analysis, which precludes meaningful peer review and comment. EPA's benefits analysis is not reproducible or adequately transparent to the public because EPA has not made important inputs and models available for public or peer review.

From the available information, EPA's benefits analysis appears unreliable. EPA purports to distinguish between the benefits of alternative drinking water exposure concentrations of 4.0 ppt, 5.0 ppt, and 10.0 ppt. However, foundational toxicological principles demonstrate that those levels are so similar that there is likely no way to discern changes in benefits between them (and EPA has not provided the information in the record to explain how it purported to do so).

Similarly, EPA did not provide the pharmacokinetics models underlying its estimates of blood serum PFOA and PFOS concentrations on which it based its benefits analysis. *See* (USEPA 2023a,b,c,d). The serum data estimate is a foundational conclusion supporting EPA's entire benefits analysis. It is the first value input in a sequence that is ultimately used to estimate the health risk reduction benefits for the proposed maximum contaminant level (MCL) and the regulatory alternatives. Without access to the models underpinning the input, the public and scientific experts cannot meaningfully understand and evaluate the scientific validity of EPA's conclusions about the relative benefits of a 4.0 ppt MCL versus a 5.0 ppt or 10.0 ppt alternative.

EPA's benefits analysis also does not consistently take alternative exposure considerations into account and improperly combines estimated benefits for PFOA and PFOS. This results in inflated estimates of the anticipated individual benefit calculation for each proposed regulatory standard and flawed human equivalent internal dose responses that introduce significant uncertainty about EPA's ultimate conclusions.

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3M Center
St. Paul, MN 55144-1000
651 733 1110

EPA's Proposed Hazard Index-Based MCL for PFHxS, PFBS, PFNA, and HFPO-DA Does Not Comply with the SDWA

EPA's proposed Hazard Index-based Maximum Contaminant Level (HI-MCL) for PFHxS, PFBS, PFNA and HFPO-DA is procedurally improper and substantively incorrect, for several reasons.

As an initial matter, the SDWA does not permit the Agency to simultaneously issue a notice of intent to regulate and a proposed MCLG and MCL. EPA may issue a *decision to regulate* at the same time that it proposes an MCLG and MCL, but it may not provide initial public notice that it is contemplating regulation at the same time it proposes the regulation. The failure to undertake the statutorily required two-step process undermines the validity of the EPA's proposals.

In addition to being procedurally improper, EPA's development of the HI-MCL is also substantively flawed. EPA's approach assumes co-occurrence of the four PFAS included in the hazard index, but EPA has not provided meaningful occurrence data showing substantial likelihood that those substances co-occur. Further, EPA's discussion of potential co-occurrence is replete with examples of EPA relying on data from sources that EPA claims supports its argument while ignoring sources that clearly undermine it. For example, the co-occurrence data presented at the system level for detection of any relevant PFAS shows wide variability among states (USEPA 2023h, p. 197), and states with the most systems tested show much lower frequency of co-occurrence detections.

EPA's interpretation of the data it selected is also flawed and has not been peer-reviewed, in violation of the SDWA. EPA created the HI-MCL after SAB review, and based it on Health-Based Water Concentrations (HBWC) for the four HI substances that were not submitted to SAB. This violates the SDWA, which requires that EPA request comments from the SAB "prior to proposal of a maximum contaminant level goal and national primary drinking water standard."[3]

The absence of necessary peer review resulted in EPA making substantive errors that could have been identified and addressed before publication of the Proposed Rule. For example, EPA's selection of reference values for the four PFAS for which it is now issuing a preliminary regulatory determination contains important technical errors, including reliance on standards or studies that have been discredited and fail to account for numerous uncertainty factors. The proposed NPDWR also contains a math error in calculating the HBWC for PFHxS that resulted in EPA proposing an HBWC of 9 ppt instead of 10 ppt.

Finally, EPA also violated the SDWA when it did not consider any alternatives for the HI-MCL itself, or for the HBWCs that underpin it. Consideration of a reasonable range of

[3] SDWA §§ 1412(b)(3)(A)(i) and (g)

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St. Paul, MN 55144-1000
651 733 1110

alternatives is required by both the SDWA, and the Unfunded Mandates Reform Act.[4] It also meant that EPA did not adequately consider the point at which benefits expected to result from the proposed HI-MCL outweigh its costs, as required by the SDWA.

[4] SDWA § 1412(b)(3)(C)(i); 2 U.S.C. § 1535.

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II. LEGAL FRAMEWORK

The SDWA regulates public water systems by limiting the allowable level of substances in drinking water.[5] Prior to promulgating an MCLG or MCL, EPA must (1) identify substances for listing on the Contaminant Candidate List ("CCL"), and (2) determine which of those substances it will regulate under the SDWA.[6] At each step, EPA must follow specific procedures, consider information prescribed by the SDWA, and offer opportunities for public engagement.

When considering which substances from the CCL to regulate, the SDWA requires EPA to consider:

(1) Whether the substance may have an adverse effect on the health of persons;

(2) Whether the substance is known to occur, or there is a substantial likelihood that the substance will occur, in public water systems with a frequency and at levels of public health concern; and

(3) Whether the regulation of such substance presents a meaningful opportunity for health risk reduction for persons served by public water systems.[7]

The decision to regulate "is the beginning of the Agency's regulatory development process, not the end."[8] As EPA continues the analyses required by the SDWA, it may determine that a chemical does not meet the statutory criteria for finalizing a NPDWR.[9] If EPA determines the three statutory criteria are met, it may make a final determination that an NPDWR is needed. That determination to regulate triggers a 24-month statutory period to publish a proposed MCLG and NPDWR, and 18 months after that to promulgate a final standard.[10] Importantly, EPA may only promulgate an NPDWR for a substance that it has determined to regulate through the public notice and comment process.[11]

After determining to regulate a substance, EPA must set an MCLG for each identified substance at a level at which no known adverse health consequences will occur.[12] EPA must then set an MCL for each substance as close to the MCLG as is feasible.[13] Under the statute,

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[5] *City of Portland, Oregon v. EPA*, 507 F.3d 706 (2007).
[6] *Id.* § 300g-1(b)(1)(B).
[7] 42 U.S.C.A. § 300g-1(b)(1)(A).
[8] 85 Fed. Reg. 14098, 14100 (Mar. 10, 2020).
[9] *Id.*
[10] *Id.* § 300g-1(b)(1)(E)I.
[11] *See* 85 Fed. Reg. at 14100 ("The development of the CCL, regulatory determinations, and any subsequent rulemaking should be viewed as a progression where each process builds upon the previous process, including the collection of data and analyses conducted.").
[12] 42 U.S.C.A. § 300g–1(b)(4)(A).
[13] *Id.* § 300g–1(b)(4)(B).

"feasible" means "feasible with the use of the best technology, treatment techniques and other means which the Administrator finds ... are available (taking cost into consideration)."[14]

The SDWA requires that, when undertaking this process, EPA base its decisions on the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices, and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data).[15] The legislative history of the 1996 SDWA Amendments makes clear that Congress intended to ensure that drinking water standards regulations promulgated under the SDWA are meaningful and science-based:

> Our intent was simple. Drinking water standards should not be set just because they are technologically feasible as they are under current law; they must also be justifiable. If we are going to demand that our states, counties and towns spend billions of dollars to comply with new chlorine standards, for example, at the very least, we owe them the assurance that these are dollars well spent. [16]

III. FACTUAL BACKGROUND

a. EPA Has a Clearly Established Process to Set a NPDWR

The process for setting an MCL begins with a determination of which chemicals should be considered for regulation. As discussed above, under the SDWA, EPA is required to publish a list of chemicals (the CCL) that are currently not subject to any proposed or promulgated NDPWRs but are known or anticipated to occur in public water systems. SDWA §1412(b)(1)(B)(i). EPA must publish this list every five years. The list is used to identify priority chemicals for regulatory decision making and information collection.

During the regulatory determination process, EPA selects a minimum of five chemicals from the CCL to evaluate for regulation.[17] Based on the criteria in § 1412(b)(1)(A)(i)-(iii), EPA must make a regulatory determination for whether the chemical ought to be regulated under the SDWA. Once EPA makes a determination to regulate the chemical, EPA must then propose an MCLG and MCL or treatment technique.

The MCLG is the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on human health would occur, allowing an adequate margin of

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[14] *Id.* § 300g–1(b)(4)(D).
[15] *Id.* at § 300g-1(b)(3)(A).
[16] Congressional Record Vol. 141, No. 189, Nov. 29, 1995; S177723; Statement of Sen. Kempthorne. *See also* Congressional Record Vol. 140, No. 62, May 18, 1994, S55929; Statement of Sen. Breaux ("…only contaminants which present a significant threat to public health will be regulated. EPA will also have to base its analysis on sound science and risk assessment when determining whether or not a contaminant poses a significant enough threat to merit regulation.").
[17] SDWA § 1412(b)(1)(B)(ii).

safety.[18] MCLGs are not enforceable but they are meant to guide public health goals. MCLGs do not take into consideration the limits of detection and treatment technology effectiveness; therefore, they are sometimes set at levels that water systems cannot meet. The way EPA determines MCLGs depends on the type of contaminant targeted for regulation. All microbial contaminants have an MCLG of zero because even one microbial contaminant can cause adverse health effects. The MCLG is also set at zero for chemicals where there is no dose at which the chemical is considered safe, including some chemicals that may cause cancer. Finally, for chemicals that are non-carcinogens but can cause adverse non-cancer health effects, the MCLG is based on a reference dose.[19]

A reference dose (RfD) is defined as an estimate of human daily exposure that is likely to be without an appreciable risk of adverse effects during a lifetime.[20] RfDs are derived using a point of departure (POD). The POD is a dose that represents the low or no effect level derived from dose-response relationships in experimental or observational studies.[21] The most common PODs used to derive RfDs are the no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or statistical benchmark dose (BMD). The BMD, currently EPA's preferred POD, is the dose or concentration that produces a predetermined change in the response rate of an adverse effect.[22] In other words, the BMD is the minimum dose expected to produce a low-level health impact. EPA takes the POD (typically the BMD) and divides that number by uncertainty factors, which are used to account for potential differences between the experimental data and real life (such as the existence of sensitive populations or lack of information). The RfD is then multiplied by body weight and divided by expected daily water consumption to provide a Drinking Water Equivalent Level (DWEL). The DWEL is then multiplied by the relative source contribution (also called the RSC), which is the portion of the total exposure that comes from the ingestion of water. The value at the end of those calculations is the MCLG.

EPA often uses several types of modeling to extrapolate from known data to support risk analyses. Physiologically Based Pharmacokinetic (PBPK) models are mathematical models that can be used to predict absorption, distribution, metabolism, and excretion (ADME) of substances in humans or animal species. Models are built using compartments that correspond to different tissues in the body and describe the relationship between the external exposure dose and the internal plasma or tissue concentration of a compound over a period of time.

Once the MCLG is calculated, EPA then crafts an enforceable standard. Typically, and at issue here, that standard is the MCL. The MCL is the maximum amount of a chemical allowed in water delivered to any user of a public water system. MCLs are set as close to the

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[18] *Id.* § 1412(b)(4)(A).
[19] *See* https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants.
[20] *See* https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system
[21] *See* EPA's IRIS Program Glossary: https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&glossaryName=IRIS%20Glossary
[22] *See* https://www.epa.gov/sites/default/files/2015-01/documents/benchmark_dose_guidance.pdf at 6.

MCLG as feasible. Feasible here means taking into consideration cost and the technical limitations of available treatments.

EPA must submit its draft MCLG and MCL for technical peer review to EPA's Science Advisory Board before they are proposed as regulations.[23]

b. History of this Rulemaking Process

EPA began the process of setting this NPDWR in March 2020, when EPA solicited public comment on the preliminary regulatory determinations for contaminants on the fourth CCL. This publication included a preliminary determination to regulate PFOA and PFOS in drinking water. The following year, in March 2021, EPA published its final determination to regulate PFOA and PFOS.[24] In November 2021, EPA requested feedback from the Science Advisory Board (SAB) [25] on four draft documents related to this rulemaking:

- *EPA's Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) (CASRN 335-67-1) in Drinking Water*
- *EPA's Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctane Sulfonic Acid (PFOS) (CASRN 1763-23-1) in Drinking Water*
- *EPA's Analysis of Cardiovascular Disease Risk Reduction as a Result of Reduced PFOA and PFOS Exposure in Drinking Water*
- *Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)*

In the first two of these documents, EPA proposed an approach to calculating MCLGs for PFOA and PFOS based on an immune effects endpoint. In other words, EPA's proposed MCLGs were based on the exposure to PFOA and PFOS that the Agency determined was expected to result in negative impacts to immune system function. In its *Review of EPA's Analyses to Support EPA's National Primary Drinking Water Rulemaking for PFAS* (the "SAB Final Report"), the SAB strongly criticized many of EPA's approaches and requested EPA provide significant clarification. SAB's criticisms included:

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[23] *See* SDWA §1412(e).

[24] *See* 86 FR 12282.

[25] The Scientific Advisory Board (SAB) is a Federal Advisory Committee made up of subject matter experts. SAB reviews technical information used by EPA for quality and relevance. The board provides advice on EPA proposed regulations and on specific questions posed by the EPA Administrator. SAB's Drinking Water Committee formed a PFAS Review Panel of 16 experts on the scientific and technical aspects of PFAS. As subject matter experts, specifically chosen to provide guidance on the scientific aspects of EPA regulations, their recommendations and analysis should have been taken seriously by EPA when it received feedback on this proposed rule.

- "EPA should provide additional transparency and completeness in its evidence identification methodology, including development of a protocol with clear inclusion/exclusion criteria and study evaluation approaches."

- "Studies, particularly human studies, that were included in the 2016 health effects summary documents (HESDs) should be considered in the same manner as the more recent studies."

- "EPA needs to provide additional details and transparency for all quantitative modeling, including that used for CSF [cancer slope factor] development, toxicokinetic modeling, and benchmark dose modeling for POD derivation. It is essential that details of the Benchmark Dose (BMD) modeling that forms the basis of the PODs are transparently available for evaluation of the methods, approaches, and results."

- "EPA should provide a stronger and more transparent justification for the choice of benchmark responses (BMRs)"

When EPA ultimately published its proposed PFAS NPDWR in March 2023, EPA shifted from relying on the immune effects endpoint to cancer endpoints for PFOA and PFOS in the proposed NPDWR.

EPA also submitted to the SAB in November 2021 its *Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances* for SAB review which would, according to EPA, "inform development of the MCLGs and NPDWR **for PFOA and PFOS**." (emphasis added). This Draft Mixture Framework did not present an MCL framework for the four Hazard Index (HI) PFAS, nor did it set proposed health-based water concentrations (HBWCs) for the HI PFAS. In this draft document, EPA acknowledged that HBWCs "would need to be calculated in order to develop component HQs [hazard quotients] and an overall PFAS mixture HI," but made no such calculation. In other words, EPA never submitted draft HBWCs to SAB for review.[26]

In March 2023, EPA proposed this NPDWR regulating PFOS, PFOA, PFHxS, HFPO-DA, PFNA, and PFBS, including HBWCs for the HI PFAS.

IV. EPA's FLAWED SYSTEMATIC REVIEW UNDERMINES THE SOUNDNESS OF EPA'S ANALYSIS FOR ALL SIX SUBSTANCES

A proper systematic review of the relevant scientific literature is the foundation for the agency to reach scientifically sound conclusions. As described by EPA's IRIS Handbook, EPA must review the full body of available scientific information, identify the subset of that information that is the best available, explain the basis for that decision, and then analyze that

[26] Moreover, EPA "emphasized" to the SAB "that the draft mixtures document is not a regulation, does not impose legally binding requirements on EPA, states, tribes, or the regulated community, and might not apply to a particular situation based on the circumstances." (USEPA SAB 2023, p. 1-2.)

information to come to an ultimate conclusion (USEPA ORD 2022, EPA 2012). The agency cannot make its regulatory decision and selectively cite scientific studies that support the decision while ignoring equally valid but contradictory scientific information. For two of the six substances—PFHxS and PFNA—EPA did not conduct a systematic review and instead relied on the conclusions of the Agency for Toxic Substances and Disease Registry (ATSDR). For the remaining four substances, EPA has selectively cited studies to support its decision.

In reviewing EPA's draft documents, EPA's own SAB and numerous other commenters pointed out several major failings, including that EPA failed to publish a pre-defined review protocol. The SAB noted

> Significant concerns that the reviews for PFOA and PFOS do not appear to have established a predefined protocol. The lack of a protocol led to a lack of clarity across each of the major systematic review steps for both chemicals and was seen as a major deficiency of the reviews. (USEPA SAB 2022, p. 3)

For example, the SAB "found that the inclusion and exclusion of epidemiologic and animal studies was inconsistent across endpoints, leading to confusion about the criteria being used." Similarly, the SAB found that EPA's literature review ignored studies that should have been considered, including some of those EPA relied on for its 2016 health advisory levels (HALs) for PFOA and PFOS, and some of which may have changed EPA's conclusions regarding the potential hazard of exposure to PFOA and PFOS at low levels.[27] Indeed, the SAB concluded that "[t]he rationale for not considering studies, particularly human studies, that were included in the [2016 HALs] is not clear or supportable. There is no reason to conclude that the earlier studies are less relevant or of lesser quality than the newer studies." (USEPA SAB 2022, p. 5; *see also* p. 14-15.) The SAB also "concluded that the decision to exclude literature published within the timeframe of the development of the 2016 health effects support document in the current literature search was unjustified." (USEPA SAB 2022, p. 5)

EPA's lack of a review protocol raises serious questions about the integrity of EPA's systematic review. It precludes clarity into how EPA decided which studies to review, how to weigh the studies it did review and, ultimately, how it decided which studies would form the foundation for its proposed levels. EPA also did not follow the same protocol across the multiple reviews it conducted, another major failure that the SAB identified (EPA SAB 2022).

EPA has not sufficiently addressed these and the SAB's other foundational concerns in the Proposed Rule. Instead, and as discussed below, EPA continues to pick and choose scientific studies based on unknown and non-transparent conditions (violating EPA's own procedures on conducting systematic reviews) which appears to have biased EPA's review to favor studies that support the low regulatory levels EPA has proposed and omit discussion of studies that do not

[27] During review hearings, SAB Board members expressed significant concern about the draft approach documents, with at least one noting they do not "represent the state of practice" around information gathering. Another Board member said there were "significant problems that really can't be fixed," and said he would reject the papers if they were being peer-reviewed for publication purposes.

support those levels. In short, EPA's systematic review was not grounded in "sound and objective scientific practices," a flaw it has not remedied.[28] These classification and review protocol errors are identified throughout the comments herein as they relate to specific topics in the rulemaking.

a. EPA's systematic review methods continue to lack transparency and consistency in evaluation of study quality.

EPA's methodology for study identification and inclusion lacks integrity and transparency. In response to SAB comments, EPA expanded its assessment to include epidemiological and animal studies identified in EPA's 2016 Health Effects Support Documents for PFOA and PFOS. However, it is unclear whether these studies were incorporated into the literature screening process applied to other citations or included based on subjective judgement. It is also unclear why 15 studies identified in the 2016 Health Effects Support Documents were not accounted for in the review.[29] EPA also implemented the use of SWIFT-Review[30] for a portion of study identification, which has yet to be validated for this purpose. This may have resulted in inadvertently excluding relevant studies. Additional study types that may have been inappropriately excluded from the review according to the reported methodology include erratums, corrections, and corrigendums. This issue is discussed in detail in Appendix A, *Detailed Technical Comments on the Non-cancer Reference Doses (RFDs) and Economic Analysis for PFOA and PFOS.*

Increased transparency in reporting is needed. The SAB recommended changes to the evidence identification step of the PFOA and PFOS systematic reviews, including providing a more transparent reporting of output. EPA responded by providing a publicly accessible interactive flow diagram. That diagram, however, does not give insight into the specific Population, Exposure, Comparator, and Outcomes (PECO) criteria that EPA decided certain studies did not meet. PECO criteria define the objectives of the review and inform the "inclusion and exclusion criteria for a review, as well as facilitating the interpretation of the directness of the findings based on how well the actual research findings represent the original question."(Morgan et al. 2018) EPA's failure to identify the PECO criteria that excluded studies did not meet precludes independent appraisal of why those studies were excluded. This issue is discussed in detail in Appendix A.

EPA did not refine study quality criteria to the topic per standard IRIS systematic review guidelines. To evaluate study quality and risk of bias in the PFOA and PFOS assessments, EPA said it used its IRIS assessment tool. EPA IRIS Handbook (USEPA ORD 2022) guidance states that to evaluate studies, chemical-, outcome- or exposure-specific considerations should be developed as needed to identify issues expected to result in critical biases and that should reduce the confidence rating of a study (ORD Handbook, p. 4-2).

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[28] 42 U.S.C. § 300g-1(i).

[29] *See* Tables A-6 and A-7 of the 2016 HESD summary tables and Interactive Reference Flow Diagram for PFOA & PFOS | Tableau Public.

[30] "SWIFT" is an acronym for Sciome Workbench for Interactive computer-Facilitated Text-mining. It is software that uses statistical modeling and machine learning to conduct automated document prioritization. *See* https://www.epa.gov/sites/default/files/2018-02/documents/d-4_swift_demo_abstract_-_nas_2018.pdf.

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651 733 1110

Contrary to EPA's own guidance, the only apparent modification EPA made to its IRIS assessment tool for study evaluation in this rulemaking was to the exposure assessment domain criteria. This modification is insufficient in that it fails to account for critical issues that could render studies unreliable for dose-response assessment – a critical part of EPA's analysis here. Critical omissions include lack of consideration of factors that are specific to exposure, outcome ascertainment, confounding factors that affect the association of interest, and sensitivity issues such as external validity and study construct. This issue is discussed in detail in Appendix A.

The study quality evaluation protocol used in EPA's assessments of PFOA and PFOS generated inconsistent study confidence ratings. EPA did not correctly evaluate and rate studies for reverse causality, which is a type of bias where the health outcome affects physiological factors that moderate exposure measurement. (Andersen et al. 2021). If reverse causality is not accounted for in a study, the observed effects may not result from the exposure and could be mischaracterized as adverse. Although guidance provided for PFAS-Specific Exposure Measures states that concern for potential bias due to reverse causality with no direct evidence should be rated as 'deficient,' EPA did not consistently rate study design aspects that may impact reverse causality in the body of evidence it considered. In a review of cross-sectional studies that fall into the category of "potential reverse causality," the Exposure Methods ratings were inconsistent and generally rated as adequate or good rather than deficient. Further, subjectivity introduced by the Guidance allows reviewers to increase confidence in studies reporting an effect if its confidence was reduced due to sensitivity only. How and when this was applied by EPA in its review here is not readily transparent. Lastly, the lack of transparency and objectivity in the study quality evaluation guidance also contributes vague overall study confidence ratings that do not appear to take the individual domain metric ratings into consideration. This issue is discussed in detail in Appendix A.

EPA's inconsistent systematic review methods violated its own guidance and resulted in exclusion of relevant studies and reliance on low-confidence studies that may be unsuitable for regulatory decision-making.

V. EPA'S PROPOSED STANDARDS FOR PFHxS, PFBA, PFNA, AND HFPO-DA ARE PROCEDURALLY AND TECHNICALLY FLAWED

a. The SDWA Does Not Permit Publication of a Preliminary Determination to Regulate at the Same Time as a Proposed NPDWR.

EPA issued its proposed NPDWRs for PFHxS, PFBA, PFNA, and HFPO-DA (the HI MCL) without adhering to the Congressionally prescribed procedure for setting MCLs under the SDWA. The Proposed Rule is therefore arbitrary and capricious and violates the SDWA. *See Chevron USA Inc. v. Natural Resources Defense Council*, 467 U.S. 837 (1984) ("[i]f the intent of Congress is clear… the agency… must give effect to the unambiguously expressed intent of Congress").

The SDWA requires EPA to make a "preliminary determination" to regulate a substance and provide notice and an opportunity for public comment on that preliminary determination.[31] The independent step of issuing notice of a preliminary determination reflects an intentional, discrete step in the regulatory process sanctioned by Congress. Once EPA has solicited and considered comment on that preliminary determination, EPA can make a final "determination to regulate." This two-step process is clearly reflected in the language of 42 USC § 300g-1 (b)(1)(B)(ii)(I)-(b)(1)(B)(ii)(III). Section (b)(1)(B)(ii)(I) states a "determination" to regulate a substance on the CCL "shall" only be issued "after notice of the preliminary determination and opportunity for public comment."

While the SDWA allows EPA to publish a proposed regulation "concurrent with the determination to regulate," *id.* at § (b)(1)(E), it does not permit the EPA to skip the "preliminary determination to regulate" step, as it did here. To the contrary, the SDWA distinguishes between the process of issuing a "preliminary determination" that is subject to public comment (i.e., a proposed rule) and the "mak[ing of]" a final determination (i.e., a final rule). *Id.* Similarly, SDWA Section (b)(1)(B)(ii)(2) lists factors that must support the final "determination," not the "preliminary determination." Further, section (b)(1)(B)(ii)(III) states the same "determination" can be made even if the substance does not appear on the CCL, as required by (b)(1)(B)(ii)(I). These distinctions confirm that Congress intended a "determination to regulate" under the SDWA to mean a final determination and not a preliminary determination. Stated differently, EPA has the authority to promulgate a final decision to regulate in the same rulemaking as a proposal for additional drinking water standards. However, the SDWA does not give EPA the authority to issue a proposed NPDWR and a preliminary regulatory determination at the same time – but this is precisely what EPA did in this rulemaking.

EPA has recognized that "[t]he development of the CCL, regulatory determinations, and any subsequent rulemaking should be viewed as a progression where each process builds upon the previous process, including the collection of data and analyses conducted."[32] EPA's truncated regulatory determination in this case minimizes time for public-review and violates the plain language of the SDWA.

b. EPA Has No Meaningful or Sound Occurrence Data for the HI MCL Substances

The SDWA requires that before it can promulgate an NPDWR, EPA must determine that, among other things, the substance is "known to occur or there is substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern."[33] Alleged co-occurrence of the four HI-PFAS is the basis for EPA's HI MCL. EPA's justification for the HI approach depends in part on the four HI-PFAS substances most frequently

[31] 42 USC § 300g-1(b)(1)(B)(ii)(I).
[32] 85 Fed. Reg. at 14100.
[33] SDWA §1412(b)(1)(A)(i) and (ii).

co-occurring as a mixture, rather than individually.[34] But EPA's analysis does not demonstrate that there is substantial likelihood that the four HI-PFAS co-occur *with each other*. Instead, EPA analyzed where any of the four HI-PFAS individual and either PFOA or PFOS co-occur.

Exhibit 6-3 summarizes co-occurrence of combinations of PFAS in the UCMR3 data. The combination of the four HI-PFAS is not listed.[35] Importantly, **it appears there were no records in the UCMR3 data of the four HI-PFAS co-occurring**.

Section 6 of the Background Support Document (USEPA 2023h) presents analyses of the co-occurrence rate of PFOA, PFOS and any of the four HI-PFAS, but does not specifically address co-occurrence of the four HI-PFAS proposed for regulation as a mixture using the HI approach. The analyses, discussion, and Exhibits 6-2, 6-4 and 6-5 also focus on co-occurrence of PFOA and PFOS with the four HI-PFAS, rather than co-occurrence of the four HI-PFAS with each other. That analysis is irrelevant to the decision to regulate the four HI-PFAS as a mixture, since neither PFOA nor PFOS is included in the group to be regulated as a mixture.

There are also significant issues with the sampling on which EPA relies that call into question the reliability of the data. Data are evaluated at the sample and PWS level, though it is not clear if sample counts represent unique locations or include multiple samples from the same location. Evaluating multiple samples from the same location within a system could overestimate the frequency of co-occurrence. The co-occurrence data presented at the system level for detection of any HI-PFAS show wide variability among states (USEPA 2023h, p. 197). And the states with the most systems tested, Michigan and Ohio, show much lower frequency of detection of any HI-PFAS (i.e., 6.5 percent and 3.9 percent respectively) than states with fewer system tested (USEPA 2023h, p. 197). This observation suggests that data from states with fewer systems sampled may not be representative of occurrence in those states.

EPA's failure to include all states' data violates the fundamental scientific principle that one cannot selectively use data to generate a preferred outcome. The data set used covers 11 states and is described as "limited to samples from non-targeted monitoring efforts where at least one HI PFAS was analyzed and PFOS and PFOA were analyzed sufficiently to determine whether one was present." Although the state of Alabama analyzed for all four HI-PFAS and PFOA and PFOS, data from Alabama are not presented and no explanation for the omission is provided (USEPA 2023h, p. 11). Sampling efforts are ongoing in 6 of the 11 states presented (Illinois, Massachusetts, Michigan, New Hampshire, New Jersey, and Vermont); for these states, data collected after May 2021 are available but are not used by EPA for the co-occurrence analysis (USEPA 2023h, p. 11). EPA's PFAS Analytical Tools webpage

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[34] For PFHxS, the median sample concentrations range from 2.14 to 11.3 ppt. The HRL for this substance is 9.0 ppt. For HFPO-DA, the median sample concentrations range from 1.7 to 9.7 ppt. The HRL for this substance is 10.0 ppt. For PFNA, the median sample concentrations range from 2.1 to 7.46 ppt. The HRL for this substance is 10.0 ppt. For PFBS, the median sample concentrations range from 1.99 to 7.26 ppt. The HRL for this substance is 2000.0 ppt. The maximum sample did not even exceed the HRL for PFBS.

[35] Many of the combinations included in Exhibit 6-3 indicate PFHpA is detected, which is irrelevant to the proposed regulation of the four HI-PFAS as a mixture, given that PFHpA is not one of the four HI-PFAS.

(https://echo.epa.gov/trends/pfas-tools) lists data for several additional states (e.g., Oregon, Rhode Island) also not considered in EPA's co-occurrence analysis.

EPA also uses different data sets for the evaluations of co-occurrence and of affected systems, creating a fundamental disconnect such that one analysis cannot be used to inform the other. For example, in estimating the number of systems affected by the proposed MCLs, EPA uses an occurrence model that incorporates data from 17 states (USEPA 2023f, p. 18678). The 17 states include Arizona, California, Delaware, Georgia, Maine, and Pennsylvania (Cadwallader 2022). For these states, EPA considers the sampling "targeted" and omits them from the co-occurrence evaluation (USEPA 2023h, p. 11). Conversely, data from the state of Colorado are included in the co-occurrence evaluation but are not included in this modeling of affected systems. Different and unstated rationale for including state data for these two purposes suggest that those criteria were arbitrary.

EPA failed to include more recent samples that would improve the representativeness of the analysis. Specifically, EPA's analysis of co-occurrence does not include samples collected after May 2021 and uses different data sets than are used for EPA's occurrence modeling. The data set used to evaluate co-occurrence is limited to data available on public state websites through August 2021, which was limited to samples collected through May 2021.

c. EPA's Interpretation of the Data It Uses as the Basis of the MCLGs and MCLs is Flawed and Has Not Undergone Peer Review in Violation of the SDWA

The HI MCL also violates the SDWA's mandate that EPA solicit peer review from its SAB prior to issuing a proposed MCL.[36] In 2021, EPA provided SAB with its *Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)* (USEPA 2021c). That document was an external peer review draft, which was not revised and published for public review until March 2023 (USEPA 2023e). This means that the Proposed Rule employs techniques regarding data requirements for mixture Health-Based Water Concentrations" but never sets out proposed HBWCs for the HI PFAS or for EPA's currently proposed HI-based MCL for those substances. In the mixtures framework document, EPA itself said that "because there are no EPA-published HBWCs (e.g., Health Advisories, MCLGs) at this time for other PFAS with federal or state assessments/RfVs (e.g., PFBS (EPA), GenX chemicals (EPA), PFHxS (ATSDR), and PFNA (ATSDR)) or chemicals categorized under PFAS 1 or PFAS 2, these values would need to be calculated in order to develop component HQs and an overall PFAS mixture HI."[37] In other words, EPA expressly did not submit its "mixtures" document as a potential MCL for public review prior to the publication of the Proposed Rule. Indeed, EPA proposed the HBWCs only after SAB reviewed its proposed mixtures framework. As a result, neither the HBWCs that form the basis for the HI-MC, nor the

[36] SDWA §§ 1412(b)(3)(A)(i) and (g).
[37] Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS), 35 (November 2021)

HI-MCL itself have been properly submitted to the SAB or peer-reviewed as required by the SDWA.[38]

The lack of peer review and submission to the SAB is significant. As noted above, it expressly violates the SDWA. The lack of peer review has even resulted in EPA making basic errors that would have been identified during the peer review process. For example, EPA makes an arithmetic error in its derivation of the HBWC for PFHxS (USEPA 2023l). Using EPA's inputs in Table 4 of the Hazard Index document (USEPA 2023l), the HBWC would be 12 ppt, and applying one significant figure, the final HWBC should be 10 ppt, not 9 ppt. This error must be corrected. This error also signals an absence of even basic quality assurance. All of EPA's calculations require comprehensive peer review before the NPDWR is finalized, and EPA must submit its proposed MCLG and NPDWR for the HI PFAS, including the HBWCs, to SAB for comment.

i. EPA's selection of reference values for the four PFAS for which it seeks to issue preliminary regulatory determinations (PFHxS, HFPO-DA, PFNA, and PFBS) is erroneous.

Putting aside EPA's violations of SDWA-mandated processes for public notice and peer review, the proposed standards for the HI PFAS are not consistent with EPA processes designed to ensure reliability and sound scientific practices. EPA relies on ATSDR for the PFHxS and PFNA reference values, and there is no evidence that EPA conducted an independent systematic review of the evidence base or assessed study quality for these compounds as recommended by the IRIS Handbook. Furthermore, because these four PFAS are considered together under the HI, EPA has not sufficiently discussed, as recommended in EPA's own RfD process recommendations (USEPA 2002), the implications of the collective uncertainty underlying all four reference values.

PFHxS. EPA's proposed reference value of 0.000002 mg/kg/day for PFHxS is based on ATSDR's (2021) Minimum Risk Level (MRL)[39], which is derived from Butenhoff et al. (2009). Butenhoff et al. (2009) observed that adult male rats exposed to PFHxS at 3 mg/kg-day exhibited thyroid follicular cell hyperplasia that may have been due to increased liver hypertrophy and induction of liver enzymes, which could in turn impact thyroid hormone metabolism. However, the authors did not measure thyroid hormones; therefore, the clinical significance of thyroid cell hyperplasia is unclear. Furthermore, in contrast to Butenhoff et al.'s (2009) findings, ATSDR (2021) concluded that liver effects in mice after exposure to PFHxS were not adverse. Had EPA evaluated Butenhoff et al. (2009) per systematic review guidance, that lack of adversity may have been identified and the study excluded.

In contrast, Chang et al. (2018), did measure thyroid stimulating hormone (TSH), and observed changes in neither TSH levels nor thyroid histopathology in mice at doses up to 3 mg/kg-day. Had EPA conducted an appropriate systematic review and assessed study quality per its IRIS Handbook, it may have considered this study, which is more reliable than Butenhoff et

[38] *See* SDWA § 1412(g).
[39] An MRL is a screening value used to identify potential environmental risk and is not a regulatory standard.

al. (2009) because it measured relevant endpoints. In other words, if EPA had conducted a truly independent systematic review of PFHxS toxicity studies, rather than rely on ATSDR's (2021) evaluation, it likely would have selected a different critical effect for PFHxS and therefore derived a different HBWC.

EPA also failed to comply with its guidance related to the application of uncertainty factors (USEPA 2002; USEPA ORD 2022). To derive the reference value for PFHxS, EPA applied a 10-fold uncertainty factor to ATSDR's MRL of 0.00002 mg/kg/day to extrapolate from subchronic to chronic exposure. This 10-fold uncertainty factor is in addition to the 30-fold uncertainty factor and 10-fold modifying factor that ATSDR applied its derivation of the MRL. The resultant combined uncertainty factor is 3,000, which highlights the substantial uncertainty of the evidence for the reference value. EPA's IRIS Handbook and EPA's recommendations on the RfD process (USEPA 2002) recommends that any composite uncertainty factor greater than 3,000 represents "excessive uncertainty" and should not be relied upon.

HFPO-DA. EPA's (2021b) selection of an RfD of 0.000003 mg/kg/day for HFPO-DA is likewise inconsistent with sound scientific process and guidance. Not only is the study it selected unpublished (DuPont 2010a), but EPA also selected a critical effect of "constellation of liver lesions." The study, which was a reproductive and developmental study in mice, indicated that the various hepatic effects were not consistently observed in male and female mice. However, EPA inappropriately combined these effects in order to consider it as a single critical effect, in violation of its own guidance. The resultant no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values are 0.1 mg/kg-day and 0.5 mg/kg-day, respectively. EPA's IRIS Handbook states that common endpoints are "the same specific outcome measurement, not just any endpoint in a common target organ" indicating that to be combined, the observed effects have to be the same.

Combining the observed liver effects is inappropriate because some of the liver effects considered in the "critical effect" were not clearly adverse; the effects were either adaptive changes or unclear in their adversity (e.g., hepatocellular hypertrophy, enlargement of liver cells, changes in cytoplasm of liver cells) (USEPA 2021b). These effects could occur through different modes of action or were not actually adverse effects (Hall et al. 2012), which makes combining them inappropriate per EPA's IRIS Handbook. Because differences between exposed and unexposed animals were only observed when all observed liver effects were combined, EPA could not have established a NOAEL and LOAEL based on any individual effect.

EPA also violated proper systematic review processes when it inexplicably disregarded other studies that did not find such a "constellation" of hepatic effects in rodents exposed to HFPO-DA. For instance, DuPont (2010b) reported a NOAEL of 0.5 mg/kg-day in a separate unpublished mouse study, rather than a NOAEL of 0.1 mg/kg-day applied by EPA. DuPont (2010b) was unable to establish a dose-response in female mice in this study (USEPA 2021b). Similarly, hepatic effects were not observed at such low doses in a DuPont chronic rat study (DuPont 2013). These scientifically flawed practices result in a critically flawed RfD value. EPA (2021b) itself demonstrates its uncertainty in the overall evidence base with its RfD by applying an uncertainty factor of 3,000. In other words, the significant uncertainty inherent in EPA's RfD highlights its unsuitability as the basis of a regulatory value. As noted for PFHxS, an

uncertainty factor of 3,000 is the maximum that could be considered as the basis of reference value according to EPA's IRIS Handbook and USEPA (2002).

PFNA. EPA's reference value for PFNA is based on ATSDR's (2021) intermediate MRL of 0.000003 mg/kg-day and is overly conservative as a result of EPA's improper data review processes. ATSDR's (2021) MRL is derived from Das et al. (2015), in which mouse pups exposed to PFNA at 3 mg/kg-day were observed to have decreased body weight and delays in development. Importantly, most of the PFNA-induced effects, including developmental effects, are directly linked to the PPARα pathway (Rosen et al. 2017; Wolf et al. 2010). As demonstrated in Wolf et al. (2010), there is a clear association between PPARα and delayed eye opening and decreased body weight in exposed mouse pups. Because the PPARα has limited relevance to humans, the selection of Das et al. (2015) as the primary basis of the MRL is improper.

Additionally, ATSDR's (2021) application of an uncertainty factor of 3 for interspecies differences was overly conservative and in violation of EPA's own guidance. As previously discussed, the limited application of PPARα to humans indicates that mice are the more sensitive species to the observed effects in Das et al. (2015) (i.e., PPARα is less active in humans than it is in mice), such that an interspecies uncertainty factor of 1 would be consistent with guidance in EPA's IRIS handbook that allows for lower uncertainty factors considering differences in cross-species toxicokinetics and toxicodynamics are accounted for. Prior to the application of an interspecies uncertainty factor, the MRL was amply protective of human health. EPA (USEPA 2023l) also acknowledges that both ATSDR and EPA are reassessing the toxicity of PFNA via a revised MRL or new IRIS assessment, respectively. This further highlights the uncertainty in the reference value and lack of basis in the most up-to-date and systematically reviewed science.

Finally, another example of poor quality assurance in this proposed rulemaking, is in Section III.B.3 of the Federal Register Notice (USEPA 2023f), where EPA incorrectly refers to the HBWC for PFNA as both 100 ppt and 10.0 ppt.

PFBS. EPA relies on its RfD of 0.0003 mg/kg/day (USEPA 2021a) as the basis of the HBWC. EPA again failed to follow processes that would have ensured its RfD was properly supported. EPA relied on Feng et al. (2017), in which mouse pups exposed to PFBS were observed to have decreased serum thyroid hormone (thyroxine [T4]) levels compared to unexposed pups. The study's authors, however, expressed uncertainty as to whether the decreased serum T4 levels were toxicologically relevant; they further state that the decreased levels were not specifically related to development (Feng et al. 2017). A proper systematic review would have taken that uncertainty into account.

The selection of thyroid hormone changes in mice as the critical effect by EPA (USEPA 2021a) in and of itself is overly conservative but is further compounded by EPA's application of an uncertainty factor of 3 for interspecies differences. Multiple studies have shown that rodents are more sensitive to alterations in thyroid hormone compared to humans (NRC 2005; Bartsch et al. 2018; Parker and York 2014; Brown-Grant 1963). In other words, without the uncertainty factor, EPA's RfD may be protective of human health, but is made unduly conservative with it.

EPA also violates its own guidance when it does not discuss the critical implications of the collective application of the uncertainty factors when considering these four PFAS together in the HI. The uncertainty factors when compared across PFHxS, HFPO-DA, PFNA, and PFBS are 3,000, 3,000, 300, and 300, respectively. Though the uncertainty factors across the four PFAS may not be purely multiplicative, EPA's own guidance (USEPA 2002) clearly recommends "limiting the total UF applied for any particular chemical to no more than 3000 and avoiding the derivation of a reference value that involves application of the full 10-fold UF in four or more areas of extrapolation" because uncertainty in four or five areas "may also indicate that the database is insufficient to derive a reference value." As stated previously, USEPA (2002) recommends "justification for the individual factors selected for each chemical," guidance that should also apply when considering uncertainty across multiple reference values under the HI. Taken together, in proposing the HI, EPA has failed to follow its own guidance, which recommends that clear justification for the uncertainty factors, consideration of areas of overlapping uncertainty, and implications for the reliability of the reference values be provided.

ii. EPA's relative source contribution value for PFHxS, HFPO-DA, PFNS, and PFBS is not based on the best available science

The relative source contribution (RSC) term used to assign exposure contribution from drinking water is a key element of MCL derivation. The smaller the RSC, the more protective the drinking water regulatory limit is in order to account for other potential sources of exposure. EPA chose the 20 percent default RSC value for HFPO-DA, PFHxS, PFNA and PFBS to develop the HBWCs used in the HI-MCLG, citing insufficient data to calculate a substance-specific RSC. EPA guidance provides that the 20 percent default should only be used when data to characterize other exposure sources is insufficient(c).

In its comments on the PFOA and PFOS MCLG derivation, the SAB suggested EPA more clearly justify the 20 percent default value, yet in the documentation for PFOA, PFOS and PFAS mixture, EPA continues to stress that data are not sufficient to characterize exposures for individual substances (USEPA 2023j). While EPA states there are not sufficient data to calculate substance-specific RSC values for the various substances, the agency nonetheless presents several pages of scientific literature regarding substance occurrence in various media (e.g., dietary sources, indoor dust, soil, sediment) (USEPA 2023e, 2022a,b). The HFPO-DA RSC development documentation cites 52 studies, 14 "gray literature sources" and 3 additional references. For PFBS, 183 peer-reviewed and grey literature references were identified that characterized occurrence in drinking water, groundwater, surface water, dietary sources, consumer products, indoor dust, indoor air, ambient air, and soil (USEPA 2022b). For PFNA and PFHxS, 176 and 177 peer-reviewed studies, respectively, and at least 12 grey literature sources included occurrence data for ambient air, indoor air, consumer products, dust, food, groundwater, drinking water, surface water, sediment, soil, and human blood/serum/urine (USEPA 2023e). There is no clear explanation for why the numerous studies presented do not provide sufficient data to calculate substance-specific RSCs, as recommended by EPA's own guidance.

In addition to the studies presented by EPA for each of the four PFAS, other studies have directly characterized exposure sources for various PFAS. Ericson et al. (2008) determined that

drinking water exposure to PFCs (including PFNA and PFHxS) may be as important as the dietary pathway. Vestergren et al. (2012) found that drinking water intake contributed 36–53 percent of the total exposure for PFHxS, PFHpA, and PFHxA.

Given the number of studies and breadth of exposure sources evaluated, inferences can reasonably be made about exposure from various sources using occurrence and concentration data presented. When the currently available data cited by EPA and the studies that directly show water is a primary contributor to exposure for each of the four HI-PFAS are considered collectively, there is likely sufficient support for chemical-specific RSC terms, similar to the chemical-specific values developed for PFOA by several states (Lindborg et al. 2022). EPA suggests that there were insufficient US-based studies, but 47, 50, and 59 of the studies presented for PFNA, PFHxS, and PFBS, respectively, were US-based (USEPA 2023e, 2022b). There is also no evidence that EPA evaluated the RSC based on these studies. Rather, EPA presented a summarized table of the concentration ranges, with no indication or evaluation of how the study findings relate to exposure contribution. This directly contradicts the intended application of EPA's Exposure Decision Tree methodology (USEPA 2000b).

d. EPA Failed to Consider Any Alternatives to the HI-MCL, in Violation of SDWA §1412 (b)(3)(C)(i)

EPA must consider a range of alternative MCLs but did not do so here in violation of the SDWA and the Unfunded Mandates Reform Act (UMRA). SDWA §1412(b)(3)(C)(i) requires EPA to consider alternative MCLs. In promulgating other NPDWRs after the 1996 SDWA Amendments, EPA has routinely considered at least four alternatives.[40] Additionally, the Unfunded Mandates Reform Act of 1995 requires EPA to consider alternative MCLs.[41] The Unfunded Mandates Reform Act of 1995 (UMRA).[42] UMRA requires any agency promulgating a rule with "Federal mandates" that may result in expenditures to State, local, and tribal governments, in the aggregate, or to the private sector, of $100 million or more in any one year to "identify and consider a reasonable number of regulatory alternatives and from those alternatives select the least costly, most cost-effective or least burdensome alternative that achieves the objectives of the rule."[43]

Here, EPA did not consider a "reasonable number of regulatory alternatives." For PFHxS, HFPO-DA and its ammonium salts, PFNA, and PFBS, EPA considered a single HBWC, which effectively functions as substance-specific MCL. Nor did EPA consider any alternatives to the HI-MCL of 1.0 itself. Clearly, the analysis of only one regulatory option is not a

[40] *See* National Primary Drinking Water Regulations: Lead and Copper Rule Revisions, 84 Fed. Reg. 61684 (2019) (considering four alternative regulatory options); National Primary Drinking Water Regulations; Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring 66 Fed. Reg. 6976 (2001) (considering four alternative MCL levels); National Primary Drinking Water Regulations; Radon-222, 60 Fed. Reg. 59246 (1999) (considering seven alternative MCL levels).
[41] EPA identified that this rule is subject to the UMRA, *see* 88 Fed.Reg. 18733 (Mar. 29, 2023) ("This action contains a Federal mandate under the Unfunded Mandates Reform Act").
[42] 2 USC § 1535 (1995)
[43] Id.

consideration of "alternatives." The lack of alternatives considered for the PFAS covered in the Hazard Index violates both the SDWA and UMRA.

Not only is the failure to consider any alternatives to the HI-MCL itself a direct violation of the SDWA, it also led to EPA's failure to identify the level at which the costs of the HI-MCL justify the benefits. The HBWCs are purely health-based and should be calculated to have a margin of safety, similar to an MCLG. But EPA effectively set MCLs for these four substances at the HBWC without considering whether the same benefits could be achieved for lower costs because it did not consider any alternatives to the HBWCs as required by the SDWA.[44]

e. EPA's Unprecedented Hazard Index Approach Violates the SDWA and is Arbitrary

EPA's proposal to regulate drinking water concentrations for the HI PFAS using the so-called "general HI approach" is arbitrary, not based on sound scientific principles, and does not conform with long-standing risk assessment practices and toxicological principles detailed in EPA's human health risk assessment guidance (USEPA 1986, 1989, 2000b). Further, the use of the general HI approach is at odds with methods currently employed in some EPA regulatory programs, and the adoption of this approach for use in National Primary Drinking Water Regulations (NPDWR) would introduce conflicting outcomes depending on PFAS present and their relative concentrations.

Moreover, EPA's decision to regulate the HI substances as a mixture led to an inflated sense of the opportunity for risk reduction. In the section on this criterion, the only factors considered discussed the substances as a group. There was no analysis of how, individually, the substances presented a meaningful opportunity to reduce risk to the public (Section VII). This omission violates the requirements for regulating new substances under the SDWA.

i. The hazard index approach is not appropriate in the regulatory context

The use of the general HI approach as proposed by EPA is contingent on potential exposure information, compound toxicology, and an acceptable noncancer hazard. In short, the general HI method applies principles of human health risk assessment, but in an inherently flawed manner. The science of cumulative risk assessment of chemical mixtures has been the topic of research and policy making for decades, and as it pertains to PFAS, even EPA acknowledged that "there is currently no consensus on whether or how PFAS should be combined for risk assessment purposes" (USEPA 2023, p. 3) as also discussed in Section V.C of the proposed rule. Nonetheless, EPA arbitrarily employs the proposed general HI approach even though, by its own admission, it is not a consensus method and is contrary to EPA's long-standing guidance and policy related to the application of risk assessment of chemical mixtures.

The general HI method is intended for "screening level" assessments that determine the need for further evaluation, rather than the basis for an expensive and complex NPDWR. In no fewer than threeEPA risk assessment guidance documents, EPA refers to the general HI

[44] *See* SDWA §1412(b)(3)(C)(i).

approach as "screening level," including: EPA's *Guidelines for Health Risk Assessment of Mixtures* (USEPA 1986), *Risk Assessment Guidance for Superfund – Part A* (USEPA 1989), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (USEPA 2000a).

ii. The hazard index approach is based entirely on unscientific assumptions of dose additivity

EPA's proposed general HI method is inconsistent with long-standing policy and science regarding chemical hazard additivity. As described below, EPA has not established that the HI-PFAS share a mode of action (MoA) that is relevant for humans, which is required to regulate groups of chemicals.[45] MoA information is critical to grouping PFAS and "[o]nly those PFAS that affect the same target organ/tissue/system should be grouped and assessed for dose additive or response additive approaches."[46] This is consistent with long-standing EPA guidance stating that multi-chemical cumulative non-cancer hazards should only be assessed for chemicals with RfDs that are based on an effect on the same target organ (USEPA 1986, 1989, 2000b.

EPA admits that the HI MCL lacks evidence of a common MoA.[47] To the contrary, the reference value for PFHxS and the RfD for PFBS are based on different thyroid effects, the HFPO-DA RfD is based on a "constellation" of liver effects, and the PFNA reference value is based on changes to body weight and development. For PFHxS and PFBS, the same thyroid endpoints are not used as the critical effects – for PFHxS the critical effect is based on thyroid follicular epithelial hypertrophy/hyperplasia in parental male rats and for PFBS the critical effect is based on decreased serum total thyroxine in newborn mice after gestational exposure to the mother. These effects are likely occurring via different MoAs due to the different life-stages affected (parental versus offspring, respectively). EPA has also not established a shared MoA or considered relative potencies of the HI-PFAS. Because the HI-PFAS lack a common toxicity endpoint, summing potential hazards (as measured with a hazard quotient or HQ), contradicts long-standing EPA guidance and widely held scientific opinion.

These differences in target organs[48] and critical effects for the four HI-PFAS are precisely why EPA did not use a target organ-specific HI approach and instead opted for the screening-level HI approach, despite its inability to accurately characterize the additivity of the four HI-PFAS. EPA guidance (USEPA 1989) recommends the use of the general HI approach as an initial screening to assess potential adverse effects and not for binding regulatory purposes. The approach assumes that simultaneous exposures to several chemicals occurring below their respective health-based thresholds could result in an adverse health effect, regardless of the chemicals' target organs or mechanisms of action. The HI is calculated as the sum of the ratios of each chemical's exposure relative to that chemical's respective health-based threshold. If the resulting general HI is less than 1, then an unacceptable hazard does not exist, and no further evaluation is needed. However, if the general HI exceeds 1, the guidance then recommends

[45] *See, e.g.,* (Anderson et al. 2022).
[46] *Id.* at 5.
[47] *See* 88 FR 18668.
[48] A target organ is an organ in the body most affected by a specific substance.

conducting a refined assessment by separating the HI evaluation by target organ and/or mechanism of action. EPA's proposed HI MCL omits the critical consideration for shared target organs and/or mechanism of action to determine potential hazard.

Because the four HI-PFAS do not share the same target organ, potential hazards calculated via the general HI method are not toxicologically accurate. EPA's proposed general HI method fails to use the target organ-specific RfDs in the most appropriate manner, resulting in a screening-level assessment when a refined target organ HI approach is available and is far more appropriate.[49] This flaw results in inaccurate and overly conservative MCLs, combined with problematic risk communication due to their flawed scientific foundation and lack of transparency.

In short, EPA's reliance on the general HI method for PFHxS, HFPO-DA, PFNA, and PFBS is contrary to long-standing practices employed in human health risk assessments, well established and scientifically sound principles of toxicology, and EPA guidance. Further, the proposed general HI approach cannot be claimed as a more health protective method. Rather, it is an inaccurate method for assessing exposures and risks to compounds with different toxicological endpoints, and because of the method's inaccuracy, cannot be used to determine health protectiveness or margin of safety. Considering these fundamental shortcomings, the use of the general HI method in the proposed NPDWR is arbitrary.

f. The Hazard Index Fails to Provide Regulatory Certainty

The unprecedented HI-MCL "standard" is not actually a fixed standard. Instead, the "standard" is based on an unlimited combination of detections of the four HI-MCL substances, all of which can be below their respective HBWC, and still be considered a violation of MCL. Similar results where all four substances are below their HBWCs can have different regulatory outcomes. EPA has not set a single MCL for the HI-PFAS. Instead, the proposed HI-MCL is actually thousands of fluid standards.

Such unpredictable and inconsistent regulatory outcomes raise a host of issues, including fundamental issues regarding fairness, equity, and regulatory certainty. There is no evidence in the Proposed Rule or supporting materials that EPA considered these issues before proposing the HI-MCL. That lack of reasoned consideration is the hallmark of arbitrary agency action.

[49] EPA wrongly refers to the general HI method as a more health protective indicator of risk and the target organ-specific HI approach as less health protective estimate of risk. Noncancer evaluations are based on threshold effects and, as a result, are either health protective or not. The contention that the general HI is "more" health protective stems from the misapplication of the long-standing approach for assessing the potential hazards associated with exposure to more than one noncarcinogen. The general HI method results in an inaccurate potential hazard calculation that unnecessarily increases uncertainty, reduces transparency, and hinders the risk communication process.

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3M Center
St. Paul, MN 55144-1000
651 733 1110

g. EPA Has Not Conducted a Benefits Analysis for the HI MCL, in Violation of the SDWA

SDWA §1412(b)(3)(C)(i) requires that EPA "shall" for each alternative MCL considered, publish and seek comment on an analysis of the quantifiable and nonquantifiable health risk reduction benefits and costs of the proposed rule. As described above in Section IV.d, EPA did not consider any alternatives for either the HBWCs or the HI MCL itself, contrary to the SDWA requirements. In addition, EPA failed to conduct any analysis of the benefits or costs of the HI-MCL, also in violation of the SDWA. EPA acknowledged in its Proposed Rule that it "has not separately presented changes in quantified costs and benefits" for the "HI approach". 88 FR 18638, 18671. Similarly EPA stated that it "has not separately quantified the benefits and costs for the alternative approach to regulate PFHxS, PFNA, PFBS, and HFPO-DA with individual MCLs instead of the HI."[50] *Id.*

Given that the HI MCL can be exceeded by a vanishingly small amount over the non-peer reviewed HBWCs (for example, 2001 ppt PFBS, where the HBWC is 2000 ppt), and that the HI MCL can be exceeded by a combination of the HI-PFAS all below HBWCs, EPA's failure to engage in SDWA-required analysis of the benefits of the proposed HI MCL leaves the public entirely without information as to the potential benefits and costs of the Proposed Rule. Moreover, any assumption by EPA of a measurable benefit related to the HI MCL is implausible. EPA proposes setting the HI MCL at the same level as the HI MCLG. EPA admits in the Proposed Rule that the MCLG represents "a level at which no known or anticipated adverse effects on the health of persons is expected to occur and which allows for an adequate margin of safety." 87 FR 36848 (March 29, 2023). Similarly, EPA set the PFBS HBWC at the same level as its lifetime health advisory for PFBS. EPA states that its "lifetime health advisories identify levels to protect all people, including sensitive populations and life stages, from adverse health effects resulting from exposure throughout their lives to…PFBS in drinking water."[51] EPA goes on to state that "the health advisory levels were calculated to offer a margin of protection against adverse health effects." In other words, EPA's Proposed Rule would set an enforceable standard at levels it concluded is protective against potential risks, with an adequate margin of safety, rather than determining an appropriate regulatory level based on the considerations enumerated in the SDWA.

EPA's failure to prepare any analysis of the benefits or costs of the HI MCL not only violates the SDWA, but also violates the APA's requirement that the Agency engage in notice and comment rulemaking. Without providing the analysis required by the SDWA for the HI MCL, the public is precluded from meaningfully commenting on the potential benefits and costs of the Proposed Rule.

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[50] Because the individual HBWCs for the HI substances function as individual MCLs (because an exceedance of one HBWC would exceed the HI MCL), establishing individual MCLs for the HI-PFAS is not an "alternative approach" but rather a description of the proposed action.

[51] *See* https://www.epa.gov/sdwa/questions-and-answers-drinking-water-health-advisories-pfoa-pfos-genx-chemicals-and-pfbs#:~:text=4.-,What%20is%20a%20lifetime%20health%20advisory%3F,or%20PFBS%20in%20drinking%20water.

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3M Center
St. Paul, MN 55144-1000
651 733 1110

VI. EPA's PROPOSED MCLGS AND MCLS FOR PFOA AND PFOS ARE NOT BASED ON BEST AVAILABLE SCIENCE

EPA's process flaws have resulted in a proposed NPDWR that does not comply with the SDWA's statutory requirement to rely only on "the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices," rendering the proposed rule arbitrary, capricious, and in excess of statutory authority.[52] An agency must be prepared to provide a "full analytical defense" of its approach.[53] As many courts have noted, "[t]he deference accorded an agency's scientific or technical expertise is not unlimited."[54]

First, as explained in Section III, EPA's evaluation of relevant scientific literature has serious procedural issues that raise significant questions regarding the Agency's scientific conclusions. For example, EPA did not follow basic principles or even its own guidance in conducting its review and evaluation analysis of studies, which resulted in the use of low-quality papers and datasets that cannot be reproduced. Flaws in EPA's scientific approach that forms the basis of the standards proposed in this rulemaking are described in detail below.

EPA acknowledges significant uncertainty in the scientific literature, to the point that it incorporated uncertainty factors so high as to be the maximum that could be considered as the basis of reference value according to EPA's IRIS Handbook. EPA cannot cite scientific uncertainty as a basis for relying on subpar studies that fit its predetermined conclusion.[55] Nor can EPA simply default to caution when scientific evidence directs the agency otherwise.[56] (EPA cannot "reject 'best available' evidence simply because of the possibility of contradiction in the future by evidence unavailable at the time of action – a possibility that will *always* be present.")

As described in the sections below, EPA's proposed NPDWRs violate numerous foundational scientific practices such that it cannot represent the "best available, peer-reviewed science," in violation of both the SDWA and the Administrative Procedures Act's requirement that an agency's actions not be arbitrary.

a. EPA Did Not Follow Best Practice and Its Own Guidelines for Data Quality Control

EPA has published a series of quality control (QC) and best practice guidelines for program development and project development (USEPA 1992,2002a), data quality objectives (USEPA 2003, 2006), and good statistical practice (USEPA, 2006). EPA has also published approved methods and software for calculating benchmark doses (BMD) and their uncertainty (USEPA 2012, 2022c) which have been developed into an interactive web site. These guidelines are intended to ensure that the resulting decisions made by EPA meet the highest scientific

[52] 42 U.S.C. § 300g-1(i).
[53] *Chemical Manufacturers Association v. EPA*, 28 F.3d 1259, 1265 (D.C. Cir. 1994)
[54] *Brower v. Evans*, 257 F.3d 1058, 1067 (9th Cir.2001).
[55] *See City of Waukesha*, 320 F.3d at 254.
[56] See *Chlorine Chemistry Council v. EPA*, 206 F.3d 1286, 1290-91 (D.C. Cir. 2000)

standards, including reproducibility of results, appropriate data treatment, ensuring representative data, and accurate identification and quantification of true risk to human populations and environmental metrics. The IRIS Handbook and USEPA (2012) provide criteria for how to review literature studies and categorize them based on availability of data, study design, testing procedures, statistical methods, and deficiencies.

The methods and procedures EPA used to support the Proposed Rule did not follow these established procedures, and lack good data practice, sound statistical analysis practice, consistency of methods and models, and the ability to replicate analytical results. EPA has not proposed data quality objectives (DQOs) or Quality Assurance Project Plans (QAPP) for any data source chosen for the Proposed Rule, and/or associated findings used to establish the MCLG. DQOs are required for any research initiative in order to document and ensure that data are collected properly, data are treated using good statistical practice, and any findings can be replicated by scientists and data analysts not working at EPA. EPA's own documents provide guidance on DQOs, program planning, good data practice, and good statistical practice (USEPA 2003, 2006, 2014).

Nor has EPA followed its own requirements and guidance (as listed in the foregoing paragraph) for collecting and analyzing data. Rather, for the MCLG and associated analyses, EPA has largely relied on previously published studies conducted by non-EPA employees for which EPA has not verified data collection, data treatment, outlier detection, variance estimation, elimination of records, or good statistical practice. For example, EPA has selected papers where the data used to calculate BMDs and other measures of risk were not publicly available or were difficult and time-consuming to obtain (e.g., Budtz-Jørgensen and Grandjean, 2018; Shearer et al., 2021). The inability to replicate study findings violates a key principle of the scientific method.[57] This action also is in direct violation of the IRIS Handbook (USEPA ORD 2022), which states that studies with no original data are "tracked for potential use in identifying missing studies, background information, or current scientific opinions," meaning they are not included in the quantitative IRIS assessment. Further, EPA's guidance for considering literature toxicity studies (USEPA ORD 2022) lists specific criteria for invalidation of studies, including "inadequate or missing analytical data," "deficiencies in reporting of study data," and "lack of appropriate statistical methodology." Had EPA's analysis comported with its guidance, many of the studies that EPA relied upon would have been categorized as invalid and therefore presumably not appropriate for use. Exclusion of significant studies, such as Budtz-Jorgensen and Grandjean (2018) and Shearer et al. (2021) would alter EPA's findings.

b. EPA Did Not Follow Its Own Guidelines on Good Statistical Practice

Throughout the technical documents supporting the rule, EPA's statistical and modeling analyses conflict with guidance (USEPA 1992, 2002, 2003, 2006a, 2006b). This failure to

[57] This is a critical and highly relevant topic given that peer review is only as good as the information provided. Lack of transparency in publications and other related issues may limit the effectiveness of peer review and the ability to replicate results of the study. *See, e.g.,* https://www.news-medical.net/life-sciences/What-is-the-Replication-Crisis.aspx; *see also* Improving transparency and scientific rigor in academic publishing (Prager et al. 2019) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6346653/.

follow the practices specified in EPA's guidance results in very low to negligible confidence in the quantitative findings on a consistent basis. Below are a few of the many examples of EPA's practices that are counter to the guidance on statistical and modeling practices cited above. Appendix A and Appendix B, *EcoStat Comments on the United States Environmental Protection Agency's Proposed Per- and Polyfluoroalkyl Substances National Primary Drinking Water Regulation*, include more fulsome explanation of each of these issues.

- Frequently, EPA does not have the original data sets used by the authors in papers EPA considers of high quality. This directly contradicts the IRIS Handbook literature screening steps that exclude studies without provided data. Therefore, EPA and other scientists cannot replicate the results of the original authors, nor can EPA evaluate the authors' consideration of non-detects, outlier detection, sensitivity studies, or data transformations.

- When building statistical models, EPA often ignores fundamental covariates like gender, ethnicity, age, body weight, geographic region, etc. Papers selected by EPA may consider these variables and provide graphics, but the factors are not considered as fundamental covariates within the models that are used to estimate BMDs or to estimate public health risk When models are incorrectly built (e.g., leaving out key variables), the effect is to generate incorrect model error estimates for hypothesis testing, which has the effect of overestimating the significance of PFAS concentrations in the model (Heinze et al 2018).

Because EPA frequently lacks the source data used in outside publications, and because these data are frequently unavailable to the public, EPA attempts to infer the statistical properties of the unavailable data for the purpose of model building. This approach is clearly a violation of EPA's QC guidelines (USEPA 1992, 2002). For example, EPA attempts to generate a "pooled variance" having only the 25^{th} and 75^{th} percentiles of a data set to infer the median and mean values. EPA states that "[i]f access to data and methods cannot occur, EPA should, to the extent practicable, apply especially rigorous robustness checks to analytical results and carefully document all checks that were undertaken." (USEPA 2002) Sound statistical practice recognizes that there are many (if not hundreds) of empirical distributions with the same 25^{th} and 75^{th} percentiles that result in different median and mean values. Accordingly, assuming any single distribution, without the ability to assess the original data, is inappropriate, unreliable, and subjective and does not adhere to the "rigorous robust checks" recommended in EPA's own guidance (USEPA 2002).

- EPA has selected papers and data sources to support the rule without establishing that the information is representative of national US populations. Therefore, findings from these papers cannot be inferred to the entire US population. Regional data, data from the Faroe Islands, data collected without a sampling frame, or data collected where sampling weights cannot be determined should not be used for setting a national standard.

- EPA has not included time-based effects in the models used to support the rule. 3M's assessment of NHANES data clearly demonstrates that changes in serum levels of PFOA

and PFOS over time highly influence the modeling results and should be considered in models for all human risk endpoints evaluated in the technical support documents.

c. EPA's Process Failures Render Its Carcinogenicity Determinations for PFOA and PFOS Unreliable

i. PFOA

The MCLG of zero for PFOA is based on EPA's determination that PFOA is "likely to be carcinogenic to humans." EPA's conclusion is reportedly based on evidence of kidney and testicular cancer in humans and testicular Leydig cell tumors ("LCTs"), pancreatic acinar cell tumors, and hepatocellular adenomas in rats. As discussed below, as a result of process failures, EPA's analysis of the evidence on which it relies is fundamentally flawed, rendering EPA's conclusion unreliable.

In determining whether a substance is a likely carcinogen, EPA follows its Guidelines for Carcinogen Risk Assessment (USEPA 2005). That Guidance directs EPA to evaluate relevant studies and make a "weight of evidence" determination, by "weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents" based on considerations of animal and human evidence, mechanisms of action and dose-response relationships (USEPA 2005, p. 1-11). Here, EPA's systematic review and evidence synthesis failures led it to inaccurately assess the weight of the evidence as it relates to PFOA. For example, tumors identified in animals have questionable relevance to humans because they have been shown to occur through the PPARα pathway, a mode of action with limited relevance to humans (Biegel et al., 2001; Corton et al., 2018). In addition, the LCT tumors observed in animals do not have a common mode of action with testicular germ cell tumors seen in humans (Klaunig et al. 2012). Additionally, an excess of renal tumors has not been reported in three rat studies (NTP 2020; Butenhoff et al. 2012; Biegel et al. 2001). Despite the limited supporting evidence for renal carcinogenicity in animal studies, EPA relied primarily on the matched case-control study on kidney cancer (Shearer et al. 2021), even though other studies on humans evaluating associations between kidney cancer and PFOA exposure also have yielded inconsistent results and do not demonstrate consistent dose-response (Steenland and Woskie 2012; Barry et al. 2013; Raleigh et al. 2014).

Moreover, the study by Shearer et al. (2021) relied upon by EPA to derive the cancer slope factor (CSF)[58] for PFOA is undermined by the study's reliance on PFOA exposure measured at a single point in time almost a decade before cancer diagnosis. This discrepancy adds uncertainty to the associations of exposure and cancer outcomes, as discussed in more detail below. Furthermore, Shearer et al. (2021) insufficiently adjusts for confounding by key risk factors, including the very limited categorical data on smoking history, body mass index, and history of hypertension. EPA's *Guidelines for Carcinogen Risk Assessment* (2005) specifically discusses the importance of confounding factors and states, "[c]ommon examples include age, socioeconomic status, smoking habits, and diet" and further "[s]tatistical analyses of the bias,

[58] A cancer slope factor is a value representing a relationship between increases in exposure dose and cancer risk.

confounding, and interaction are part of addressing the significance of an association and the power of a study to detect an effect." EPA failed to follow its guidance when using Shearer et al. (2021) without consideration of these important variables.

Contrasts in PFOA levels in this study cohort were also modest—comparing the upper quartile of >7.3 μg/L PFOA to a lower quartile of <4.0 μg/L PFOA—and substantially smaller than exposure contrasts in more highly exposed populations that showed no significant difference in kidney cancer risk (e.g., Raleigh et al. 2014). The reference group (i.e., the least exposed group) in Shearer et al. (2021) also had fewer cases (47 cases) than the control group (81 controls), which may have biased the statistical comparisons for the other exposure categories. This distribution of 81 controls and only 47 cases in the referent group is counterintuitive because one would expect a more similar distribution among the least exposed. Neither Shearer et al. nor EPA commented on this referent group, which becomes the main driver in the subsequent calculations for the other three exposure categories. This shortcoming another example of EPA's attempts to infer statistical properties as discussed in Section IV.b. Other scientific literature indicates no association between PFOA exposure and kidney cancer risk; for example, a significant association or exposure-response trend was not observed between PFOA exposure and kidney cancer incidence or mortality in several other human epidemiological studies, including those from highly exposed occupational cohorts (e.g., Barry et al. 2013; Raleigh et al. 2014). The fact that there was little to no association between exposure to PFOA in workers with occupational exposure to high levels of PFAS and kidney cancer should have been considered by EPA as strong evidence against carcinogenicity, but , as a result of its deficient review processes, EPA appears to have largely disregarded this evidence.

Finally, the mechanistic weight of evidence for carcinogenicity indicates that PFOA is more likely to act via a threshold mode of action. EPA concludes that "most of the evidence for mutagenicity is consistently negative." This means that best practice would be for EPA to identify a dose below which toxicity does not occur (the threshold) and, accordingly, set an MCLG based on that dose (rather than assuming a zero MCLG). EPA's overall conclusions, however, assume a linear-no threshold model of carcinogenicity based on default assumptions of EPA's Cancer Guidelines (USEPA 2005) rather than analysis of the weight of evidence. As detailed in the section below on evidence of PFOS carcinogenicity, many of the modes of action for carcinogenicity of PFOA identified in animals do not apply to humans (e.g., PPARα pathways) and best practice dictates that EPA's assessment of carcinogenic mode of action should be revised to reflect its conclusion that most of the evidence for mutagenicity is consistently negative, indicating the linear no-threshold model of carcinogenicity is not appropriate for PFOA.

1. Evidence for PFOA Carcinogenicity and Derivation of the Cancer Slope Factor

EPA failed to apply applicable guidance in evaluating the evidence of carcinogenicity and deriving a CSF for PFOA. EPA's IRIS Handbook indicates that "consistency across studies or experiment" should be considered as part of the evidence synthesis step. Additionally, EPA's Cancer Risk Assessment Guidelines (USEPA 2005) recommend that, "[w]hen multiple estimates

[of cancer risk] can be developed, all datasets should be considered, and a judgment made about how best to represent the human cancer risk."

Contrary to this guidance, the proposed rule makes clear that EPA failed to consider all datasets relevant to potential cancer risk. As discussed below, in evaluating carcinogenicity, EPA incorrectly excluded several occupational exposure studies (Steenland and Woskie et al. 2012; Raleigh et al. 2014; Barry et al. 2013) which collectively demonstrate limited or no association with kidney cancers among workers with 10- to 100-fold greater exposure to PFOA than seen in the general population. Instead, EPA relies on Shearer et al. (2021), a matched case-control study on kidney cancer (324 cases, 324 matched controls) from the Prostate, Lung, Colorectal, and Ovarian Screening Trial (PLCO), which has critical flaws, as detailed below (*e.g.* a single serum measurement, potential reverse causation), that undermine the integrity of EPA's conclusion.

a. EPA incorrectly excluded occupational studies with greater exposures than Shearer et al. (2021)

Steenland and Woskie (2012) is an occupational cohort mortality study of DuPont workers (n = 5,791) with PFOA exposures, which reported a total of 12 kidney cancer deaths. This study observed significant elevated risk of kidney cancer death only in the highest exposure quartile. EPA identified this as a medium confidence study but stated that it did not consider it further because of the small number of observed cancer cases and because "information on a range of exposures more relevant to the general population were available from Shearer et al. (2021)" (USEPA 2023a). However, the range of exposures in Steenland and Woskie (2012) was actually 10 to 100 times higher than the general population, an indication that kidney cancer is not associated with general population-levels of exposure to PFOA.[59]

EPA also improperly excluded Barry et al. (2013), which is a community/worker cohort study of 32,254 residents (28,285 community members and 3,713 DuPont workers) with residential exposure to PFOA in their drinking water for which there were a total of 105 kidney cancer cases (87 from the community and 18 from the DuPont workers). This study also did not find a significant association of kidney cancer cases among workers who had serum concentrations that were 10-fold greater than the community population in Shearer et al. (2021). EPA stated Barry et al. (2013) was not suitable for dose-response analysis because it was performed in the same study area as Vieira et al. (2013) and may involve a number of the same participants. In addition, EPA stated that Barry et al. (2013) lacked the necessary exposure measurements for CSF calculation. However, a later study, Bartell and Vieria (2021), reports the necessary exposure data from Barry et al. (2013), which EPA did not acknowledge or explain

[59] EPA did not acknowledge that the observed kidney cancer cases could have been confounded by occupational exposure to tetrafluoroethylene (TFE), a known rodent renal carcinogen. EPA also failed to address that Steenland communicated in a recent publication (Bartell and Vieira 2021) that there was a major error in the cumulative ppm-years quartile analyses where the quartile PFOA exposure categories should have been defined as cumulative ng/mL-years (ppb-years) and not ppm-years. Therefore, the exposures in this study were actually lower (i.e., more relevant to the general population) and the reported cancers may have been due to TFE exposures and not PFOA.

why these data did not make this study appropriate for inclusion in its analysis, and thus arbitrarily excluded Barry et al. (2013).

EPA also incorrectly excluded Raleigh et al. (2014), reportedly based on concerns of exposure assessment methods and study quality as well as the small number of cases (USEPA 2023a). Raleigh et al. (2014) is an occupational cohort mortality and cancer incidence study of 3M workers (n= 4,668) with exposure to the manufacture of the ammonium salt of PFOA (i.e., APFO) that reported 16 kidney cancer cases and was not confounded by TFE exposure. The authors did not find an excess of kidney cancer cases beyond what would be expected in the general population. EPA stated that it excluded this study because it used modeled estimates of PFOA air concentrations in the workplace rather than biomonitoring measurements and because of concerns about absorption of inhaled PFOA. However, EPA did not appropriately consider the totality of other studies that found that these workers did likely have high PFOA exposures consistent with the higher PFOA serum concentrations (Olsen et al. 2000, 2003; Raleigh et al. 2013, 2014). Other studies have also concluded that PFOA is efficiently absorbed in rodents following inhalation of PFOA (Griffith and Long 1980; Kennedy et al. 2004). Therefore, EPA mischaracterized the quality of the data from Raleigh et al. (2014), resulting in the arbitrary exclusion of this study.

EPA's failure to collectively synthesize evidence from the occupational exposure studies resulted in a misinterpretation of the weight of evidence. Though individually the three occupational studies may not have been suitable to calculate a CSF, EPA failed to consider that, collectively the PFOA exposures in these three worker studies were one to two orders of magnitude greater than the general population serum PFOA concentrations reported in Shearer et al. (2021) yet showed little to no association with kidney cancer.[60] In Shearer et al. (2021), 324 kidney cancer cases originated from a cohort of 150,000 adults aged 55 – 74 with kidney cancer cases representing 0.22% of the cohort. In the three occupational cohorts by Steenland and Woskie (2012), Raleigh et al. (2014), and Barry et al. (2013) which had cohorts of 5,791, 4,668, and 3,713 (total = 14,172) workers respectively, there were a total of 52 kidney cancer deaths and cases representing 0.37% of the combined three cohorts. Though EPA labels each of these as small studies, they are collectively comparable to Shearer et al. (2021) in the percentage of kidney cancer cases.[61]

Therefore, among these three occupational analyses, which likely represent the highest exposed individuals based on overall reported biomonitoring data, only one analysis (Steenland and Woskie 2012) showed a statistically signficant associaton with kidney cancer, but this was confounded by the authors' decision to not adjust for TFE exposure. EPA did not synthesize the evidence across these studies, as is recommended by the IRIS Handbook and Cancer Guidelines,

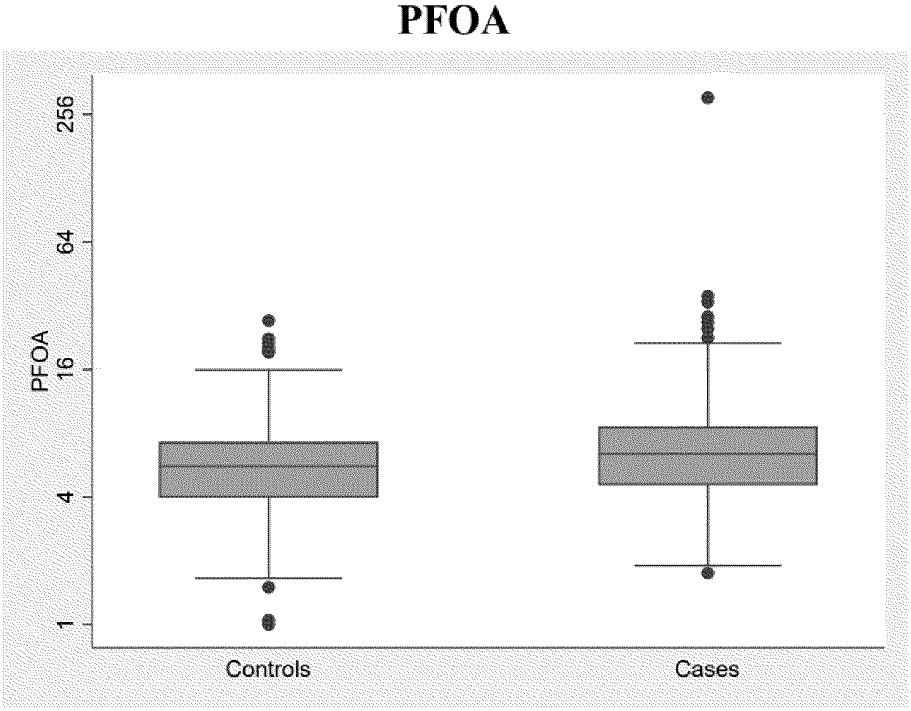
[60] In fact, Steenland et al. (2022) found that the risk of kidney cancer demonstrated in Shearer et al. (2021) decreased above 13 ng/mL serum PFOA. Combining Shearer et al. and Barry et al. together showed essentially no additional risk of kidney cancer above 10-13 ng/mL.

[61] The ability to collectively compare studies is the reason to do a systematic review, and demonstrates the value gained from such meta-analyses.

to inform its approach to the CSF and as a result did not appropriately assess the overall weight of evidence for carcinogenicity.

b. EPA did not properly assess Shearer et al. (2021) for flaws that undermine its reliability

Because EPA excluded the above occupational studies from consideration for the CSF, it instead inappropriately relied solely on Shearer et al. (2021) where a single measurement of serum PFOA was used to calculate the CSF.



Both EPA and Shearer et al. state the long half-life of elimination of PFOA indicates that a single serum measurement could be sufficient to provide an accurate and precise measurement of a person's long-term PFOA exposure. This assertion ignores the considerable uncertainty regarding the distribution, calculation, and measurement biases associated with the serum elimination half-lives of PFOA in humans as discussed in a series of publications (Dourson and Gadagbui 2021; Campbell et al. 2022a,b; Post et al. 2022). Shearer et al.'s (2021) conclusion that a single PFOA measurement is sufficient based on PFOA's long-half life in humans contradicts fundamental considerations of the connection between toxicodynamics, toxicokinetics, and time (Rozman et al. 1996). This highlights the limitations of using serum concentrations measured 2 to 18 years prior to the diagnosis of the disease. If the serum elimination half-life ranges from 0.5 to less than 3.0 years, then a PFOA measurement taken, on average, 8.8 years prior to the diagnosis of kidney cancer could be anywhere from 3 to greater than 5 half-lives from the diagnosis of kidney cancer. This discrepancy limits the accuracy of the reported serum concentrations in Shearer et al. (2021).

Shearer et al. (2021) also did not appropriately address reverse causation, which is a type of pharmacokinetic bias (Andersen et al. 2021) and occurs when a physiological outcome (e.g., estimated glomerular filtration rate [eGFR]), which affects the exposure assessment, has been *moderated by the health outcome itself*. The pharmacokinetic bias occurs when there is a sufficient window of time for the disease state to influence physiological factors that can bias the exposure assessment. EPA's IRIS Handbook recommends evaluating epidemiological studies for reverse causality and if reverse causality is a concern in the observed association of the exposure and health outcome, then a study should be labelled as deficient or critically deficient. In Shearer et al. (2021), the lack of an association between eGFR, PFOA, and kidney cancer does not conclusively demonstrate a lack of reverse causation, but it should have been considered as a factor because the eGFR was measured, on average, 8.8 years *prior to* the diagnosis of kidney cancer. There is the possibility of pre-diagnostic conditions that result in declining renal function. EPA therefore violated its own guidance in suggesting the lack of an association between a single eGFR measurement, and the diagnosis of kidney cancer eliminates the concern about this type of pharmacokinetic bias in the association between the exposure to PFOA and kidney cancer.

c. EPA uses inconsistent methods to calculate the cancer slope factor resulting in an overly conservative value

The cancer slope factor (CSF) describes the relationship between dose and cancer risk. EPA considers the slope factor as the upper-bound estimate of risk per increment of dose that can be used to estimate risk of cancer for different exposure levels (USEPA 2005). Thus, a steeper slope, or greater CSF, indicates that cancer risks are expected to increase more per each unit increase in dose. EPA's Cancer Guidelines (USEPA 2005) state that CSFs are derived for substances that are assumed to have a linear no-threshold mode of action or as a default if a different mode of action cannot be identified. This means that EPA assumes that even at doses below a carcinogenic point of departure, there is a nonzero risk of cancer. CSFs can be derived from either animal or human studies but should be derived based on the best practices in EPA's Cancer Guidelines.

EPA's derivation of the CSF lacks transparency and EPA inconsistently selects studies and analysis techniques, resulting in a CSF that is not based on the best available data. EPA relied solely on the relative risk of renal cell carcinoma from Shearer et al. (2021) to calculate the CSF, which as described above has critical limitations that make it unreliable. EPA's CSF derivation is based on a simple regression model originally used by the California Office of Environmental Health Hazard Assessment (OEHHA) (CalEPA 2021; OEHHA 2004), which is used to estimate the dose-response between PFOA and renal cell carcinoma risk. The CSF is then calculated as the excess cancer risk associated with each ng/mL increase in serum PFOA (internal CSF).

Results of EPA's analysis of Shearer et al. (2021) are reported in Table E-42 in the PFOA MCLG Appendix excerpted below. PFOA dose levels in each quartile of exposure (represented as x_i) were supposedly calculated as the midpoint of the reported PFOA range in ng/mL from Shearer et al. (2021). However, as seen in the second and third rows of excerpted Table E-42

below, the x_i values of 2.75 and 4.4 are not within their respective PFOA ranges in the leftmost column. Thus, these values do not actually represent the midpoint of the categories used by Shearer et al. (2021).

Table E-42 from the PFOA MCLG Appendix demonstrating the odds ratios for PFOA serum concentrations and renal cell carcinoma from Shearer et al. (2021).

Table E-42. ORs for the association between PFOA serum concentrations and RCC in Shearer et al. (2021, 7161466) and data used for CSF calculations

PFOA Range (ng/mL)	x_i	OR_i	LCI_i	UCI_i	$Var(OR_i)$	w_i	w_ix_i	$w_ix_i^2$	$w_ix_iOR_i$	cases	controls
< 4	0 (reference)	1	-	-						47	81
4.0–5.5	2.75	1.47	0.77	2.80	0.234	4.267	11.734	32.267	17.248	83	79
5.5–7.3	4.4	1.24	0.64	2.41	0.176	5.685	25.012	110.053	31.015	69	83
7.3–27.2	15.25	2.63	1.33	5.20	0.837	1.195	18.224	277.909	47.928	125	81

Based on the analysis outputs in Table E-43 of the PFOA MLCG Appendix, EPA calculates the CSF of 0.00352 $(ng/mL)^{-1}$ which represents the upper 95th percentile of the slope.

EPA also calculated CSFs based on Vieira et al. (2013) which is a study based on 58 kidney cancer cases exposed via drinking water and compared to greater than 7,000 controls. EPA calculates CSFs by either including or excluding the highest exposure level from that study (Table E-43 PFOA MCLG Appendix). EPA failed to explain why it chose not to use the regression model provided by California's Office of Environmental Health Hazard Assessment (OEHHA) and instead used the midpoint ranges of the Vieira et al. (2013) categorical data. This practice is inconsistent with the approach EPA applied to Shearer et al. (2021) to derive the CSF. This inconsistency of methods to derive a CSF from these two studies is arbitrary, lacks sufficient justification, and in the absence of a sensitivity analysis, prevents understanding of the ramifications of this arbitrary choice.

It is important to note that EPA's and OEHHA's approach to the derivation of the CSF are distinctly different and when followed with the same datasets, will result in different CSFs. OEHHA chose to use the central estimate of the slopes (i.e., the slopes themselves). This is because OEHHA combined the results of two separate studies (i.e., Shearer et al. 2021 and Vieira et al. 2013) to develop its final overall CSF. OEHHA determined this combination of different studies and different study sites would account for much of the variance likely to occur across different PFOA-kidney cancer sites and therefore using the geometric mean of the two slopes was a better representation of potential cancer risks across the general population. In contrast, because EPA did not appropriately synthesize the evidence, it only relied on Shearer et al. (2021) and instead based its estimate of the slope on the upper 95th percent confidence interval. Thus, California's CSF of 0.00178 $(ng/mL)^{-1}$ is approximately half that of EPA's CSF of 0.00352 $(ng/mL)^{-1}$. Notably, the California CSF is nearly identical to the CSF derived from the pooled data analysis of the Shearer et al. (2021) and Barry et al. (2013) as published in

Steenland et al. (2022).[62] Additionally, EPA's Cancer Guidelines allow for "combining data from different datasets in a joint analysis" (USEPA 2005, p. 3-25). Therefore, EPA should have considered this approach, which may better reflect the overall evidence base.

ii. PFOS

The agency's conclusion that PFOS is likely to be carcinogenic to humans is likewise undermined by the lack of a reliable process for identifying and evaluating available evidence. As a result, EPA's conclusion is inconsistent with the evidence that EPA presents, as well as with fundamental scientific principles.[63] The vast majority of the studies that EPA produced and analyzed reported no effects, no effects of statistical significance, or effects that are inapplicable for human risk assessment because of species differences. EPA's conclusion that the weight of evidence supports the classification that PFOS is likely to be carcinogenic to humans is inconsistent with the weight of the evidence to the contrary, as further detailed in this section. Of critical importance, the PFOS cancer assessment as written was not reviewed by the SAB, counter to the Cancer Guidelines (USEPA 2005) that state, "[g]enerally, cancer risk decisions strive to be "scientifically defensible, consistent with the agency's statutory mission, and responsive to the needs of decision-makers" (NRC, 1994). Scientific defensibility would be evaluated through use of EPA's Science Advisory Board, EPA's Office of Pesticide Programs' Scientific Advisory Panel, or other independent expert peer review panels to determine whether a consensus among scientific experts exists." EPA's conclusions on the carcinogenicity of PFOS have been proposed without sufficient peer review, in violation of EPA's own Cancer Guidelines.

1. Epidemiological Evidence

EPA is inconsistent in its presentation of epidemiological data regarding PFOS (USEPA 2023c).[64] EPA summarized epidemiological studies regarding PFOS and their reliability in USEPA (2023c). In a previous assessment that EPA conducted of pre-2016 epidemiology studies of PFOS for its 2016 Health Effects Support Document for PFOS (USEPA 2016),[65] EPA concluded that Jørgensen (2011), Eriksen (2009) and Grice (2007) did not support EPA's new conclusion in the proposed NPDWR regarding PFOS carcinogenicity.[66] Nonetheless, in EPA's weight-of-evidence conclusion for carcinogenicity, the agency misleadingly stated that Grice (2007) "observed that prostate cancers were among the most frequently reported malignancies."

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[62] Steenland et al. (2022), which calculated a CSF from pooled data from Shearer et al. (2021) and Barry et al. (2013), recognized that the CSF derivations from Shearer et al. and Barry et al. were statistically different due to differences in the dose-response relationship at different exposure levels.

[63] In its November 2021 draft PFOS MCLG document submitted to SAB, EPA said there was "suggestive evidence of carcinogenic potential" of PFOS in humans. Now, without providing adequate justification, the Agency has switched its carcinogenicity determination for PFOS despite no new evidence and came to different conclusions about studies it had previously reviewed.

[64] EPA stated that it "identified 15 epidemiological" studies, of which "8 were classified as medium confidence, 6 as low confidence, and 1 was considered uninformative" (p. 3-260). In another section (p. 3-263), the agency states that, "of the 15 studies identified since the 2016 assessment (Figure 3-73), seven were considered medium confidence and six were low confidence," and that figure shows two studies as critically deficient.

[65] See (USEPA 2023c at Figure 3-72, p. 3-262).

[66] See (USEPA 2023c at 3-260-261).

This directly contradicts the original authors' conclusions that they "observed no association between working in a PFOS-exposed job and several cancers, common health conditions, and birth weight" (Grice 2007).

The majority of the studies identified by EPA as relevant for assessing whether PFOS is carcinogenic concluded no, or in one case, even a reduced risk of cancer from PFOS exposure, as follows:

- Bonefeld-Jørgensen et al. (2011): "the association was of a low magnitude and could not be separated from the effects of other perfluorosulfonated compound exposures" (p. 3-283).
- Cohn et al. (2020):" maternal PFOS was associated with a decreased daughters' breast cancers risk" (p. 3-265).
- Ducatman et al. (2015): "No association between PFOS exposure and prostate cancer was reported […] in a study of the association between PFOS serum concentrations and prostate specific antigen (a biomarker of prostate cancer)" (p. 3-282).
- Eriksen et al. (2009): "No elevated bladder cancer risk was observed in a nested case-control study in a Danish cohort" (p. 3-261).
- Fry and Power (2017): "Cancer mortality based on Public-use Linked Mortality Files was not associated with PFOS exposure" (p. 3-266).
- Grice et al. (2007): "they did not reach statistical significance" (p. 3-261).
- Hurley et al. (2018):" A nested case-control study did not observe an association between breast cancer identified through California cancer registry and PFOS concentrations in serum" (p. 3-265).
- Shearer et al. (2021): "reported a statistically significant positive trend in risk of renal cell carcinoma" but "the association with PFOS was attenuated after adjusting for other PFAS […]. There was no association when evaluated on a per doubling of PFOS after adjusting for other PFAS" (p. 3-265).

In particular, there is a lack of confidence in EPA's review methodology, especially as it relates the Eriksen et al. (2009) study when compared to the Shearer et al. (2021) study. Both studies used the same methodology during the same time period. Both studies were published in the Journal of the National Cancer Institute. The Shearer et al. study originated from the PLCO screening trial study that enrolled approximately 150,000 individuals. These participants were enrolled between 1993 – 2001. Single measurement blood (serum) samples were collected at enrollment. At a later date, these samples were measured for PFOA and PFOS. A case control study was much later conducted of those who subsequently were diagnosed with kidney cancer (324 cases, 324 controls) and their archived serum sample for PFOS and PFOA. The Eriksen study originated from the prospective cohort Danish Diet, Cancer, and Health Study which had a cohort of 57,053 individuals aged 50 -65 years, born in Denmark with no previous cancer diagnoses. These participants were enrolled between 1993 – 1997. As with Shearer et al., there was only a single measure of blood (plasma) taken for each participant. Eriksen et al. followed the cancer experience in this cohort through mid-2006. Cases were ascertained through the

Danish National Cancer Registry. A total of 713 prostate cancer cases, 332 bladder cancer cases, 128 pancreatic cancer cases, and 67 liver cancer cases were identified in this follow-up time period. A total of 772 noncancer cases were selected as controls. Archived plasma samples were measured for PFOA and PFOS. Eriksen concluded there was no clear differences in risk for these cancers in relation to plasma concentrations of PFOA and PFOS.

Unlike Shearer et al. (who assert that a single measurement can be used), however, Eriksen et al. wrote, "Consequently, misclassification may have occurred because the concentration may have occurred because the concentration at one moment in time may not reliably reflect the relevant plasma concentrations decades ago or at other times." Eriksen is the largest study, to date, to examine prostate, pancreas, and especially liver cancer, in the general population with PFOS exposure. (The Eriksen et al. study also analyzed for serum PFOA concentrations).

EPA judged both studies by Shearer et al. and Eriksen et al. to result in overall "adequate" confidence with confounding to be deficient in both studies (i.e., both had the same qualitative measurements for cigarette smoking). Given the same methodology, EPA considered Shearer et al. to have good metric scores for participant selection, exposure measurement, outcome, and analysis, whereas Eriksen et al. only received one good metric for participant selection. The mere fact that the EPA has considered PFOS to be likely carcinogenic (based on liver cancer in rats) but utterly failed to mention the Eriksen et al. study for its null liver cancer results in the PFOS final report illustrates inconsistency and apparent arbitrariness EPA's carcinogenicity assessment process.

In conclusion, EPA's process errors led it to reach a carcinogenicity determination that is contrary to the weight of epidemiological evidence in violation of EPA's own Cancer Guidelines.

2. Animal Evidence

EPA made similar process errors in determining that PFOS is "*likely to be carcinogenic to humans*" based on the results of neoplastic tumor data for the liver and pancreatic islet cells from a 2-year chronic dietary study (cited as Thomford, 2002 and Butenhoff et al. 2012, for the original study report and published peer-reviewed manuscript, respectively). While the original study data (by Thomford 2002) reported statistically significant increases in liver adenoma incidences in both male and female rats at the highest dose, it did not conclude such for the pancreatic islet cell tumors.

With regards to the hepatocellular tumor data observed in rats, EPA did not take the known biological plausibility into consideration as it related to human health and used two different models to interpret animal studies regarding PFOS carcinogenicity, which violates its own *Guidelines for Carcinogenic Risk Assessment*. In the draft PFOS appendix (USEPA 2023d), EPA states about data on hepatocellular adenomas and carcinomas in female rats, "the best fitting model was the Multistage Degree 1 model based on adequate p-values" (p. E-55 and p. E-58). It based its selection of a BMDL10[67] on this model. For data for hepatocellular

[67] BMDL10 is the benchmark dose level corresponding to the 95% lower confidence limit of a 10% change.

adenomas in male rats, EPA stated "the best fitting model was the Multistage Degree 4 model based on adequate p-values" (p.E-47). EPA fails to explain the use of different models for studies involving male and female rats in evaluating the evidence of carcinogenicity. In doing so, EPA violates its 2005 *Guidelines for Carcinogen Risk Assessment*, which states, "goodness-of-fit to the experimental observations is not by itself an effective means of discriminating among models that adequately fit the data."

EPA deemed the study by Butenhoff et al (2012) a "high confidence study" (USEPA 2023c, p. 3-260), which should add to the importance of its correct interpretation and the representation of the study's result. However, EPA over-interpreted the importance of a "statistically significant trend of increased incidence of pancreatic islet cell carcinomas with increased PFOS dose" in male rats in the cancer classification section (USEPA 2023c, p. 3-296). It is important to understand that a trend, even if it is statistically significant, simply indicates a non-zero slope among data points. A trend is non-quantitative and does not imply that the magnitude of the increase in effect over increasing dose ever reaches biological significance, or that it would result in the observation of statistically significant increase in effects. A trend simply means that there is a consistent change within the observed parameters across the doses that were investigated. This does not necessarily mean that it continues to persist when additional experimental data is introduced, or that it ever reaches statistical or biological significance before reaching a physiological maximum dose limit such as stomach capacity for dosing, or the natural lifetime of rats.

With regards to the pancreatic islet cells tumors, the EPA improperly employed an alternative statistical approach which led to a statistical significance in trend for the pancreatic islet cell carcinoma. Specifically, the original study report by Thomford (2002) calculated the total tumor incidence rate based on the total number of the tissues examined per specific dose group upon study termination at the end of two years. Given that age-related mortality is quite common among rodents in long-term studies, it is worth noting that the original statistical trend analysis (reported in Thomford 2002) did adjust for survival and survival was taken into account for the logistic regression of tumor prevalence and binary regression analyses. The EPA, on the other hand, calculated the tumor incidence rate based on the number of animals alive at the time when the tumor first occurred, which was an attempt to adjust for survival as well as excluding a subset of rats from control (n=10) and the highest dose group (n=10) that were sacrificed at week 52. While the EPA does not have any specific publication on how to analyze tumor incidence data, the guidance document from U.S. FDA Center for Drug Evaluation and Research (Lin 2007) summarizes various ways of analyzing tumor data in rodents by adjusting for intercurrent mortality, it did not, however, mention this particular approach taken by the EPA.

It was also not best practice to exclude subsets of rats from control (n=10) and the highest dose group (n=10) that were sacrificed at week 52 from the overall trend analysis for tumors, given that the trend test was adjusted for survival. All the animals in these two subgroups were subject to the same rigor in terms of specimen collections and pathology evaluations for potential presence or progression of tumor formations, if any. This was the ultimate purpose of the 2-year cancer study hence if anything, the interim evaluations (with proper survival time adjustment) did not "dilute", but rather, reflect additional statistical power to ascertain the likeliness of tumor

outcome. Furthermore, in accordance with the guidance from the American Statistical Association (Wasserstein and Lazar 2016), a hard cut-off for statistical significance on its own should not be used to make scientific conclusions – "Scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold." Therefore, the interpretation should not be based on whether a p-value is above or below 0.05. On that note, the relationship between pancreatic islet cell carcinoma and PFOS treatment is further called into question because there was no increased incidence of pancreatic islet cell hyperplasia (Thomford 2002). This is important because an increase in islet cell hyperplasia is typically viewed as a continuum to develop islet cell neoplasm.

Lastly, best practice required consideration that it has been well-documented that there are substantial differences in pancreatic islet cells between rodents and humans in terms of anatomy, cellular components, gene expressions, and functional aspect of insulin secretion (Brissova et al. 2015; Steiner et al. 2010). For instance, human islet cells contain less β-cells and more α-cells relative to rodents; and the pancreas tissue in rats are highly vascular. The species difference in pancreatic islet architecture and composition begs the question regarding the interpretation and extrapolation of rodent data finding to humans.

3. Mechanistic Evidence

EPA's processes also undermine its conclusion that PFOS is likely to be carcinogenic to humans based on mechanistic evidence. Mechanistic evidence is critical to support the relevance of data to carcinogenicity, with specific focus on relevance to carcinogenicity in humans. Mechanistic information is relevant to assess the applicability of findings in animals to human cancer risk. EPA (USEPA 2005) specifically emphasizes the importance of making "decisions about potential modes of action and the relevance of animal tumor findings to humans." As discussed below, profound uncertainties compromise the agency's following statement about hepatic tumors in animals: "the available studies provide varying levels of support for the role of several plausible MoAs: PPARα activation, chimeric antigen receptor (CAR) activation, hepatocyte nuclear factor 4 alpha (HNF4α) suppression, cytotoxicity, genotoxicity, oxidative stress, and immunosuppression." (USEPA 2023c, p.3-284). Each of these modes of action is discussed below.

PPARα Activation. EPA's treatment of PPARα as a viable theory for carcinogenicity applicable to humans directly contradicts its own scientists' conclusions. EPA scientists previously published a peer-reviewed article with the title "The PPARα-dependent rodent liver tumor response is **not** relevant to humans" (Corton 2018) (emphasis added), which EPA cites in the proposed NPDWR. The agency failed to acknowledge its own scientists' key finding that "[t]he PPARα-dependent rodent liver tumor response is **not** relevant to humans." EPA's insistence on the relevance of this pathway with respect to PFOA and PFOS is further drawn into question by findings from EPA scientists who demonstrated last year (Evans et al. 2022) that the endogenous fatty acid oleic acid, which is also ubiquitous in the diet, is a more potent PPARα activator than are PFOA (by more than 1 order of magnitude) and PFOS (by more than 2 orders of magnitude). If PPARα activation were a relevant pathway to human liver tumors, that disease state presumably would be at epidemic levels, based on oleic acid alone.

In addition, EPA (Evans et al. 2022) reported concentrations of PFOS and PFOA that did not induce PPARα activity, which demonstrates that this alleged key MOA for carcinogenicity is, if anything, a proven threshold effect. Best practice would be to apply those insights to the carcinogenicity assessment of PFOS and PFOA and abandon the principle of a linear non-threshold dose response.

CAR Activation. In 2016, EPA referenced Hall et al.'s (2012) conclusion that, "CAR activation can lead to hepatocyte proliferation and hepatocarcinogenesis in animals. The human CAR receptor is relatively resistant to mitogenic effects and less likely to induce cancers through this mechanism." EPA referenced the same publication elsewhere in the 2023 draft proposal for PFOS but neglected to report the same conclusion regarding the implausibility of CAR as MoA for PFOS carcinogenicity. EPA vaguely alluded to Hall's conclusion on CAR in the PFOA draft proposal but failed to acknowledge its fundamental implications for human cancer risk.

Every event that is elicited by receptor binding is a threshold effect. A zero-effect threshold is inevitable at concentrations where insufficient numbers of activating molecules are present to trigger a biological signaling cascade and, thus, a response. Receptor-mediated theories warrant dismissal if proven inapplicable for human risk assessment; otherwise, they should be considered threshold effects. EPA did neither.

HNF4*a* Suppression. Beggs (2016) reported that concentrations of 10,000 nanomolar (nM) PFOA and PFOS had statistically significant impacts on HNF4α expression in primary human hepatocytes—and lower concentrations (i.e., 10, 100, 500, 1,000 nM) did not. This observation demonstrates the existence of a threshold below which no effect was observed. Best practice is to discontinue the use of a non-threshold approach for both PFOS and PFOA and instead use PBPK modeling based on concentrations in drinking water to compare *in vitro* no-effect concentrations to expected concentration within human hepatocytes.

Cytotoxicity. In the draft document for PFOS (USEPA 2023c, p. 3-292), EPA states, "the available data indicate a parallel dose response for cytotoxicity and the formation of liver tumors as evidence in Table 3-24 and Table 3-25." It is unclear how EPA reached this conclusion from data that only show statistical significance for hepatocellular adenomas and combined hepatocellular adenomas and carcinomas, and for none of the other (cytotoxicity) endpoints. Variations on a cellular level cannot cause statistically significant tumor formation at a dose where those cellular changes are not also statistically significantly increased. A molecular event cannot be responsible for a pathological response if the dose-response curves are parallel and not intersecting. For PFOA, EPA presents evidence of cytotoxicity *in vivo* (i.e., "significantly increased single cell (hepatocyte) death and in necrosis in male and female was reported in Sprague-Dawley rats, with a significant dose-response trend"), but fails to conduct a dose-response assessment. Only effect concentrations of *in vitro* assays are mentioned in the draft document, none of which are lower than 10 μM. EPA lists non-cytotoxic concentrations but fails to use them as demonstrable no-effect levels to justify a threshold assessment of carcinogenicity.

The assessment of cytotoxicity lacks the diligence that is warranted if it is considered a key event in carcinogenesis.[68]

Genotoxicity. EPA concluded based on the available in vivo mutagenicity study (Wang et al. 2015) that "the evidence for mutagenicity of PFOS in vivo is negative" (USEPA 2023c, p. 3-269). Addressing DNA damage, the agency stated, "it is important to note that rat models could be ineffective for determining micronucleus formation if study authors do not use appropriate methodologies because the spleen will remove micronucleated cells" (USEPA 2023c, p.3-269). This draws the biological relevance of other models and findings into question because an effective removal of micronucleated cells implies the neutralization of this hazard. EPA should explain why said findings in other models are applicable for assessing potential human carcinogenicity.

Immunosuppression. EPA (USEPA 2023c, p.3-295) states that "the only available study in Sprague-Dawley rats […] does not indicate that immunosuppressive effects are occurring at or below doses that result in tumorigenesis." This finding demonstrates that there is no toxicological evidence that immunosuppression is a plausible MoA on the organism level because a mechanism that supposedly underlies a carcinogenic effect should occur at the same doses that cause tumors. EPA ignores the fundamental logic that a response (e.g., cancer) that occurs at doses below the no-observable-effect-level (NOEL) of another response (e.g., immunosuppressive effects) cannot be linked to or caused by the latter. By insisting that both are linked, EPA violates the basic principle of dose-response. According to EPA's Vocabulary Catalog for Drinking Water Technical & Legal Terms (see https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=Drink%20Water%20Tech%2FLegal%202009), the NOEL is defined as a "dose level at which no effects are noted" and dose response is defined as "the quantitative relationship between the amount of exposure to a substance and the extent of toxic injury produced". If the extent of toxic injury from immunosuppression is zero, then it cannot be in a quantitative relationship with cancer that allegedly occurs below the NOEL of immunosuppression.

The perpetual inconsistency of EPA's findings and interpretations warrants a detailed analysis to compare and contrast reported dose-responses and clinical relevance of experimental models.

4. Structural Similarities

EPA inappropriately attempts to rely on the structural similarity between PFOA and PFOS to conclude that its carcinogenicity determination PFOA applies to PFOS. EPA's

[68] It is inappropriate for EPA to set a MCLG at zero based on carcinogenicity when a substance does not have a linear mode of carcinogenic action. *Chemistry Council v. EPA*, 206 F.3d 1285, 1287 (D.C. Cir. 2000). When a substance exhibits a "cytotoxic" mode of action, no carcinogenic effects at low doses, a zero MCLG based on carcinogenicity is not in line with the goals of the SDWA. While there is uncertainty in the range at which no known or anticipated adverse effects on the health of persons occur, this does not mean that EPA can simply default to zero. Uncertainty allows EPA to choose the lowest MCLG within the window of uncertainty but it does not justify choosing an MCLG outside of the range of uncertainty. *Id.* at 1290.

reasoning of structural similarity for cancer risk read-across (USEPA 2023c, p. 3-296) between PFOA and PFOS is also not supported by evidence. EPA states in its publication by Patlewicz et al. (2019) that "the Environmental Protection Agency had the greatest experience in using read-across" but failed to apply any of the best practices – or even apply its own Generalized Read-Across Tool (https://www.epa.gov/chemical-research/generalized-read-across-genra#:~:text=Chemical%20read%2Dacross%20is%20a,(e.g.%2C%20structural%20similarity). EPA also did not follow the seven key steps in the workflow: 1. Decision context 2. Data gap analysis 3. Overarching similarity rationale 4. Analog identification 5. Analog evaluation 6. Data gap filling 7. Uncertainty assessment. The two PFAS substances differ in a key functional group, in that PFOA is a perfluoroalkyl carboxylic acid and PFOS is a perfluoroalkyl sulfonic acid. Carboxylic acids and sulfonic acids possess different physical-chemical properties, which not only explains their different technical applications but also suggests differences in disposition and dynamics on biological receptor sites. The agency stated that a "similar set of non-cancer effects have been observed after exposure to either PFOA or PFOS in humans and animal toxicological studies," implying that those effects were of relevance for cancer risk assessment, when in fact, only the consideration of key events that actually lead to cancer is of relevance. By definition, non-cancer events are not applicable for cancer risk assessment.

d. EPA's Approach to Assessing the Overall Weight of Evidence for Non-Cancer Health Effects of PFOA and PFOS is Not Consistent with Guidance and Methods are Neither Transparent nor Reproducible

EPA likewise did not follow its own guidance in determining that PFOA and PFOS exposure is associated with numerous noncancer health effects including, but not limited to: "effects on the liver (e.g., liver cell death), growth and development (e.g., low birth weight), hormone levels, kidney, immune system, lipid levels (e.g., high cholesterol), the nervous system, and reproduction." For each type of health effect listed, EPA has not followed its own guidance (i.e., the IRIS Handbook) in evaluating the weight of evidence of the science, which shows, at most, inconsistent associations of the effects with PFOS and PFOA exposures. For several endpoints, EPA improperly conflates changes in biomarkers (e.g., antibody response, cholesterol, liver enzymes) with increased risk of adverse disease outcomes in humans.

Agencies cannot disregard available scientific evidence that is better than the evidence on which it relies.[69] However, this is exactly what EPA did in this Proposed Rule. As summarized below, EPA disregarded legitimate studies for reasons that are unclear or not justified in its Proposed Rule.[70] Key scientific evidence and uncertainties for each health endpoint as well as EPA's failure to properly review and evaluate the evidence are summarized below, using immune system effects as an example.

In EPA's draft toxicity assessments for PFOA and PFOS (USEPA 2023a,b), EPA derived multiple candidate RfDs across four non-cancer health outcomes comprising four endpoints (i.e.,

[69] *Kern County Farm Bureau v. Allen*, 450 F.3d 1072, 1080 (9th Cir.2006).
[70] Ultimately, "[t]he presumption of agency expertise may be rebutted if the agency's decisions, although based on scientific experience, are not reasoned." *Greenpeace v. NMFS*, 80 F.Supp.2d 1137, 1147 (W.D. Wash. 2000).

decreased antibody response, low birth weight, increased total cholesterol, and elevated alanine transaminase (ALT)[71]) from both epidemiological and animal toxicological studies that EPA deemed to have the "strongest weight of evidence" (USEPA 2023a,b). However, as described in Sections V.d – V.f above, EPA's process failures mean that none of these endpoints are, in fact, supported by the weight of evidence. Nonetheless, EPA determined that *"candidate RfDs derived from epidemiological studies were all within 1 order of magnitude of each other (10^{-7} to 10^{-8} mg/kg/day), regardless of endpoint, health outcome, or study population . . . In fact, [for PFOA] candidate RfDs within the immune, developmental, and cardiovascular outcomes are the same value"* (USEPA 2023a). EPA made similar conclusions for PFOS, as the candidate RfDs based on epidemiological studies *"within the developmental and cardiovascular outcomes are the same value"* (USEPA 2023b). As a result, EPA selected an overall RfD of 3×10^{-8} mg/kg/day for PFOA and 1×10^{-7} for PFOS.

As described in the following discussion, the range of estimated RfD values for PFOA that account for uncertainty is quite large. If uncertainties in each step of RfD derivation were estimated for each of the "co-critical endpoints" identified by EPA, it is unlikely that the resulting range of RfD values for each co-critical endpoint would be the same. To further increase confidence in the overall RfD, best practice would be to calculate ranges of RfD values that account for uncertainties within each of the endpoints identified as co-critical.

i. EPA relied on studies that used outdated and uncorrected NHANES data and did not conduct its own analysis or verify data accuracy

Many of EPA's conclusions related to non-cancer health impacts rely on previously published papers that used data sets that were ultimately rejected by the National Health and Nutrition Examination Survey (NHANES), the reporting entity, because they did not meet NHANES data quality requirements. EPA has largely relied on previously published statistical relationships between PFAS compounds and health outcomes that rely on NHANES data. NHANES regularly updates all its datasets, which in turn affects any previous quantitative analyses.[72] In 2021 and 2022, the NHANES Biospecimen Program processes were reevaluated to monitor quality control after a procedural error was identified. Following a comprehensive review of all surplus sample datasets generated between 1999 and 2018, NHANES modified certain data files to remove 15-20% of PFAS records that were initially included in error because it said that data did not meet program standards. Revised files were released in April 2022 (CDC 2022).[73]

While EPA notes the possibility of NHANES data updates, without conducting additional analyses, EPA cannot understand the ramification of these updates. EPA has not provided details on the data used in its analyses, or the year class of the data and it is thus very likely that

[71] ALT is an enzyme found primarily in the liver that can be used to assess liver health.
[72] *See* https://www.cdc.gov/nchs/nhanes/new_nhanes.htm and https://www.cdc.gov/nchs/nhanes/archive_new_nhanes.htm
[73] 3M queries to the Biospecimen Program email address were not answered so 3M cannot determine exactly which records were removed.

EPA findings using NHANES are based on uncorrected data. Best practice is for EPA to provide details on the data updates incorporated into its models.

In short, any and all previously published analyses EPA relies on that use NHANES PFAS data contain an unknown number of errors, which invalidates the published statistical relationships.

ii. EPA's assessment of developmental effects is flawed

In evaluating the impacts of PFOA/PFOS on development effects (namely, low birth weight), EPA did not appropriately employ methods described in the IRIS Guidance for evaluation of study quality and risk of bias.

EPA (USEPA 2023a,b) considered associations between PFOA and PFOS exposures and multiple developmental outcomes, including birth weight, birth length, head circumference, diagnosed condition of low birth weight,[74] or small for gestational age,[75] gestational duration, or diagnosed conditions such as preterm birth.[76] EPA determined that there was **moderate** evidence of an association between PFOA or PFOS and developmental effects based on epidemiologic literature. As discussed below, this determination was not supported by the underlying evidence and appears to be based primarily on inconsistently observed decreases in birth weight.

EPA also did not appropriately consider uncertainties – most of which directly implicate bias in studies' results. These uncertainties include:

- Potential bias due to pregnancy hemodynamics and sample timing
- Mixed evidence for gestational duration, measured as gestational age or preterm birth
- Inconsistent evidence with rapid growth measures, including postnatal height and adiposity up to age 2
- Little evidence for increased fetal loss
- No evidence for increased birth defects
- Limited dose-response evidence in birth weight deficit studies

Additional details regarding the strength of evidence related to developmental outcomes are described in the EPA Evidence Stream and Summary Judgments (USEPA 2023a Table 3-10; USEPA 2023b, Table 3-12). EPA's determination of a "moderate" level of evidence is not supported by the findings presented. Decreases in birth weight have not been shown to represent adverse effects or other clinically meaningful health effects. In the appraisal of study quality and risk of bias, EPA did not evaluate studies consistently, which led to the selection of candidate studies for POD development with critical limitations. PODs are estimates of the dose levels at which an adverse response is not expected; they are typically derived near the low end of the

[74] LBW- defined as a birth weight less than 5 pounds, 8 ounces, or <2500g; (Cutland et al. 2017)
[75] SGA - birth weight <10th percentile for gestational age; (Osuchukwu and Reed 2023)
[76] Gestational age < 37 weeks

observable range of data by using dose-response analyses within the selected studies. The PODs are then used as the basis for toxicity value calculations. Selection of reliable studies with limited bias is critically important for limiting the uncertainty in the derived POD and subsequent toxicity values.

1. Evidence integration of developmental outcomes demonstrated inconsistent evidence for an effect from PFOA/PFOS exposure.

EPA's categorization of the evidence regarding developmental outcomes is inconsistent with EPA's own criteria for an evidence synthesis judgement of "moderate" evidence in human studies. In order for evidence to be characterized as "moderate," the IRIS Handbook states that the evidence "*includes at least one high or medium confidence study reporting an association and additional information increasing certainty in the evidence. For multiple studies, there is primarily consistent evidence of an association with reasonable support for adversity, but there might be some uncertainty due to potential chance, bias, or confounding or because of the indirectness of some measures"* (USEPA ORD 2022, Table 6-4). IRIS guidance also states that supplementary evidence may address some of the uncertainty factors and raise a set of studies from "slight" to "moderate" evidence rating. Given the lack of consistency in the scientific literature, it is unclear how EPA concluded that there is "moderate" evidence that PFOA/PFOS affect developmental outcomes.

Moreover, EPA's determination of "moderate" evidence for developmental outcomes is a broad judgement that obscures the fact that such a designation is not consistent with EPA guidance for specific categories such as birth weight, birth length, head circumference, LBW, SGA, gestational duration, fetal loss, post-natal growth, and birth defects (USEPA 2023a Table 3-10; USEPA 2023a Table 3-12). EPA presented inconsistent or limited evidence of associations between PFOA/PFOS and each of the specific developmental outcomes, and did not provide judgements for any one of the specific developmental outcomes separately. Therefore, the strength of each evidence base is unclear.

In reviewing EPA's draft documents, the SAB stated that it was "not aware of evidence for associations of PFOA and PFOS with adverse consequences such as developmental delays in low birth weight/small for gestational age infants." (USEPA SAB 2023, p. 21). In short, EPA did not show consistent evidence that met the criteria for "moderate" evidence of an association between PFOA or PFOS exposure and developmental outcomes. Yet despite the uncertainties in the evidence of a relationship between PFOA or PFOS exposure and developmental outcomes, as acknowledged by EPA's own SAB, EPA selected decreases in birth weight as a critical endpoint and used it in POD derivation. Best practice is for EPA to follow its own guidance and determine evidence judgements for specific outcomes to select appropriate critical endpoints.

2. EPA did not appropriately consider the lack of consistency or plausibility demonstrated within the evidence base for decreased birth weight and incidence of adverse effects such as small for gestational age or low birth weight.

In reviewing EPA's draft documents, SAB recommended that EPA "*clearly demonstrate that the endpoints selected for POD development are well established, sensitive, adverse or precursor to adverse"* (USEPA 2023c, p. 20). Due to the lack of evidence for associations between PFOA and PFOS exposure and developmental outcomes (e.g., fetal loss or birth defects), lack of consistency in evidence for outcomes of LBW or SGA, and lack of evidence that measured decreases in birth weight are clinically relevant developmental outcomes, EPA has failed to meet the standard SAB deemed appropriate.

Two thirds of the studies (6 of 9) for PFOA showed some increased risk of either SGA or LBW, but did not have statistically significant results, meaning those studies are not reliable predictors of developmental effects. Critically, only 5 of the 11 examined PFOA in early pregnancy, which is the only period of exposure timing that is considered a lower risk of bias due to changes in pregnancy hemodynamics (Meng et al. 2018; Hjermitslev et al. 2020; Manzano-Salgado et al. 2017; Wikstrom et al. 2020; Chang et al. 2022). Of these 5 studies, only 2 identified statistically significant associations (Wikstrom et al. 2020; Chang et al. 2022). Of those, EPA selected one as a candidate study (Wikstrom et al. 2020). However, serum volume increases by about 50% during pregnancy, peaking at 30-35 weeks gestation (Salas et al. 2006), and glomerular filtration rate (GFR) increases similarly (40-50%) (Cheung and Lafayette 2013). These increases lead to a decrease in maternal serum PFAS concentration during pregnancy (Monroy et al. 2008; Steenland et al. 2018; Kato et al. 2014) and the magnitude of increases can be inversely correlated with birth weight. First trimester serum PFAS measures have less chance for bias from sample timing (USEPA 2023a, p. 3-212). Additionally, two meta-analyses by Dzierlenga et al. (2020) and Steenland et al. (2018) found that when PFOA was measured in early pregnancy, there was little to no association with LBW, suggesting that the timing of serum measurement is critical for accurate interpretation of study results.

While EPA described the collective evidence as "supportive" of an increased risk of LBW or SGA with PFOA/PFOS exposure, this is inconsistent with the fact that less than half of the studies reported statistically significant results, demonstrating that there was not consistent evidence of an association between PFOA/PFOS and these outcomes. Among the studies for PFOS, 5 of 10 studies examined PFAS measured in early pregnancy (Meng et al. 2018; Hjermitslev et al. 2019; Manzano-Salgado et al. 2017; Wikstrom et al. 2020; Chang et al. 2022), one of which was selected as a candidate study. Of the 5 studies, 2 reported statistically significant associations. Of the 7 high- or medium confidence studies, 2 reported statistically significant increased risks of SGA and only 2 of the 4 high- or medium-confidence studies reported increased risks of LBW (USEPA 2023b, p. 3-206-210).

EPA considered 6 high confidence studies of PFOA for POD development (Chu et al. 2020; Govarts et al. 2016; Sagiv et al. 2018; Starling et al. 2017; Wikstrom et al. 2020; Yao et al. 2021) (USEPA 2023a, p. 4-9). 2 of those were used for RfD determination because serum PFAS

was measured in the first trimester (Sagiv et al. 2018; Wikstrom et al. 2020) (USEPA 2023a, p. 4-43). The agency also considered 6 high confidence studies of PFOS for POD development (Chu et al. 2020; Darrow et al. 2013; Sagiv et al. 2018; Starling et al. 2017; Wikstrom et al. 2020; Yao et al. 2021) (USEPA 2023b, p. 4-9), and the 2 that were used for RfD determination were the same as those chosen for PFOA (USEPA 2023b, p. 4-39).

For 5 of the studies, it is unknown if the study populations had clinically relevant changes in birth weights with PFOA or PFOS exposure (Sagiv et al. 2018; Starling et al. 2017; Wikstrom et al. 2020; Yao et al. 2021), because only mean or median birth weights were reported, none of which were <2500g. Among a Belgian birth cohort of 248 mother-infant pairs, the number of LBW infants was not reported, nor was the risk of LBW with PFOA or PFOS exposure examined, so it is unknown if there was an increased risk of an adverse effect in this population (Govarts et al. 2016).

The remaining 2 studies reported the risk of an LBW birth in the population. A study of the births among women in the C8 population of highly exposed individuals observed no significant associations between LBW births and PFOA or PFOS exposure (Darrow et al. 2013). In a study of 372 births in Guangzhou between July and October 2013 observed no significant associations between LBW and PFOA exposure. A statistically significant association was observed between LBW and PFOS (OR=2.43, 95% CI: 1.09-5.147), but not by quartiles of PFOS exposure. Authors also noted that the relationship between PFAS and birth outcomes was controversial due to concerns regarding effective dose, reverse causality, and sample timing. Based on the limited reporting on birth weights and inconsistent evidence of increased risk of LBW in the candidate studies, the evidence for an adverse effect with PFOA or PFOS exposure in that study is not clear.

3. Candidate study selection for developmental effects was not transparent

In reviewing EPA's draft documents, the SAB recommended "that additional clarification and detail be included to support the selection of the critical effect and why this effect, beyond having the lowest POD_{HED}, is the most scientifically appropriate choice as well as being the most protective of public health." (USEPA 2023j, p. 38). In other words, SAB told EPA that it needed to show why critical studies were selected beyond simply having the lowest POD. EPA failed to do so with respect to its analysis of developmental effects.

The IRIS Handbook recommends that only well conducted high or medium confidence human and animal toxicological studies be considered for POD derivation (USEPA ORD 2022). EPA chose 6 studies for POD development for PFOA (Chu et al. 2020; Govarts et al. 2016; Sagiv et al. 2018; Starling et al. 2017; Wikstrom et al. 2020; Yao et al. 2021), and six for PFOS (Chu et al. 2020; Sagiv et al. 2018; Starling et al. 2017; Wikstrom et al. 2020; Darrow et al. 2013; Yao et al. 2021). EPA ultimately chose Wikstrom et al. (2020) for RfD derivation for both compounds. EPA did not describe why these studies were chosen among the multiple medium and high-quality studies for POD derivation, as the SAB requested. Over 30 medium or high confidence studies of birth weight and PFOA were available, and nearly 40 medium or high

confidence studies of PFOS and birth weight. All of the studies selected as candidates were rated high confidence, though 4 of the studies measured PFAS later in pregnancy or after delivery, making them subject to biases from pregnancy hemodynamics (Chu et al. 2020; Darrow et al. 2013; Govarts et al. 2016; Starling et al. 2017; Yao et al. 2021). Had EPA's critical appraisal been conducted consistent with recommendations of the SAB and the IRIS Handbook and taken factors specific to PFAS measurement (like timing) into consideration, these studies likely would not have been considered high confidence due to this bias alone.

Both candidate studies selected for the derivation of the RfD for developmental effects measured PFAS in maternal serum taken in early pregnancy – Wikstrom et al. (2020) measured serum PFAS at a median of 10 weeks (range 3-27 weeks), and Sagiv et al. (2018) measured PFAS in a comparable time frame (median 9 weeks; range 5-19 weeks). The Sagiv study also adjusted for estimated glomerular filtration rate (eGFR) to account for blood volume increase and higher flow rate in pregnancy. Despite the additional adjustments for eGFR by Sagiv et al. (2018), Wikstrom et al. (2020) was ultimately used for RfD derivation instead. EPA's rationale for choosing the Wikstrom study over Sagiv is not clear. EPA stated: "The RfD for low birth weight from Wikström et al. (2020) was selected as the basis for the health outcome-specific RfD for developmental effects as it was the lowest and therefore most health protective candidate RfD from these two studies" (USEPA 2023a, p. 4-52, USEPA 2023b, p. 4-48). EPA offered this rationale despite the SAB's recommendation, "that additional clarification and detail be included to support the selection of the critical effect and why this effect, beyond having the lowest PODHED, is the most scientifically appropriate choice as well as being the most protective of public health" (USEPA 2023j, p. 38).

EPA selected Wikstrom et al. (2020) as "the most scientifically appropriate choice," yet it is unclear whether there were clinically significant birth weight changes, and neither co-exposures to other PFAS nor eGFR levels were accounted for in the study's analyses. Thus, EPA failed to follow the SAB's recommendation to provide additional clarification and detail in its justification for outcome-specific study selection other than having the lowest candidate RfD.

iii. EPA's assessment of cholesterol[77] is inconsistent with best practice

EPA similarly did not adequately address the SAB request for transparency in its selection of outcome-specific studies for cardiovascular disease POD derivation. EPA acknowledges that the evidence for most cardiovascular-related endpoints such as changes in blood pressure, hypertension, coronary heart disease, and stroke is inconsistent (USEPA 2023a, b). Despite this limited evidence, however, EPA selects total cholesterol as the basis of the POD for cardiovascular effects. A complete and rigorous risk of bias assessment is needed to address underlying uncertainties and limitations in the available evidence base for changes in serum lipids, such as cholesterol. Contrary to SAB recommendations, the IRIS Handbook, and its own statements, for cardiovascular disease (CVD) outcomes, EPA failed to consider high-confidence and medium-confidence studies, including those that did not support an association between PFOA and PFOS exposure and CVD. EPA states that "*only well-conducted high or medium*

[77] EPA's conclusions regarding cardiovascular disease appear to be driven by its finding of an association between cardiovascular disease and cholesterol, which was the result of a flawed process, as discussed herein.

confidence human and animal toxicological studies were considered for POD derivation, as recommended in the IRIS Handbook {U.S. EPA, 2022, 10476098}" (USEPA 2023a,b; p. 4-1). EPA's statement misleadingly suggests that it considered both high-confidence and medium-confidence studies. In fact, EPA considered three studies for derivation of a cardiovascular POD for PFOA and PFOS (Dong et al. 2019; Lin et al. 2019; Steenland et al. 2009); these three studies are all described as "medium-confidence" in the draft assessment (USEPA 2023a,b; p. 4-7). However, EPA identified additional medium and high confidence studies but did not consider them for POD derivation.

Although EPA provides some information regarding evidence integration, the agency does not address the SAB's request for explanation of why a specific study was selected for POD derivation among multiple comparable choices for CVD outcome evaluation. Specifically, EPA does not explicitly describe why the high-confidence (Gardener et al. 2021; Li et al. 2021) and other medium-confidence studies (Averina et al. 2021; Christensen et al. 2019; Domazet et al. 2016; Donat-Vargas et al. 2019; Fan et al. 2020; Han et al. 2021; Jain and Ducatman 2018; Jain 2019; Kang et al. 2018; Kobayashi et al. 2022; Lin et al. 2009, 2019, 2020; Liu et al. 2018, 2020; Mora et al. 2018; Papadopoulou et al. 2021; Skuladottir et al. 2015; Spratlen et al. 2020; Tian et al. 2021; Zare Jeddi et al. 2021; Eriksen et al. 2013; Fisher et al. 2013; Geiger et al. 2014; Nelson et al. 2010; Sakr et al. 2007; Timmermann et al. 2014; Winquist and Steenland 2014) were not further considered for POD derivation.

Specific information on the selection criteria used by EPA to pare down the list of medium- and high-quality studies described in the Study Evaluations is necessary to provide confidence in the CVD POD derivation and toxicity assessment. Some studies not considered for POD derivation have study design components that may provide more confidence in the observed exposure-response relationships, including longitudinal designs or collection of multiple serum measurements (e.g., Donat-Vargas et al. 2019, Convertino et al. 2018). EPA did not provide justification and transparently describe the process used to select the three studies that were considered for dose-response evaluation (Dong et al., 2019; Lin et al. 2019; Steenland et al. 2009). Further, additional clarification on how to interpret "multiple judgments" within the findings of the study evaluation process is needed. For example, Steenland et al. (2009) was considered deficient (or "Low Confidence") in some EPA judgments (USEPA 2023a,b; see Figure 3-33), but EPA ultimately treated it as having adequate or "Medium Confidence."

Another deficiency that is contrary to the IRIS Handbook's guidance for study evaluation is EPA's inadequate control for confounding or correlated exposures (e.g., diet, family history, or co-exposure to other PFAS). EPA did not follow best practice as described in the IRIS handbook in that it heavily weighted studies that failed to consider confounding factors, such as family history and dietary factors, which are established contributors to CVD and serum lipids. However, none of the three studies considered by the USEPA for CVD POD derivation (Dong et al. 2019; Lin et al. 2019; Steenland et al. 2009) adjusted analyses to account for family history. Additionally, Dong et al. (2019) and Steenland et al. (2009) do not adjust for dietary habits or cholesterol intake. Intake of saturated fats, trans-fats, polyunsaturated fats, and monounsaturated fats are typically controlled for in randomized controlled trials evaluating impacts of cholesterol intake on TC, LDL-C and HDL-C, as intake is known to affect serum lipoprotein levels (Vincent

et al. 2019; Allen et al. 2016; Mensink et al. 2003). Cholesterol intake has also been shown to affect serum lipoproteins (Vincent et al. 2019). Because of these relationships between dietary patterns and circulating lipoproteins, the National Academies and USDA Dietary Guidelines recommend limiting trans and saturated fats and dietary cholesterol (while maintaining a healthy diet) as a major focus for reducing TC and LDL concentrations (USDA and HHS 2020). Lin et al. (2019) adjusted for "*percent of daily calories from fat*" and daily fiber intake from a "*semi-quantitative food frequency questionnaire with 177 items that measured dietary habits over the previous year.*" In their longitudinal analysis, Lin et al. (2019) found that associations between baseline PFAS and TC did not translate to an increased risk of hypercholesterolemia or hypertriglyceridemia in the lifestyle intervention group, indicating an effect of diet and exercise. Through use of poorly controlled cross-sectional analyses as the basis for RfD development, EPA failed to account for the effects of diet and exercise, well known contributors to CVD outcomes, in its assessment.

1. Contrary to EPA's best practices for systematic review and guidance, EPA did not evaluate study quality consistently for CVD

EPA did not transparently document risk of bias in each domain for each endpoint to ensure that the study quality evaluations are relevant to the endpoint being evaluated, as requested by the SAB. The SAB noted that:

> a protocol for risk of bias assessment and, more importantly, how that approach was used in the synthesis of evidence for each particular health endpoint is not clearly presented; and therefore, the results cannot be confidently evaluated for accuracy or transparency, or for consistency across health endpoints. This is especially important when a proposed systematic review protocol has not been previously registered or published. (USEPA SAB 2022, p. 6)

EPA's own best practices, as described in the IRIS Handbook, require that individual studies be evaluated for risk of bias and rated according to the Health Assessment Workplace Collaborative (HAWC) database. Here, EPA failed to comply with that guidance and best practice by failing to evaluate the risk of bias for each endpoint within a study that evaluated multiple endpoints. EPA presents Study Quality Evaluation results for each study with CVD outcomes, including serum lipid changes (see USEPA 2023a,b Figures 3-30 to 3-36). According to EPA, each study was evaluated for risk of bias using multiple study domains, including participant selection, exposure measurement, outcome ascertainment, confounding, analysis, selective reporting, and sensitivity. Results from each of these domains are synthesized into a characterization of the overall confidence in the individual study. Although individual studies were evaluated for risk of bias within each of these domains, review of the justifications supporting the risk of bias ratings provided in the HAWC database indicates that the risk of bias ratings for each domain are not necessarily determined relative to each individual endpoint considered in a study.

For example, EPA rated the domains for outcome ascertainment and results in Lin et al. (2019) as "Good" for serum lipids because "*blood samples were collected at baseline, annual, and semi-annual follow-visits*" (see USEPA 2023d for details). However, Lin et al. (2019) only collected PFOA and PFOS concentrations at baseline and the TC measurements considered as

the basis for POD derivation were also collected only at baseline. Therefore, this rating is misleading for the TC measurements considered by EPA if repeated measurements are part of the justification for a "Good" rating.

In another example, EPA rated the domains for participant selection, exposure measurement, outcome, and analysis in Gardener et al. (2021) as "Good," and these individual domain ratings contributed to the overall confidence categorization as a "High Confidence" study. However, as described within EPA's HAWC documentation, Gardener et al. (2021) is a pilot study that uses a non-nationally representative sample of pregnant women in the Vanguard Pilot Study of the National Children's Study. Although Gardener et al. (2021) evaluated serum lipid concentrations in pregnant women, the EPA's justifications regarding the quality of the outcome, confounding adjustments, and endpoint analysis specifically refer to the gestational age and birth weight endpoints only. Justifications for the confidence ratings of serum lipids as an endpoint in Gardener et al. (2021) are not provided in EPA's HAWC documentation.

By not properly conducting a systematic review and assessing studies for bias within individual endpoints, EPA did not correctly determine which endpoints were suitable for further evaluation. Thus, relevant endpoints and data may have been excluded or unreliable endpoints were included because EPA rated the study overall instead of refining its rating based on a specific endpoint of interest.

iv. EPA's assessment of liver effects is was not performed consistent with best practices.

EPA's assessment of liver effects of exposure to PFOA and PFOS is inconsistent with its own scientists' and the SAB's conclusions and again reflects EPA's failure to engage in a proper systematic review and evidence assessment process. As part of the hazard characterization and dose-response step, the IRIS Handbook states that EPA should consider the dose-response pattern in the relevant dose range and relevance of specific health outcomes in humans. In contrast to this recommendation, EPA cites animal studies showing liver effects which involve mechanisms of action with questionable relevance to humans, such as pathways moderated by peroxisome proliferator-activated receptor-alpha ("PPARα"). EPA also did not consider EFSA (2020), which noted there is evidence for elevated ALT due to PFOA exposure, but the adversity of this effect is uncertain because of the low magnitude of increases and no associations with liver disease. EPA even acknowledges that studies "have questioned the biological significance of relatively small increases in serum ALT (i.e., less than 2-fold) reported in animal toxicological studies (Hall. et al. 2012)." For PFOA and PFOS, EPA fails to characterize the biological relevance of changes in ALT or other liver biomarkers in the context of quantitative clinical outcomes. SAB similarly noted that "the limited available information does not demonstrate an increase in liver disease" (USEPA SAB 2022).

As an example of its failures in conducting systematic review and assessing study quality, EPA inappropriately based its candidate PFOS RfD for elevated ALT on a study by Nian et al., (2019). This was a cross-sectional study from China that reported a 4.1 percent change (95% CI: 0.6, 7.7) in ALT for every 1 ng-mL increase in PFOS. Excluding individuals who were taking medications, this percent change was reduced to 3.8 which was not statistically significant (95%

CI: -0.2, 7.8). Confounding variables were also not adequately controlled as most were described as binary (yes/no) which included alcohol, smoking and diet, which limits quantitative assessment. In addition, confounding from other PFAS were not adjusted for in the analysis of PFOS and PFOA. In EPA's section on Study Evaluation for Epidemiology Studies of PFOS and Hepatic Effects (page 3-25), EPA states that the Nian et al., (2019) approach to study participant selection and recruitment was not described in the paper. However, EPA still rates participant selection as "adequate." Given this information was not provided, EPA should have rated participant selection as "inadequate" based on its own criteria.

v. EPA's assessment of immunotoxicology is inconsistent with agency guidance.

In assessing immune efforts, EPA did not appropriately employ methods described in the IRIS Handbook for evaluation of study quality and risk of bias in evaluating vaccine repose. EPA did not evaluate evidence consistently across studies, nor did it synthesize evidence according to guidance. This omission again led to the selection of candidate studies for point of departure (POD) development with critical limitations. Selection of reliable studies with limited bias is critically important for limiting the uncertainty in the derived POD and subsequent toxicity values. If EPA had appropriately refined the study evaluation to the vaccine endpoint, thus accounting for aspects SAB recommended, a high level of uncertainty would have been found in the body of evidence. EPA failed to follow IRIS guidance to refine the study evaluation tool to the topic, including modifications to evaluation criteria to include factors specific to the exposure and outcome of interest, as well as potential confounders that specifically affect these associations. Such considerations would allow for the evaluation of specific factors critical to the overall study reliability conclusions. As a result of these process errors, the evidence presented does not support antibody response to vaccine as a critical endpoint and leads to a high level of uncertainty in the calculated toxicity values derived for this endpoint.

EPA (USEPA 2023a,b) considered multiple outcomes under the category of immune function, including vaccine response, infectious disease, immune hypersensitivity (allergy, asthma), and autoimmune disease. EPA determined that there was **moderate** evidence for an association between PFOA/PFOS exposure and immunosuppressive effects in human studies. This conclusion was based on its findings in PFOA studies of "*largely consistent decreases in antibody response following vaccinations (against two different infectious agents: tetanus and diphtheria) in multiple medium confidence studies in children*" (USEPA 2023a, p. 3-133), and a "*largely consistent decrease in antibody response following vaccinations (against three different infectious agents) in multiple medium confidence studies in children*" for PFOS (USEPA 2023b, p. 3-122). However, uncertainties in the conclusions for both PFOA and PFOS reflect:

- Inconsistent findings of decreased vaccine response in adult populations
- Inconsistent and/or imprecise findings of increased infectious disease
- Mixed findings of hypersensitivity, including allergy, asthma, and eczema
- Mixed findings for autoimmune disease

Additional details regarding the strength of evidence for outcomes related to immune function are described in the EPA Evidence Stream and Summary Judgments (USEPA 2023a, Table 3-7; USEPA 2023b, Table 3-10).

1. EPA's Selection of Candidate Studies Was Neither Transparent Nor Consistent

The SAB provided specific guidance to EPA that in selecting endpoints for POD development, "[*i*]*nternal inconsistencies in the criteria used for selection of endpoints for POD development should be addressed. It is also important to explain why a specific study of a health endpoint was selected when there are several possible choices*." This guidance from the SAB related to all PODs EPA considered. EPA's response was that it presented evidence integration judgments for each health outcome, including the rationale for the selection of a particular study for POD derivation (USEPA 2023c, p. 20-21). Although EPA provided some discussion of evidence integration, it did not explain the choice of study for POD derivation among multiple medium-confidence studies. The studies selected for POD development had critical deficiencies that should have excluded them from consideration.

First, the evidence base for vaccine response was not consistent. For example, the associations between vaccine response for tetanus or diphtheria with PFOA or PFOS exposures were not consistent either by age nor by vaccine type across several studies (Grandjean et al. 2012; Grandjean et al. 2017a,b; Mogensen et al. 2015; Shih et al. 2021). All of these studies were conducted based on cohorts from the Faroe Islands. Authors noted in 2012 that although negative associations were observed with vaccine antibodies, "*the overlapping confidence intervals and the lack of comparative toxicology studies prevent inference in regard to causal attribution*" (Grandjean et al. 2012). Similarly in 2017 they noted, "*inter-correlations between serum-PFAS concentrations prenatally and at different ages make it difficult to determine accurately the possible age-dependent roles of individual PFASs in regard to immune function outcomes"* (Grandjean et al. 2017b). The Agency did not adequately discuss the sporadic findings and uncertainties within the studies examining the Faroe Islands cohorts and to resolve those uncertainties before selecting a candidate study from this group of Faroe Islands cohorts (Butz-Jorgensen and Grandjean 2018).

The alternate candidate study selected by EPA also had critical limitations that should have been identified as part of a proper systematic review. Timmermann et al. (2021) was a cross-sectional analysis of vaccine response in Greenlandic children. Because the exposure and outcome are measured at the same time in a cross-sectional study, the study cannot determine if there is a temporal link between the exposure and the outcome. In addition, the timing of its exposure measurement is unclear compared to vaccination, as vaccination records were not available for nearly half (163/338 children) of the study population, which means the authors estimated the date of vaccination for purposes of evaluating antibody response. Notably, the

authors acknowledged that using an estimated date of vaccination likely caused information bias, possibly due to long and varied time intervals since the most recent vaccination. [78]

2. EPA did not appropriately employ methods described in the IRIS guidance for evaluation of study quality and risk of bias in evaluating vaccine response.

EPA's failure to follow its IRIS Handbook for evaluation of study quality and risk of bias led it to reach conclusions opposite those that would have been reached by an independent assessment of the evidence that did follow EPA's IRIS Guidance. According to IRIS guidance, additional chemical, outcome, or exposure-specific considerations for evaluating studies should be developed in order to identify issues that would be expected to result in critical biases and reduce the confidence rating of a study (USEPA ORD 2022, p. 4-2). Based on this guidance, the criteria for assessing bias in several of the evaluation domains (exposure assessment, outcome ascertainment, confounding, and sensitivity) should have accounted for factors specific to the exposure and outcome of interest, as well as potential confounders that specifically affect these associations. Such considerations would allow for the evaluation of specific factors critical to the overall study reliability conclusions.

An independent assessment was performed by ToxStrategies for studies examining vaccine response and PFOA exposure using the same IRIS framework for systematic review and critical appraisal of studies used by the EPA in the draft toxicity assessment for PFOA (USEPA 2023a, p. 1-10). *See* Appendix A. The independent assessment followed the IRIS guidance to modify several of the evaluation domains specific to the topic in order to identify critical issues regarding study quality and risk of bias, including consideration of factors that are specific to either the exposure, outcome ascertainment, confounding factors that affect the association of interest, and sensitivity issues including external validity and study construct. In contrast, the only apparent modification EPA made to its tool was to the exposure assessment domain criteria. This and missed critical issues that could render studies unreliable for dose-response assessment.

After identification and critical appraisal of studies examining vaccine response and PFOA exposure in the independent assessment, all studies received an overall rating of "deficient" or "critically deficient." Each study had deficiencies in participant selection, timing of exposure and outcome measures, or confounding, which resulted in a body of evidence that was of low quality with a high risk of bias. Based on these findings, vaccine response was not considered a critical endpoint for PFOA exposure, and no studies qualified for POD development.

Significant additional flaws and limitations in EPA's assessment of immunotoxicology, including EPA's failure to consider the conclusions of other agencies regarding immune effects

[78] Timmermann et al. (2022) is also a poor choice because the children examined in that study had very different chemical exposure levels than American children. They had high levels of mercury and PCB concentrations compared to American children, and PFOS concentrations that were twice as high as American or Faroese children.

as a critical endpoint (and the Grandjean et al. (2012) study in particular), are described in further detail in Appendix A.

e. Significant Uncertainty in Benchmark Dose (BMD) Derivation Approaches Preclude Confidence in the Risk Values Calculated by EPA for Non-Cancer Endpoints

EPA also violated best practices and its own guidance when it failed to independently model and verify the underlying analyses to increase confidence and transparency in the BMDL derivation of each co-critical effect. Properly conducting BMD analysis is critical because the points of departure derived from the BMD analysis are the basis of EPA's proposed non-cancer RfDs. EPA does not transparently describe its process for key study selection or the impact of uncertainties in BMDL derivation arising from 1) the lack of consideration of pooled analyses, 2) reliance upon modeling assumptions, 3) model selection; or 4) benchmark response (BMR)[79] selection. These issues are discussed below and in detail in Appendices A and B.

i. EPA was not transparent and consistent in selecting key studies and models for BMD derivation

EPA's IRIS handbook and risk assessment best practice requires that the process for selection of key studies for use in BMD and BMDL derivation be clearly described, including identifying data quality objectives to ensure consistency and transparency. But here EPA did not propose data quality objectives, and it did not follow requirements for data quality assurance. As EPA itself has noted "[t]he strength of the DQA is that it is designed to promote an understanding of how well the data satisfy their intended use by progressing in a logical and efficient manner." (USEPA 2000c, p. 0-3). As a result of this process failure, key studies had critical deficiencies that preclude confidence in their findings and the subsequently derived regression coefficients or BMD(L)s. Dose-response models and BMD(L)s derived from poor quality or limited studies may not accurately describe the true exposure-response relationship and will therefore lead to inaccurate PODs and uncertainty in RfD derivation.

Additionally, when provided with multiple models from a given study or dataset, EPA provides minimal and inconsistent justification for selection of a single model for POD derivation. For some endpoints, EPA does provide limited justification for selection of individual models within a study; however, these justifications (e.g., selection based on p-values) are not statistically defensible nor do they align with EPA guidance for model selection (USEPA 2012). Other justifications, such as stated confidence in the BMDL or potential for confounding, are not transparently defined or consistently applied. As the range of BMD(L)s both within and among studies for a given endpoint can be uncertain, it is critical for the EPA to show a transparent model selection process to increase confidence that the POD is representative of the exposure-response and not biased towards an overestimation of risk. In other words, EPA's lack of transparency in how it selected models could lead EPA to rely on models that overestimate risk or select PODs that are highly uncertain. In addition to the lack of transparent study and

[79] A benchmark response is a predetermined change in response. It is used in determining a benchmark dose, which is the dose that corresponds to a specific change in adverse response, i.e., the benchmark response.

model selection, EPA did not validate or compare BMD(L)s derived from individual studies with BMD(L)s derived from pooled regression coefficients (when available). This issue is discussed in detail in Appendix A.

ii. EPA's BMD values have a high level of uncertainty

For derivation of BMD(L)s, EPA used a non-standard approach and relied on previously developed models or pre-defined regression coefficients as presented in the published literature. The use of non-standard approaches violates EPA's own guidance and means that its analyses do not accurately reflect the true underlying dose-response relationships. Traditionally, benchmark dose modeling is conducted by fitting dose-response models to mean or proportional responses at given exposures; EPA's (2012) BMDS guidance is designed for these traditional dose-response models. EPA did not independently validate or verify the published regression coefficients, nor did it transparently report the details of BMD modeling from the candidate studies. Key modeling information, as recommended in EPA's benchmark dose modeling guidance (USEPA 2012), is consistently absent from the published models, including analyses of model shape, model fit, the distribution or variance of the regression coefficients, and background [P(0)] responses. EPA did not critically evaluate the underlying response data to fill gaps in reporting of the modeling approaches or results. Therefore, EPA relied on assumptions regarding model shape, model fit, coefficient variance, model distribution, confounding, and background (or "zero-exposure") responses. Without verification of these factors, EPA cannot confirm that its assumptions are reasonable approximations of the underlying data, nor can it confirm that the estimated BMD(L)s accurately describe the dose-response. Moreover, EPA derived BMD and BMDLs from models with non-significant exposure parameters and with no consideration of model fit. EPA's benchmark dose guidance (USEPA 2012) states that modeled datasets should, at minimum, have a statistically or biologically significant dose-response trend. This issue is discussed in detail in Appendices A and B.

iii. EPA failed to demonstrate that use of a non-standard BMD approach is biologically appropriate

EPA discusses uncertainties in the draft toxicity assessments for PFOA and PFOS introduced through the use of regression coefficients (a non-standard approach) instead of response data for BMD modeling of epidemiological data. As noted above, the use of non-standard approaches may have also led EPA to make erroneous conclusions about the relationships of exposure and effects observed in human epidemiological studies. EPA used the information from Steenland et al. (2009) to validate the use of regression coefficients; Steenland et al. (2009) was selected due to the accessibility of the mean response information underlying the regression coefficients. EPA states that the difference in BMDLs generated through use of regression coefficients instead of mean response information is less than 3-fold different and therefore acceptable; EPA has not, however, demonstrated that this relationship is consistent across PFAS compounds, endpoints, studies, or publicly available information such as NHANES. EPA did not evaluate additional datasets with the raw data or mean response information in order to quantitatively justify that the BMDLs generated through this non-traditional approach are comparable to those generated through use of mean response information. Some of the publications relied upon by EPA, including the key study for total

cholesterol (Dong et al. 2019), are based on NHANES or other publicly available information and, as such, further sensitivity analyses should have been performed using these additional studies and endpoints to provide confidence in the approach used to derive BMD(L)s for PFOA and PFOS. The uncertainty analysis conducted by EPA is not sufficient for validating its use of regression coefficients instead of response data. This issue is discussed in detail in Appendix A.

iv. EPA's BMR selections are neither adequately justified nor consistently applied

BMD modeling approaches used by EPA were non-standard and relied upon published regression coefficients. EPA did not address the inconsistency in methods and approaches used for BMD(L) calculation, nor did it thoroughly consider or evaluate the sensitivity of selected models to changes in biological cutoffs or alternative BMR assumptions. Each of the endpoints selected as critical effects by EPA (e.g., serum lipids, birth weight, and vaccine response) have widely accepted clinical cutoffs that are considered biologically significant. However, EPA did not establish that the underlying exposures are significantly associated with the measured outcomes, after accounting for confounding, or increased incidence of adverse responses such as infection or cardiovascular disease. EPA may be inappropriately applying BMRs to evaluate changes in adverse outcome probability for non-adverse effects. This means that EPA may be deriving MBDs based on arbitrary changes in responses that are not actually adverse. Additional transparency is needed in order to understand 1) the methods used by EPA to estimate background exposure and probability; 2) justifications for BMR selection; 3) the impact of using alternative BMRs based on clinical cut-points on BMD(L) derivation; and 4) consideration of the strength of association between exposure and response. Additionally, in order to derive study-specific BMRs for Extra Risk, EPA relied on estimations of the study-specific intercepts of the study-reported regression coefficients, or slopes, in order to estimate response in an unexposed population; these estimations of the outcome probability in unexposed populations does not account for model uncertainty, variance in regression coefficients, or consideration of US population responses. Differences in BMR type, BMR sensitivity, and estimations of model intercepts (or hypothetical responses in unexposed populations) impact the estimation of the BMD(L) and subsequently derived RfD. This issue is discussed in detail in Appendix A.

v. EPA did not estimate the impact of modeling assumptions on derived BMDLs or how changes in these assumptions affect BMDL sensitivity

EPA used many assumptions to estimate BMD(L)s for changes in birth weight, immune response, and serum total cholesterol. Each assumption adds some quantifiable uncertainty to the derived BMD(L)s used for POD derivation. **Using analyses of changes in birth weight as an example, variations in estimations of background exposure, BMR type, and background incidence of low birth weight may increase the derived BMDL by approximately 30% to 210%, depending on the study and assumptions.** Uncertainty in the derived BMDLs, based on assumptions required to conduct modeling, impacts confidence in the derived PODs. EPA did not quantify or discuss the potential uncertainty in the BMDLs used for POD derivation or the sensitivity of the BMDLs to changes in the underlying assumptions. This critical oversight means that the PODs EPA used to derive RfDs may have significant uncertainty making its

assessment of non-cancer health effects unreliable. This issue is discussed in detail in Appendix A.

f. EPA Did Not Follow SAB Recommendations to Address Lack of Transparency, Lack of Reproducibility, and High Levels of Uncertainty in its Use of PBPK Models

PBPK models were used to simulate dosimetry during pregnancy and lactation for endpoints in human neonates and children. The SAB considered EPA's use of compartment based PBPK models to be reasonable but requested that details and assumptions required to run the model be documented sufficiently to allow reproduction of the simulations. EPA failed to address SAB comments regarding clarity of the PBPK model and EPA's lack of evaluation of the PBPK model performance. EPA placed the PBPK model code on Github to allow reproduction of simulations but failed to provide sufficient documentation or a required header file ('linear_interp.h') needed to compile and run the code. As a result, the conversion of the point of departure (POD) to the POD human equivalent dose (POD_{HED}) could not be reproduced and remains uncertain. These issues are discussed below and in detail in Appendix A.

i. EPA failed to adequately perform sensitivity analysis for PBPK modeling and provide a quantitative assessment of model performance.

EPA also failed to address SAB's recommendation that EPA better characterize the uncertainty that results from different parameters/assumptions by considering sensitivity analyses or Monte Carlo simulations with a range or distribution of values. EPA did not perform a quantitative assessment of model performance and, as such, failed to address SAB's comment. Best practice frameworks recommend the use of global and local sensitivity analysis (Johnson et al. 2021). EPA only performed local one-at-a-time sensitivity analysis. The parameter(s) driving the output value (i.e., intake-based HED derived from a serum measurement) were not identified and sufficient quantification was not provided in EPA's one-at-a-time sensitivity analysis to fully assess the overall relative importance of all model parameters. This issue is discussed in detail in Appendix A.

ii. EPA did not follow SAB's recommendation to use the Goeden et al. (2019) model as a more 'fit for purpose' model for deriving MCLGs

SAB recommended that EPA consider its use of the Verner et al. (2016) models and whether the Goeden et al. (2019) model that incorporates age-specific toxicokinetic and exposure factors would be more appropriate for deriving drinking water MCLGs. EPA compared use of the Verner and Goeden models and concluded that there was no "substantial improvement" in the outcome when modeled using either method. This statement was not supported by a side-by-side comparison of results or sufficient information to allow for assessment and an understanding of whether the appropriate model was selected. Data should be presented to support how the decision to use constant daily dose versus age-specific toxicokinetic factors (e.g., volume of distribution) and exposure factors (milk and drinking water intake) affects the model outcome. This issue is discussed in detail in Appendix A.

iii. EPA failed to account for life stage-specific variables in the PBPK model that impact the resulting POD_{HED}

The PBPK model used by EPA does not account for life stage (maternal, fetal, infant) differences in parameters such as elimination and clearance rate, half-life, and volume of distribution (Vd), as recommended by the SAB. To clarify the uncertainty in life stage-specific variables, age-related differences in chemical-specific parameters should be considered to better explain the variability observed (i.e., lack of fit) in predicted child serum levels compared to reported child serum levels of PFOA and PFOS (see Figures F-15 and F-12 in draft Appendices for PFOA and PFOS, respectively). Consideration of life stage-specific variables may also impact the resulting POD_{HED}. This issue is discussed in detail in Appendix A.

iv. EPA failed to quantitatively characterize uncertainty for PBPK modeling and HED calculations

Monte Carlo simulations recommended by the SAB were not performed by EPA for PBPK modeling of co-critical endpoints including vaccine response and birth weight to inform the variability inherent in the modeling approach. In addition, the variability of chemical-specific parameters used to calculate the HED for total cholesterol was not quantified by EPA. Therefore, range of uncertainty in the resulting POD_{HED} estimations were also not considered by EPA. This issue is discussed in detail in Appendix A.

VII. THE PROPOSED MCLs ARE NOT "FEASIBLE"

After determining to regulate a substance, EPA must set a "maximum contaminant level goal" (MCLG) for each identified substance at a level at which no known adverse health consequences will occur.[80] EPA must then set a "maximum contaminant level" (MCL) for each substance as close to the MCLG as is feasible.[81] Under the statute, "feasible" means "feasible with the use of the best technology, treatment techniques and other means which the Administrator finds... are available (taking cost into consideration)."[82] Some basic factors such as insufficient lab capacity and inability to reliably measure samples at the ultra-low levels in the proposed NPDWR render the proposed MCLs infeasible, contrary to SDWA requirements.

a. There is Insufficient Analytical Laboratory Capacity to Process the Quantity of Samples Required Under the Proposed Rule

EPA overstates the number of approved laboratories for the analysis of PFAS in drinking water and overestimates laboratory capacity. As of March 2023, there are 53 laboratories approved to support UCMR5, only 46 of which accept commercial samples (USEPA 2023g). As of April 21, 2023, the National Environmental Laboratory Accreditation Program (NELAP) Accreditation Management System lists only 38 total active laboratories certified to perform

[80] 42 U.S.C. § 300g–1(b)(4)(A).
[81] *Id.* § 300g–1(b)(4)(B).
[82] *Id.* § 300g–1(b)(4)(D).

either EPA Method 533, 537.1, or both, and that accept commercial samples for drinking water (NELAP 2023).

Moreover, analytical capacity varies by laboratory and, for that reason, the number of approved laboratories is a poor indicator of overall capacity. The larger laboratory networks are currently at or near capacity for PFAS analyses in non-drinking water matrices (e.g., non-potable waters, soils); as a result, customers are experiencing considerable delays in receiving analytical results. In the past year, 3M has experienced several commercial testing labs move from standard 10 business day turnaround times for analysis of PFAS in water to straining to achieve turnaround times of less than 30 business days, despite adding equipment and other resources. This has impacted the ability to meet required timelines for regulatory-related obligations, as well as the operation, installation, and optimization of water treatment processes. The current PFAS testing capacity constraint is occurring *prior* to finalization of the EPA 1633 method, a more resource intensive test method than is currently employed by commercial contract testing labs. Further capacity constraints are expected after finalization and implementation of the EPA 1633 method. In fact, Metropolitan Council Environmental Services, which administers industrial discharge permits in Minnesota, notified 3M that there are only a small number of laboratories in North American that can perform EPA draft method 1633, and that turnaround times for analytical results can be as long as 4 months. It is not realistic to expect that growth in laboratory services will keep pace with increased demand, given all that is required to construct, permit, and staff an analytical laboratory.

b. Testing Methods Do Not Provide the Analytical Capacity to Identify or Distinguish Between the Ultra-low Levels at Issue in the Proposed Rule

The proposed MCLs for PFOA and PFOS are set at the practical quantitation level (PQL) of 4.0 ng/L and EPA proposes setting a rule trigger level of one-third the MCL to determine compliance monitoring frequency (USEPA 2023f, p. 18681). The PQL is defined as "the lowest concentration that PFOA and PFOS can be reliably quantified" (USEPA 2023f, p. 18666). By definition, measurement results less than the PQL are not reliably quantified and therefore not suitable for quantitative comparison against a standard. EPA notes that most of the laboratories seeking UCMR 5 approval included a calibration standard below the 4.0 ng/L PQL, while also noting that, "measuring PFOA and PFOS results below the PQLs may not be achievable from all laboratories" (USEPA 2023f, p. 18867). EPA also assumes the laboratory market for PFAS analyses will expand (USEPA 2023f, p. 18867). It is not safe to assume that as the market grows, new laboratories will have the same proficiency as existing experienced laboratories that already may not be able to measure below the PQL.

VIII. EPA's BENEFITS ANALYSIS DOES NOT COMPLY WITH THE SDWA

The SDWA requires EPA to analyze the "[q]uantifiable and nonquantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of the treatment to comply" with each alternative

level the Agency considers.[83] As discussed below, EPA's benefits analysis fails to comply with this requirement and is arbitrary, opaque, and counter to fundamentals of toxicology.

a. EPA's Selection of Alternative MCLs for PFOA and PFOS is Arbitrary

In promulgating NPDWRs since the 1996 SDWA Amendments, which first require consideration of alternatives, EPA has routinely considered at least four regulatory alternatives.[84] As discussed below, in this rulemaking EPA considers only two theoretical alternatives to the proposed MCL of 4.0 ppt for PFOA and PFOS: 5.0 ppt and 10.0 ppt. EPA justifies its selection of regulatory alternatives not based on meaningful toxicological considerations, but instead on arbitrary comparisons to analytical levels and inapplicable state regulations. EPA states (USEPA 2023f) that it "considered an MCL of 5.0 ppt for PFOA and PFOS because it is 25 percent above the [practical quantitation limit] PQL of 4.0 ppt." EPA notes that this selection was based on input from a commenter in EPA's outreach consultations who "suggested the Agency consider a buffer of approximately 20 percent if the MCL is close to the quantitation level because water systems operate with a margin of safety and plan for performance that maintains water quality below quantitation levels." Thus, this value is intended to be a buffer between the PQL and MCL that could allow utilities to manage treatment approaches. EPA states that it disagrees that such a consideration is necessary but nonetheless applies the value yielded by the approach.

EPA (USEPA 2023f) also states that it "considered the MCL of 10.0 ppt to evaluate the national costs and benefits and whether the expected reduction in costs would change EPA's determination of the level at which the benefits would justify the costs (see Safe Drinking Water Act [SDWA] Section 1412(b)(6)(A))." The Agency maintains that this regulatory alternative level is consistent with State-enacted MCLs for certain PFAS, citing New York's PFOA and PFOS MCLs of 10 ppt.[85] There is no evidence that EPA considered different approaches nor the toxicological bases of various states' MCLs.

b. As a Matter of Toxicology, the "Alternatives" EPA Selected All Represent the Same Level of Exposure.

The alternatives EPA considered for PFOA and PFOS are meaningless, in violation of SDWA §1412 (b)(3)(C)(i). EPA prepared a health risk reduction and cost analysis and quantified health outcomes in the benefits analysis for the proposed NPDWR, where it purported to distinguish between national benefits at drinking water concentrations of PFOS and PFOA at 4.0 ppt, 5.0 ppt, and 10.0 ppt (USEPA 2023i). It is not possible to determine how EPA conducted its benefits analysis because EPA did not make its model or important inputs into the model available in the public docket. What is clear is that EPA failed to acknowledge that

[83] SDWA §1412(b)(3)(C)(i)(I).
[84] *See* National Primary Drinking Water Regulations: Lead and Copper Rule Revisions, 84 Fed. Reg. 61684 (2019) (considering four alternative regulatory options); National Primary Drinking Water Regulations; Arsenic and Clarifications to Compliance and New Source Contaminants Monitoring 66 Fed. Reg. 6976 (2001) (considering four alternative MCL levels); and National Primary Drinking Water Regulations; Radon-222, 60 Fed. Reg. 59246 (1999) (considering seven alternative MCL levels).
[85] EPA ignores that states have implemented a range of PFAS MCLs, some greater than 10 ppt., without further explanation for its use of 10ppt.

chemical exposures from drinking water at 4.0 ppt, 5.0 ppt, and 10.0 ppt are toxicologically indistinguishable based on fundamental principles of toxicology and dose-response (Waddell 2008, 2010) and further detailed below. The numerically quantified health outcomes for those concentrations are not meaningful for public health.

Toxicology at its most fundamental level is based on the chemical reaction of a substance with a biological receptor. The activity of such chemical reactions is measured based on a logarithmic scale (Waddell 2008). Thus, dose-response relationships which describe the relationship of the amount of a substance to the effects from these biological reactions are assessed using a logarithmic scale. Consequently, when considering a logarithmic scale, only doses that differ by an order of magnitude (*i.e.,* 10-fold) or more are biologically distinguishable.[86] EPA even incorporates this concept into its own definition of a reference dose (USEPA 1993) "is an estimate **(with uncertainty spanning perhaps an order of magnitude)** of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." [emphasis added]. This definition highlights that it is not meaningful to distinguish between exposure doses occurring within an order of magnitude (*i.e.,* 10-fold) of one another.

EPA's attempt to differentiate among health effects associated with the proposed MCL and the two regulatory alternatives—4.0 ppt, 5.0 ppt, and 10.0 ppt—is at best a theoretical exercise that lacks any toxicological relevance. This lack of relevance becomes obvious when human exposure doses are derived from the respective concentrations in drinking water and compared on a logarithmic scale.

However, the EPA (USEPA 2019) *Exposure Factors Handbook* provides information on drinking water intakes, and the following calculations can be conducted for any age group without yielding fundamentally different results. For this calculation (Table 7-1, Figure 7-2), the two-day average per capita estimates of combined direct and indirect water ingestion for all ages at the 95th percentile, which EPA listed as 37.1 ml/kg-d, was applied.

[86] The logarithmic nature of toxicology is also the reason why the dose selection for dose-response studies is generally advised to span two to four orders of magnitude (e.g., OECD, 2018 Test No. 408; USEPA, 2000 Health Effects Test Guidelines OPPTS 870.3050): it allows for an investigation of equidistant doses on the logarithmic scale in half-unit steps, e.g. log(1)=0, log(3.16)=0.5, log(10)=1, log(31.62)=1.5, log(100)=2, etc..

3M Company

3M Center
St. Paul, MN 55144-1000
651 733 1110

Table VII-1. Calculation of Hypothetical Exposure Doses (pg/kg-d) at Each Regulatory Alternative.

Exposure Dose by Data Transformation	4.0 ppt	5.0 ppt	10.0 ppt
Dose pg/kg-d	148.4	185.5	371.0

And displayed graphically:

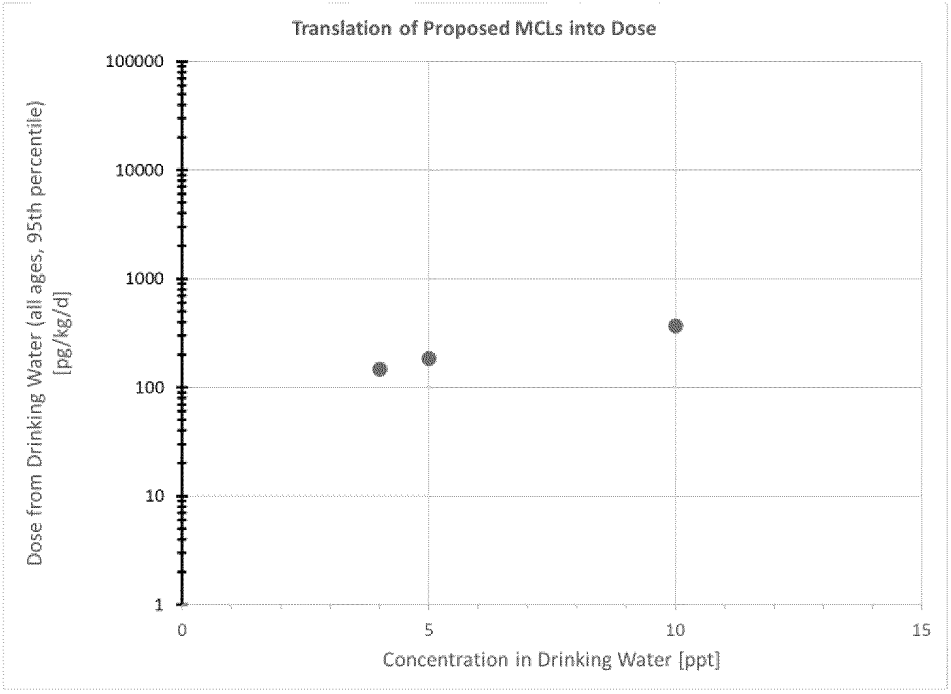

Figure. VII-1. Presentation of Exposure Doses Resulting from Proposed PFOA and PFOS Regulatory Alternatives.

The plots of daily exposures from drinking water that contains 4.0 ppt, 5.0 ppt, or 10.0 ppt of a substance (Figure 9-2) powerfully clarifies why dose should be considered on a logarithmic scale. In this figure, the y-axis is adjusted to a logarithmic scale to demonstrate that the three doses are actually all within one order of magnitude of each other (i.e., between 100 and 1000 pg/kg/d, a 10-fold range). In fact, the difference is within 2.5-fold. Accordingly, applying EPA's definition of a reference dose, there would be no discernable differences between exposures occurring at 4.0 ppt, 5.0 ppt, or 10.0 ppt. Therefore, when presented on a toxicologically accurate scale, these three exposures cannot be expected to be biologically different from one another. Any hypothesized health benefits from choosing one of the proposed concentrations over the other are just that: hypothetical and speculative.

c. The Uncertainties in Parameters Used by EPA Thwart the Ability to Accurately Distinguish Between 4.0, 5.0, and 10.0 ppt.

Even though EPA listed numerous uncertainties in its benefits analysis, it failed to acknowledge that these uncertainties make it impossible to practically distinguish effects at

concentrations of 4.0 ppt, 5.0 ppt, and 10.0 ppt. A slight change in assumptions within the spectrum of uncertainties might mathematically result in completely different concentrations in drinking water. In other words, the uncertainties in EPA's analysis are so great that they dwarf the difference between these toxicologically indistinct alternatives such that they are not true alternatives.

The calculations in Table 7-1 represent daily exposure doses. In contrast, EPA derived human equivalent internal doses using sophisticated models, which are based on numerous assumptions regarding intra- and interspecies variables in toxicokinetics (e.g., volume of distribution, half-life, tissue distribution), toxicodynamics (e.g., gender differences, age differences, susceptible life stages, differences in adverse outcome pathways), exposure (e.g., translation of concentration in rat chow into systemic exposure dose, relative source contribution assumptions, deterministic vs. probabilistic exposure modeling), and more. The six tables named "Limitations and Uncertainties" in the Economic Analysis draft (USEPA 2023i) further document the myriad assumptions that underpin EPA's analysis.

Every assumption used for these models and endpoints introduces uncertainty. Multiple uncertainties can have combinations of effects. Those effects can be additive, synergistic, potentiating, or antagonistic, which in turn introduces even higher levels of uncertainty regarding the accuracy of the predicted effects at the three alternative drinking water concentrations—without even considering the precision of said models. The compounding effects of multiple uncertainties far outweigh the *de minimis* differences of exposures on the logarithmic scale, which makes any attempt to distinguish between the health benefits of 4.0 ppt, 5.0 ppt, and 10.0 ppt not only futile but impossible.

d. EPA's Calculation of PFAS Serum Concentration Lacks Transparency

In the Economic Analysis, EPA (USEPA 2023i) states that it "developed single-compartment PK models for adult males and females to estimate blood serum PFOA and PFOS concentrations," noting that they are described in the MCLG documents. EPA then states that it compares the differences in serum concentrations at each regulatory alternative level to published coefficients of changes in serum concentrations that have been associated with health effects (e.g., reduced birth weight). Although EPA states the pharmacokinetics models are described in the PFOA and PFOS MCLG documents (USEPA 2023a,b,c,d), neither these specific models nor the blood serum predictions are provided in the referenced material.

EPA's documents describe other pharmacokinetics models used for cross-species dosimetry or predicting points of departure to derive reference doses, but the "single-compartment pharmacokinetics models" used for predicting serum concentrations from drinking water – and subsequently for calculating benefits – are not described. EPA's entire benefits analysis hinges on these predicted serum data. It is the first parameter entered into the sequence of analyses that are used to estimate the health risk reduction benefits for the proposed MCL and the regulatory alternatives (e.g., Figure 6.1 of USEPA 2023i). EPA failed to clearly provide its predictions of the serum concentrations expected in populations consuming drinking water at the proposed MCL of 4.0 ppt and each regulatory alternative (5.0 ppt and 10.0 ppt) and identify if there are meaningful differences between the steady-state serum concentrations at each

alternative. Importantly, there is no evidence that these pharmacokinetics models have been peer-reviewed. EPA's lack of transparency in model details, data outputs, assessment of uncertainty, and interpretation of results are underlying critical deficiencies. Such an analysis requires peer review before it is used to support regulatory decision-making. Moreover, EPA's lack of transparency is particularly important with respect to serum concentration calculations because the outputs of those calculations are used to determine difference in benefits at each regulatory alternative.

e. Demonstration of Overlap in Serum Concentrations at Each Regulatory Alternative

Though EPA does not make available either its model or its predictions of serum concentrations, EPA cites a first-order single-compartment model pharmacokinetics model (Bartell 2017; Lu and Bartell 2020) that it adapts to calculate PFNA serum concentrations from drinking water exposures (USEPA 2023k). To highlight the shortcomings in EPA's approach, this same model could be used to predict PFOA and PFOS steady state serum concentrations at the proposed MCL and each regulatory alternative. The following example analysis is intended to illustrate that the small, predicted differences in serum concentrations are not meaningful because they do not account for uncertainties and inherent variability in the model input parameters (e.g., half-life).

Table 7-2 demonstrates the model's outputs using NHANES geometric mean serum concentrations as the starting serum concentrations and assumes the model's defaults for other toxicokinetic and intake parameters. The half-life parameter was adjusted based on the range of half-lives reported by EPA to illustrate how altering only the half-life parameter impacts the modeled serum concentrations. EPA (USEPA 2023a,c) states that, in humans, the half-lives of PFOA can range from 1.7 years (Xu et al. 2020) to 4.4 years (Fu et al. 2016). For PFOS, half-lives can range from 1.04 (Xu et al. 2020) to 60.9 years (Fu et al. 2016). For the calculation of points of departure, EPA (USEPA 2023a,c) selected a half-life of 2.7 years for PFOA (Li et al. 2017) and a half-life of 3.4 years for PFOS (Li et al. 2018), which is consistent with the model default (Lu and Bartell 2020).

As illustrated in Table 7-2, there is significant overlap in potential serum concentrations when inputting a range of half-lives for each regulatory alternative. For example, for PFOA, the predicted serum concentration at the 10.0 ppt and the shortest half-life (1.7 years) is 2.54 ng/ml which is ***less than*** the serum concentration of 2.64 ng/ml predicted at the longest half-life (4.71 years) and the lowest regulatory level (4.0 ppt). When EPA's selected half-lives are applied to the comparison of 4.0 ppt and 10.0 ppt, there is less than a 0.82 ng/mL difference in the predicted PFOA and PFOS serum concentrations (Table 9-2). **These minimal differences in serum concentrations do not represent a meaningful difference in dose. Thus, there are likely not biologically relevant differences in effects between these regulatory alternatives.**

Table VII-2. Predicted Steady State Serum Concentrations (ng/mL) at Each Regulatory Alternative Using Lu and Bartell 2020.

PFAS	Half-life (years)	4.0 ppt	5.0 ppt	10.0 ppt	NHANES Geometric Mean (95% CI)	NHANES 95th Percentile (95% CI)
PFOA	1.7	2.02	2.11	2.54	1.42 (1.33-1.52)	3.77 (3.17-5.07)
	2.3 (model default)	2.14	2.26	2.85		
	2.7 (EPA)	2.23	2.36	3.06		
	4.7	2.64	2.88	4.09		
PFOS	1.04	5.36	5.40	5.60	4.25 (3.90-4.62)	14.6 (13.1-16.5)
	3.4 (model default and EPA)	5.72	5.85	6.49		
	60.9	14.46	16.78	28.36		

Notes:

Model Source: Lu S, Bartell SM. Serum PFAS Calculator for Adults, Version 1.2, 2020, www.ics.uci.edu/~sbartell/pfascalc.html.

Calculations assume a default starting serum concentration based on the NHANES geometric mean values for PFOA and PFOS (NHANES 2017-2018 Total Population https://www.cdc.gov/exposurereport/data_tables.html)

CI = confidence interval

Half-life Sources:

Model Default: PFOA is from Bartell et al. 2010 and PFOS is from Li et al. 2018

EPA: PFOA Li et al 2017 and PFOS Li et al 2018

The above analysis demonstrates that considerations of variability are critical in conducting an accurate scientific assessment of serum concentrations. EPA correctly notes that factors such as age and health status of individuals can impact toxicokinetic parameters such as half-lives (USEPA 2023a,c). However, it is not clear if or how such biological variability was accounted for in EPA's assessment of serum concentrations. EPA (USEPA 2023c) also states that "linear PFOS molecules exhibit longer half-lives than branched forms," but it is not clear if EPA considered those differences. Variability in other toxicokinetic parameters, such as volume of distribution or clearance rates, would add further uncertainty to the serum predictions. This inherent uncertainty in the alternatives analysis renders the overlap in serum concentrations at 4 ppt and the regulatory alternatives too great to be biologically distinct.

Additionally, EPA's apparent approach to predicting serum concentrations based on intake of drinking water contradicts its own statements in the MCLG documents (USEPA 2023a,c). In describing studies on half-lives for both PFOA and PFOS, EPA states, "**there is insufficient data to correlate PFOS [and PFOA] intake measurements to serum/plasma** and urine concentrations" [emphasis added]. Given this conclusion, it is unclear why EPA determined that predicting serum concentrations as the basis of the benefits analysis was appropriate, in light of the significant population and biological variability in the underlying estimates of exposure and toxicokinetics. EPA's approach is not scientifically supportable.

These critical flaws in EPA's prediction of serum concentrations are then propagated through its benefits analysis, where EPA attempts to apply exposure-response relationships to assess associations with adverse disease outcomes and other estimates of impacted populations.

There is simply no basis for distinguishing health outcomes across the regulatory alternative concentrations. Because there are no biologically meaningful differences between the serum concentrations at each regulatory alternative concentration (as explained above), the outputs of the benefits analysis also are neither meaningful nor valid. EPA has not chosen appropriate regulatory alternatives and there are likely no distinctly quantifiable health benefits at each of the alternatives.

f. Exposure-Response Relationships Were Improperly Selected

To calculate the health-risk reduction benefits based on serum concentrations, EPA extracts from literature or independently reanalyzes various exposure-response slope factors that are intended to demonstrate a quantitative relationship between a change in serum concentrations and a specific health effect. For both PFOA and PFOS, EPA evaluates the health effects of reductions in birth weight and increases in total cholesterol. EPA also considers increases in renal cell carcinoma risk for PFOA and increases in blood pressure for PFOS. For each endpoint, EPA selects relationships between serum levels and health effects that are not supported by the underlying studies or are based on uncertain reanalysis of data. These flawed analyses add to the misleading conclusions associated with basing the analysis on inappropriate and indistinguishable regulatory alternatives.

For reduced birth weight, EPA uses an exposure-response slope factor of –10.5 g per ng/mL for PFOS from Steenland et al. (2018), which is a random effects meta-analysis based on 24 studies. Contrary to EPA's assessment, however, Steenland et al (2018) concludes, "current human evidence provides only modest support for decreased birth weight with increasing PFOA. Studies with a wide range of exposure, and studies with blood sampled early in pregnancy, **showed little or no association of PFOA with birth weight**. These are studies in which confounding and reverse causality would be of less importance." (Emphasis added). In other words, EPA relies on an association for an endpoint that is not supported by the underlying publication. For PFOS, EPA conducts its own meta-analysis of data presented in Dzierlenga, Crawford et al. (2020) deriving an exposure-response slope factor of –3.0 g per ng/mL, even though Dzeirlenga et al. (2020) itself found that "when blood was drawn at the very beginning of pregnancy, there was essential no relation of birth weight to PFOS." This meta-analysis has not been peer reviewed, which calls into question the validity of EPA's reanalysis methods.

For the endpoints that EPA suggests are associated with cardiovascular disease (e.g., increased cholesterol), EPA also inappropriately derives exposure-response slope factors and ignores their biological relevance. For total cholesterol, EPA conducted its own meta-analysis and only included studies that had linear associations (6 studies for PFOA and 5 studies for PFOS) (USEPA 2023k). This selection criterion biases the results and misrepresents the overall weight of evidence, because other studies that did not show linear associations (6 studies for PFOA and 7 studies for PFOS) were ignored altogether in the calculation of the exposure-response slope factor. Like the birth weight analysis for PFOS, this analysis is not peer reviewed. EPA (USEPA 2023i) also states that it used "untransformed serum PFOA/PFOS," which means that it did not evaluate the relationship using a log scale. The importance of using a log scale is described in Section VII.b above. The associations with total cholesterol also are not biologically significant. For example, EPA derives an exposure-response slope factor for

PFOA equal to 0.08 mg/dL per ng/mL, which means that for every 1 ng/mL increase in serum PFOA, total cholesterol increases by 0.08 mg/dL. Based on the demonstration of serum concentrations described in Section VII.d above, the difference in serum concentrations between 4.0 ppt and 10.0 ppt was less than 1 ng/mL. A change of 0.08 mg/dL of total cholesterol is not biologically meaningful, since total cholesterol is typically reported in mg/dL as whole integers (e.g., 175 mg/dL or 200 mg/dL); cholesterol is not measured or reported to the hundredths of mg/dL. Thus, a potential change in total cholesterol going from a drinking water exposure at 4.0 ppt to 10.0 ppt would not likely be measurable. For PFOS, the exposure-response slope factor is 1.57 ng/dL per ng/mL, which also does not represent a biologically significant change in cholesterol, especially over small changes in serum concentrations.

The exposure-response slope factor of 0.00178 per ng/mL for PFOA and renal cell carcinoma risk is apparently derived from Shearer et al (2021). This publication and its supporting information, however, do not report this value. Shearer et al (2021) instead reports odds ratios, which are not linear associations. EPA should transparently describe how it generated this exposure-response slope factor. Additionally, as described previously (see Section V.c), this study is fundamentally flawed and did not show consistent dose-response relationships. Thus, deriving an exposure-response slope factor from a study that did not demonstrate a linear dose-response is not scientifically valid. Notably, EPA does not assess risks of cancer from PFOS exposure as part of the benefits analysis. This omission may indicate that there is not enough evidence to support a quantifiable association between PFOS exposure and cancer, which contradicts EPA's conclusions that PFOS is "likely to be carcinogenic."

EPA's approach to selection of exposure-response slope factors is scientifically flawed, lacks transparency, and disregards the biological relationship of exposure and effects. EPA should consider and discuss the exposure-response slope factors in the context of biologically relevant effects and obtain peer review for any novel analyses. EPA's analysis egregiously misrepresents any meaningful determination of health risk reduction benefits between the proposed MCL and regulatory alternatives.

g. EPA's Estimate of Decreased Cardiovascular Disease (CVD) Risk is Not Reproducible or Transparent

The estimated CVD risk reduction derived by EPA in the Economic Analysis for the proposed PFOA and PFOS NPDWR is systematically flawed. Issues with the estimated CVD risk reductions stem from deviations from EPA's guidance for study selection and dose-response analysis and are compounded by a lack of transparency and reproducibility in EPA's methods.

i. EPA's study quality evaluation and study selection process are not consistent and are not transparent

EPA used meta-analytic approaches to derive a pooled estimate of the slope of a linear function of exposure-response between serum PFOA and PFOS (ng/dL) and serum total cholesterol (TC) (mg/dL) for use in the Economic Analysis (USEPA 2023c). These pooled slope estimates are developed independently for PFOA and for PFOS. Pooling information across epidemiological literature through use of meta-analysis allows for incorporation of individual-

study uncertainty and consideration of the full range of observed exposure-response relationships across epidemiological studies; this allows EPA to use the full body of evidence in lieu of selecting an observed exposure-response slope from one single study. The first step of this process is identification of studies that meet inclusion criteria for the meta-analysis. EPA relied upon the literature review processes from the Agency for Toxic Substances and Disease Registry (ATSDR, 2021) and EPA risk assessments (USEPA 2023a,b). These approaches identified 80 studies on PFAS (see USEPA 2023c, Figure F-1). From those studies, EPA further limited the included studies by the following criteria: the study must 1) be conducted on adults in the general population; 2) quantitatively measure TC and high-density lipoprotein cholesterol (HDLC); 3) evaluate exposure of PFOA and PFOS. Additional exclusion criteria included: 1) pregnant women, infants, or children; 2) reporting of only relative risks or odds ratios for hyperlipidemia or hypercholesterolemia as these measurements of response could not be used. EPA also stated that "*studies performed on specific population subsets, such as occupational populations, were not considered for inclusion in the meta-analysis due to the potential for greater levels of exposure to PFOA and PFOS in these populations compared to the general population*" (USEPA 2023k, p. F-2). In other words, EPA excluded studies on members of the population expected to have higher-than-average concentrations of PFOA and PFOS in their blood.

In the Economic Analysis, EPA states that "*[a]ll studies were evaluated for risk of bias, selective reporting, and sensitivity as applied in developing EPA's Toxicity Assessments and Proposed Maximum Contaminant Level Goals for PFOA and PFOS in Drinking Water (U.S. EPA, 2023a; U.S. EPA, 2023b)*" (USEPA 2023c, p. F-8). However as noted in Section V.d.iii, the risk of bias analyses presented by EPA and its systematic review methods lack transparency and consistency in the evaluation of study quality. Despite the lack of transparency and consistency in the process, EPA assigned a determination regarding its confidence in each study (based on EPA IRIS protocol for risk of bias, selective reporting, and sensitivity; *see* EPA 2023a,b, p. 3-147). However, the study quality ranking was not used as an exclusion criterion for the meta-analysis. Therefore, studies considered as "low confidence" by EPA (based on the study quality evaluation) were not excluded from the pooled analysis.

A total of 23 studies on PFAS and TC and HDLC in the general population were considered for inclusion in the meta-analysis (USEPA 2023c, p. F-2). Of the 23 studies considered for the Economic Analysis by EPA (USEPA 2023c), 14 total studies on adults in general populations met EPA's inclusion criteria. Eleven of the studies evaluated the relationship between serum TC and PFOA and 12 studies evaluated serum TC and PFOS. Each of these 14 studies are described in USEPA 2023c, Table F-1. This includes: **6 studies** on serum TC and PFOA/PFOS from NHANES[87] that represents the general US population (Dong et al. 2019; Fan et al. 2020; He et al. 2018; Jain 2019; Liu et al. 2018; Nelson et al. 2010); **2 studies** from other US populations, including prediabetic adults from a diabetes prevention program (Lin et al. 2019) and a potentially highly exposed population (Steenland et al. 2009); and **6 studies** on serum TC and PFOA/PFOS in other countries, including Canada (Fisher et al. 2013), a Canadian

[87] Studies based on NHANES are cross-sectional in nature, and therefore have limited utility for purposes of establishing causality (see discussion at the end of this section). Also see Section V.d.i noting significant concerns regarding studies using uncorrected NHANES data.

Inuit population (Château-Degat et al. 2010), Sweden (Li et al. 2020), Taiwan (Yang et al. 2018; C.Y. Lin et al. 2020) and China (Fu et al. 2014).

EPA does state reasons for exclusion of several additional general population studies that met its initial inclusion criteria (e.g., Eriksen et al. 2013; Fitz-Simon et al. 2013; Huang et al. 2018; Convertino et al. 2018). However, EPA does not clearly explain why other studies on adults in general populations (e.g., Donat-Vargas et al. 2019), clinical trials (e.g., Liu et al. 2020) or highly exposed populations (e.g., Canova et al. 2020; Zare Jeddi et al. 2021) were not considered. Despite being a clinical trial, in which exposure and response are typically known, Convertino et al. (2018) was judged "low confidence" or "uninformative" by EPA due to residual confounding by socioeconomic status (SES) and "*lack of information on allocation of participants to treatment levels*" (USEPA 2023a, p. C-23, C-44). However, other "low confidence" studies were included in the meta-analyses; in the Economic Analysis, four included studies were designated as "low confidence" due to deficiencies in participant selection, outcome assessment, or confounding domains (Fu et al. 2014; He et al. 2018; Yang et al. 2018; Y. Li et al. 2020). EPA conducted a sensitivity analysis to evaluate the impact of excluding all "low confidence", or higher risk of bias studies (reported in EPA 2023c, Tables F-2 and F-3), however EPA did not conduct sensitivity analyses to evaluate the impact of removing He et al. (2018), a low confidence study, from the "linear models only" pooled estimate or removal of all "low confidence" studies from the US/Canada only models. Inclusion of these low confidence studies may introduce bias into the pooled estimates. Additionally, this sensitivity analysis does not address studies not included in the "all studies" analysis. EPA should demonstrate that the pooled slope estimates are not biased through inclusion and exclusion of specific studies through 1) consistency in application of exclusion criteria; and 2) sensitivity analyses that quantify the impact of inclusion and exclusion of individual studies on the pooled slope estimates. Without additional sensitivity analyses, EPA cannot demonstrate that the pooled effects are not sensitive to (or driven by) one study, lower quality studies, or other specific populations that are not generalizable to the US.

Confidence in the sensitivity analyses that measure the impact of inclusion/exclusion of low confidence studies is further weakened by the lack of transparency and consistency in EPA's determinations of study quality (as noted in Section V.d.iii *supra*). Many of the studies considered "medium quality" by EPA have critical deficiencies, including inadequate control for confounding or correlated exposures and/or cross-sectional study designs. Without additional sensitivity analyses, including the exclusion of cross-sectional studies and further exclusion of "low confidence" studies, EPA cannot demonstrate that the meta-analyses are not sensitive to inclusion or exclusion of specific studies and improve confidence in the pooled slope estimates

Highly exposed populations include both occupational cohorts and communities that were exposed to elevated levels of PFAS in drinking water. Although EPA states that "*studies performed on specific population subsets, such as occupational populations, were not considered for inclusion in the meta-analysis due to the potential for greater levels of exposure to PFOA and PFOS in these populations compared to the general population*" (USEPA 2023k, p. F-2), this judgment is not consistently applied. For example, EPA included Steenland et al. (2009) in the meta-analysis despite the fact that "*Steenland et al. (2009) retained the results from a study of a highly exposed population in the United States (the C8 Health Project cohort)*" (USEPA 2023c, p. F-

4). Some of the studies **not** included in the meta-analysis (e.g., Eriksen et al. 2013; Fitz-Simon et al. 2013) **are** included as key studies in the PFOA (USEPA 2023a, Table A-6) or PFOS (USEPA 2023b, Table A-6) risk assessments. It is unclear why EPA would find those studies appropriate for use in risk assessments but not in derivation of a dose-response curve for its benefits analysis.[88] Exclusion of studies EPA itself identified as "key" or studies from highly exposed populations create substantial risk of biasing the results of the meta-analysis and limiting generalizability of the findings. These risks can only properly be addressed by EPA through inclusion in the meta-analysis and use of sensitivity analyses to measure the impact of omission.

Occupational exposures were excluded from the pooled analysis (e.g., Olsen et al., 2001, 2003; Olsen et al 2007; Costa et al. 2009). However, the estimated slopes used in the pooled assessment are an estimate of change in TC per ng/mL PFAS exposure, therefore information from these studies would be expected to be informative despite the expected difference in exposure levels. The models used in the meta-analysis are a continuous function of the relationship between exposure and TC outcomes (i.e., straight lines), and so the highly exposed, or occupational, groups should be just an extension of the same dose-response slope.

Further, occupational studies typically represent highly exposed populations and a lack of increased odds of CVD risk in these populations would indicate a potential lack of response in the general population with lower exposures. As noted by EPA (USEPA 2023a, p. 3-174), the occupational studies "*suggest no association between PFOA and TC in workers*", in part due to a lack of statistically significant associations for the observed increases in serum TC and the reported inverse association between changes in PFOA and serum TC reported by Olsen et al. (2012). EPA states that "*[c]ross-sectional occupational studies… reported positive associations between PFOS and increased serum TC…however, the association was not observed in longitudinal analyses*,"[89] which weakens the strength of the causal association as the significant associations were only observed in cross-sectional analyses that cannot establish a temporal relationship[90] between exposure and response (USEPA 2023b, p. 3-145). Findings from longitudinal analyses should hold greater weight in the evidence synthesis because they can establish that exposure precedes the observed response. Accordingly, best practice would be to benchmark the slopes of the pooled analyses against these occupational studies to ensure that the proposed exposure-response relationship is coherent across the full body of evidence. Additional sensitivity analyses should also be conducted with inclusion of these occupational populations. For example, EPA conducts a sensitivity analysis excluding "non-US/Canada and high exposure studies" but does not evaluate the pooled results from US/Canada populations including those high-exposure populations. These additional sensitivity analyses are necessary to ensure that the

[88] Although information required for incorporation of Erikson et al. (2013) and Fitz-Simon et al. (2013) into the pooled analyses were not available in the publications, EPA did not indicate that it attempted to contact the authors or to re-assess the underlying evidence to incorporate these study populations into the meta-analysis, which is recommended by Cochrane review processes to reduce bias from under-reporting in the primary literature.

[89] A longitudinal study is defined by repeated collections of sampling data in the same individuals over a period of time (typically years). A cohort study is a common example.

[90] Temporality is a criterion of the Bradford Hill criteria, an established and well-accepted list of criteria used to consider causal associations in epidemiology.

pooled slope used for the economic benefits analysis is representative of the reliable (or high-quality) studies from relevant populations.

EPA's reliance in its benefit analysis on cross-sectional studies is also in contradiction with its statement that "*the main considerations specific to evaluating the quality of studies on serum lipids included use of medications, fasting, and potential for reverse causality*." (USEPA 2023c, p. F-8). Cross-sectional studies, such as those based on NHANES data, cannot establish temporality and findings may be due to reverse causality. In other words, cross-sectional studies measure exposure and response simultaneously, and therefore cannot establish that the exposure occurred prior to onset of the measured disease or response outcome. When the exposure and response are measured simultaneously, it cannot be demonstrated that the measured exposure is not affected (or caused) by the response. As noted by Dong et al. (2019), "*The NHANES data are capable of examining the association but cannot address the issue of causality. Similar to other cross-sectional studies, this study* ***cannot answer*** *whether: 1) exposure to PFASs elevates the cholesterol level; 2) high cholesterol levels allow the storage of PFASs easier; or 3) joint factors simultaneously affect both PFASs and cholesterol*". *See also, e.g.,* Andersen et al. (2021); Fragki (2021). Therefore, inclusion of cross-sectional analyses in the meta-analyses is a limitation that must be addressed by EPA.

In summary, EPA does not clearly state the reasoning for inclusion or exclusion of all relevant studies from the meta-analyses. The studies selected for the economic benefits analysis are inconsistent with the studies included in the risk assessment for RfD derivation. This inconsistency limits confidence that that the meta-analyses for CVD risk include all applicable information, which then impacts confidence in the estimated economic benefits.

ii. EPA's dose-response model selection process is not transparent or consistent with generally accepted risk assessment and statistical approaches.

Of the pooled model options presented in EPA's Economic Analysis appendices (USEPA 2023c, Tables F-2 and F-3) EPA selected "linear models only" for use in its CVD risk reduction analysis. This means that EPA chose to include only models that describe a linear relationship (straight line) between exposure and response and excluded studies that fit a linear regression to logarithmically transformed data (i.e., log-linear models). Use of only studies with slope estimates based on linear models, instead of logarithmic or other transformations, limits analyses to 4 of the 14 studies on serum TC and PFOA and 5 of 15 studies on serum TC and PFOS (USEPA 2023c, Tables F-2 and F-3). In addition, studies considered "low confidence" by EPA are included in the limited numbers of studies included in the "linear models only" analyses. EPA's use of the "linear models only" resulted in the exclusion of higher-quality studies and could bias the analysis. Because of the significant likelihood that the "linear models only" approach omits critical information and biases the results, a proper analysis would require demonstration that the findings from the limited "linear models only" analyses are representative of the body of evidence and are not biased by the study selection criteria.

In other analyses in this rulemaking, EPA has relied on studies using logarithmically transformed data for estimating the slope of the exposure-response and BMD(L) derivation (e.g.,

Budtz-Jorgensen and Grandjean, 2018). However, EPA states that, for the economic benefits analysis, it "*selected the pooled slope estimate based on the studies using linear models to ease interpretability and to reduce bias due to backtransformations of effect estimates with log-transformed outcomes or exposures*" (USEPA 2023c, p. 6-55). EPA failed to show that its justification for use of the linear models was based on scientific accuracy; instead, the justification indicates that the selection of models was based on ease of use and not based on best science. Although conversion of non-linear studies into useable linear slope estimates requires mathematical assumptions that impart uncertainties in the backtransformed[91] estimates, EPA relied upon log-transformed evidence (e.g., Grandjean et al. 2012; Budtz-Jorgensen and Grandjean 2018) in support of derivation of PODs for RfD development and demonstrated a clear willingness to modify and make assumptions from the underlying evidence (see USEPA 2023a,b Appendix E for details of BMD modeling). For example, EPA estimated BMRs from Budtz-Jorgensen and Grandjean (2018) measured as the "*log2[tetanus antibody concentration]*" (p. USEPA 2023a, p.E-1). This means that EPA had to backtransform the evidence from Budtz-Jorgensen and Grandjean (2018) in derivation of the RfD. Therefore, the rationale to select the pooled slope estimate based only on linear models "*to reduce bias due to backtransformations of effect estimates*" is not consistent with approaches used by EPA in its risk assessments in the supporting documents for this Proposed Rule.

In addition, EPA's decision to base the pooled slop estimate only on linear models[92] removes a large portion of the complete body of evidence and does not integrate the findings from all studies. Critically, this approach likely biases the pooled estimate toward finding a statistically significant effect through 1) exclusion of higher quality studies; 2) exclusion of additional populations of interest; and 3) exclusion of non-linear models may better capture the observed dose-response relationship. As evidenced by the sensitivity and other meta-analytic models (e.g., Table F-2 and Figure F-4), inclusion of these additional studies results in a lack of a statistically significant dose-response between PFOA and TC. Meaning, overall, the full body of evidence indicates that there is likely no significant effect between PFOA/PFOS and serum TC. The fact that the "linear models only" analysis is the ***only*** pooled analysis of PFOA exposures that identified a statistically significant slope (p-value < 0.05) (see Table F-2) indicates that the "linear models only" analysis is not representative of the full body of evidence. For PFOS and TC, the pooled dose-response using *"linear models only"* was not statistically significant (p-value > 0.05). Inclusion of additional studies with non-linear models identified a statically significant (p-value < 0.05), albeit shallow, pooled slope estimate for some of the modeled relationships between PFOS and serum TC (Table F-3). The analyses presented in EPA's (2023c) Tables F-2 and F-3 show the meaningful impact that inclusion and exclusion of individual studies has on pooled slope estimates. Therefore, EPA must carefully evaluate its decision to use the "linear models only" slope estimates for the economic analysis and provide

[91] Backtransformation is defined as converting a transformed number (i.e., a log or square root of a measurement) to its untransformed equivalent (i.e., exponentiation or squaring of the log or square root).

[92] A linear (i.e., straight line) model is equivalent to a linear regression model with the function $y = mx + b$, where y = response; m = slope; x = dose; b = intercept. Non-linear models incorporate other parameters, such as exponential functions, or use transformation (e.g., logarithm) of the dose or response variable to improve description of the observed dose-response. Non-linear models allow for fitting either 1) a linear model to log-transformed dose and/or response data or 2) fitting a curve to the observed data, for which the slope is not constant and may be more steep or more shallow than the rest of the model in the exposure region of interest.

additional justification for the use of these models in lieu of models that incorporate more information. This justification is critical due to the differences between the "linear models only" and models with more complete information, both in terms of the magnitude and the significance of the pooled slope estimates.

Further, inclusion of linear-only models assumes that a linear dose-response best explains the observed dose-response relationships between PFAS exposures and serum TC changes. However, EPA has not clearly shown that linear assumptions are appropriate or consistent with underlying toxicological evidence, nor has it provided the information required for peer or public review. Non-linear models incorporate other parameters, such as exponential functions, or use transformation (e.g., logarithm) of the dose or response variable to improve description of the observed dose-response. Use of these non-linear models may allow for improved predictivity of the observed relationship between exposure and response.

Contrary to EPA guidance for dose-response analysis, EPA does not describe relative model fit for each of the included studies or the appropriateness or impact of linear assumptions. As stated by EPA BMDS guidance, "*an important criterion for selecting a fitted model is that the model provides an adequate description of the data, especially in the region of the BMR*" (USEPA 2012, p. 33).[93] Although EPA is not using a BMD to support this economic assessment, the model fitting criteria prescribed by EPA's BMDS guidance are generally accepted statistical practice. Evaluating the model's ability to predict the observed response (or "model fit") is a critical step in basic regression statistics. EPA's BMDS guidance also recommends visual inspection and plotting of residuals in order to evaluate deviations of the model predictions from the observed response. In selecting models, EPA recommends a stepwise process that 1) assesses the goodness-of-fit; 2) rejects models that do not adequately describe data in the dose-response region of interest; and 3) applies additional "*somewhat arbitrary*" defaults for model selection (EPA 2012, p. 39-40). Here, EPA has not shown that the linear models fit the observed TC responses from individual studies, nor that they accurately predict responses at exposures relevant to the general population. Moreover, EPA has not shown that the non-linear or logarithmically transformed models fail to more accurately describe the observed exposure-response. In the absence of causality information among the epidemiological literature, which is the case here, toxicological information could be used to inform on the expected model shape and the appropriateness of assuming linearity. EPA acknowledges this potential issue in its discussion of model limitations and uncertainties (EPA 2021; Table 7) when it states "*the derivation of PFOA/PFOS exposure-response functions for the relationship between PFOA/PFOS serum and TC assumes that there are no threshold serum concentrations below which effects do not occur.*" However, the impact of this uncertainty is described only as "uncertain" and not further addressed by EPA. Therefore, projecting economic impacts based on models that do not clearly demonstrate an exposure-response may overstate the predicted economic benefit.

For PFOA, when looking at the full body of evidence and pooled meta-analytic slope estimates (shown in Table F-2), EPA's pooled slope estimates are only statistically significant when using linear models only. The estimated slopes from the linear models, only, also indicate

[93] See Sections II.a and V.e for further explanation of BMDs and their import.

a steeper (or more potent) dose-response compared to slopes generated from pooled estimates of all studies and all lower risk of bias studies. This inconsistency indicates that the linear models likely are not adequately describing the full body of underlying evidence.

For PFOS, only two models from the studies EPA selected for determining the slope of the dose-response relationship have a statistically significant slope (p-value < 0.05): the serum PFOS and TC model including all lower risk of bias studies and the model excluding Jain et al. 2019 (shown in Table F-3). However, with little or no explanation, EPA changed its criteria for statistical significance (using and alpha value of 0.1 instead of 0.05) to support selection of the "linear models only" estimate that is not statistically significant (p=0.064). As stated by the USEPA, "*When including the five studies reporting linear associations, there was a positive increase in TC of 0.08 (95% CI: -0.01, 0.16) mg/dL per ng/mL serum PFOS (p-value=0.064, I2=84%) that was significant at the 0.10 level.*" (EPA 2023c, p. F-16). As stated in the Economic Analysis, the USEPA noted that "*While the association for PFOS and TC is not significant at the 0.05 confidence level, it is significant at the 0.10 confidence level (p = .064).*" (EPA 2023c, p. 6-55). No justification was provided for the change in the confidence level used to denote statistical significance. Notably, EPA also did not apply this change in criteria consistently, as evidenced by the statement "*When all studies were combined (12 studies, 15 results), EPA observed a* ***borderline statistically significant*** *positive increase in TC of 0.066 (95% CI: -0.001, 0.132) mg/dL per ng/mL serum PFOS* ***(p-value=0.055****, I2=100%) (Table F-3, Figure F-8).*" (p. F-16) [emphasis added]. The term "borderline statistically significant" is typically used when a study does not achieve statistical significance, but the p-value is close to the pre-determined cutoff. EPA does not explain why a p-value of 0.055 for the "all studies" model was considered "borderline" but the p-value of 0.064 for the "linear models only" is considered statistically significant. This illustrates that EPA is not consistently applying the criteria for statistical significance across models. Although changes in the criteria used for denoting statistical significance may be statistically and scientifically appropriate, these changes are typically made to make the criteria more stringent to adjust for multiple comparisons or reduce the risk of making a Type I error[94]. Any justification to change the criteria from the standard accepted value of a p-value of 0.05 should be done *a priori* and justified scientifically. EPA has failed to show that the change in p-value criteria to 0.10 was done prior to analyses, is consistently applied, or is supported by the underlying biology.

Based on the reported meta-analyses (Tables F-2 and F-3), it is not clear that there is a statistically significant dose-response relationship between PFOA/PFOS and serum TC when the full body of evidence is considered. Use of information with no significant change in response is not consistent with EPA guidance for dose-response modeling (USEPA 2012). Therefore, based on EPA's own guidance and widely accepted risk assessment practice, the available body of evidence indicates that use of changes in serum TC as the basis for EPA's CVD risk reduction model is not appropriate. Despite the lack of statistically significant slopes in the pooled analyses for PFOA and PFOS when all studies are included, or when only linear models were included for PFOS, EPA justifies its choice for use of serum TC in the CVD risk reduction

[94] A Type I Error is also called a "false-positive"; it is an error that occurs when a researcher identifies a statistically significant association when there is no true association. Criteria for defining statistical significance traditionally accept a Type I Error rate of 5% (or $p < 0.05$), or 95% confidence in the observed effect.

model by stating "*The literature provides sufficient support of a positive association (e.g., Château-Degat et al., 2010; Dong et al., 2019; U.S. EPA, 2023d; U.S. EPA, 2023e). The studies are large with more than 700 and 8,900 participants, respectively (Château-Degat et al., 2010; Dong et al., 2019) and have low risk of bias*." (USEPA 2023c, p. 6-55). However, as already described, EPA's literature review lacked guardrails designed to support the reliability of such conclusions. Had EPA followed appropriate systematic review processes, it likely would have found that the overall body of evidence (shown visually in Figures F-4 and F-8) is not clearly supportive of an exposure-response association and the sensitivity analyses (presented in Tables F-2 and F-3) do not support the conclusion of a significant relationship between PFOA or PFOS and serum TC across the pooled body of information. This indicates that the use of serum TC as the basis for the economic benefits analysis may overstate the expected reductions in serum TC with reductions in PFOA/PFOS, thereby also overstating the economic benefits. As a result of these process and analytical failures, EPA has not shown that the pooled dose-response functions are reliable or consistent with the underlying biology. Therefore, any use of these functions to estimate economic benefits from reduced health impacts is uncertain and unreliable.

Additional considerations of model applicability specific to meta-analyses, such as inter-study heterogeneity, must be addressed by EPA. In meta-analyses, the pooled estimate is intended to be derived from a body of comparable studies on similar populations. Inter-study heterogeneity, measured as I^2, describes the amount of variability in the response between studies and measures the probability that the pooled estimate contains information from populations that are ***not*** similar. This estimate reflects differences in study design, study population, and data analysis, among other study- and population-level differences. Increased inter-study heterogeneity decreases confidence in the generalizability and utility of the pooled estimate. For the analyses presented by EPA (2023c, Tables F-2 and F-3), the measured heterogeneity for the meta-analyses is relatively high (>75%) for most models. EPA does not discuss the impact this high level of heterogeneity has on its confidence in the meta-analytic models. Heterogeneity could be introduced into these models through differences in underlying population demographics, which is evidenced by the reduction in I^2 estimates for PFOA and PFOS when non-US/Canada and high exposure studies are excluded (see Tables F-2 and F-3). EPA uses "the large degree of heterogeneity in the pooled associations when all data were included" to justify use of the meta-analyses using linear models only (EPA 2023c, P. F-16). However, the I^2 is not meaningfully lower when comparing the PFOA "linear only" model with those for "all studies" or "all lower risk of bias studies" (I^2 range of 87.19 - 89.49; see EPA 2023c, Table F-2). Additionally, the PFOA and PFOS models that "exclude non-US/Canada and high exposure studies" have 1) more included studies, 2) a lower I^2 (or less heterogeneity) compared to the linear models only, and 3) are more representative of the US population that EPA is evaluating in its CVD risk reduction models. Based on these considerations, the model that uses only studies from the US/Canada, which do not show a statistically significant dose-response, are likely 1) more statistically appropriate and 2) generalizable to the United States population for whom this economic analysis is based. EPA should provide additional justification to explain its rationale for use of the "linear models only" in lieu of the US/Canada-based population studies.

In summary, EPA did not provide clear or consistent rationales for its selection of the "linear only" meta-analytic models for PFOA and PFOS for use in the CVD risk reduction analysis. Accordingly, the slopes selected for the CVD risk reduction analysis are unreliable and not consistent with EPA guidance.

iii. Dose-response slopes used by EPA for benefits analysis are different from those used in its risk assessment (i.e., RfD derivation).

As discussed in (USEPA 2023a,b), EPA uses the slope estimate from the exposure-response measured by Dong et al. (2019) as a basis for RfD derivation. EPA presents the slopes from Dong et al. (2019) in its sensitivity analyses, but fails to describe why the slope used in RfD derivation is different than that used for estimating the economic benefits. For example, EPA derives a benchmark dose (BMD) and benchmark dose lower limit (BMDL) based on the slopes, or regression coefficients, reported by Dong et al. (2019) (see USEPA 2023a, p. E-297 to E-300; USEPA 2023b, p. E-25 to E-29) and Steenland et al. (2019) (see USEPA 2023a, p. E-301 to E-306; USEPA 2023b, p. E- 29 to E-34), and the mean differences in serum TC by quartiles of exposure reported by Lin et al. (2019) (see USEPA 2023a, p. E-306 to E-307; USEPA 2023b, p. E-35 to E-36). Each of these individual studies are included in the meta-analysis. A summary of the derived BMD(L)s is presented in the main text (USEPA 2023a p. 4-33; USEPA 2023b. p. 4-29) and the appendices for the Proposed MCLGs for PFOA (USEPA 2023a, p. E-308, Table E-27) and PFOS (USEPA 2023b, p. E-37, Table E-25). The BMDLs from Dong et al. (2019) and Steenland et al. (2009) are used to derive candidate RfDs for PFOA (USEPA 2023a, p. 4-48) and PFOS (USEPA 2023b, p. 4-43). From the candidate RfDs, EPA chose the value of 3×10^{-8} mg/kg/day for PFOA and 1×10^{-7} mg/kg/day for PFOS derived from the BMDLs from Dong et al. (2019) as the basis for considering an RfD for CVD effects (USEPA 2023a, p. 4-52; USEPA 2023b, p. 4-48). Although EPA chose to use the slopes from a single study (Dong et al. 2019) to derive a BMDL and RfD for PFOA and PFOS, EPA used the pooled slope from the meta-analysis as the basis for the economic analysis. EPA does not provide justification for the lack of consistency in dose-response estimation between the risk assessments and the economic analysis. The difference in methodologies applied by EPA is unexplainable and there is no apparent reason as to why it is appropriate for EPA to use different dose-response slopes between the risk assessments and the economic analysis. As described in Section VII.g, the pooled slopes derived from the meta-analyses could be considered for RfD derivation, however EPA does not describe the meta-analyses in the Proposed MCLG risk assessment documentation. For PFOA, the slope estimates are relatively comparable (i.e., 1.48 mg/dL per ng/mL from Dong et al. 2019 and 1.57 mg/dL per ng/mL from the "linear models only" meta-analysis presented in the economic analysis; Table F-2). However, for PFOS, the slope estimates are drastically different (i.e., 0.40 mg/dL per ng/mL from Dong et al. 2019 and 0.079 mg/dL per ng/mL from the "linear models only" meta-analysis presented in the economic analysis; Table F-3). EPA must explain why Dong et al. (2019) was used as the basis for PFOA and PFOS RfDs, whereas a pooled slope estimate from studies using linear models was employed for estimating the economic benefit of reducing PFOA/PFOS levels to the RfDs.

iv. EPA does not transparently describe how the selected dose-response models inform the economic benefits analysis for CVD risk and fails to illuminate the impact on a benefit reduction analysis for PFOA and PFOS individually.

EPA states that it used the pooled slope estimates for PFOA and PFOS derived from the "linear models only" in order to inform the CVD risk reduction model. However, EPA does not transparently describe in its methods how these pooled slope estimates directly impact the models and estimated CVD risk. Outputs are reported as a pooled estimate of CVD benefits for PFOA and PFOS (see examples in USEPA 2021c, Table 6; USEPA 2023c Table 6-20). However, the estimated impact on serum TC per ng/mL PFOA (estimated at 1.574 mg/dL per ng/mL PFOA) is drastically steeper than that of the impact per ng/mL PFOS (estimated at 0.079 mg/dL per ng/mL PFOS). Even accepting that the dose-response slopes selected by EPA are appropriate, the slope for PFOA is nearly two orders-of-magnitude steeper, compared to PFOS, and therefore should have a larger impact on the estimated economic impact. EPA does not transparently describe its methods for integrating these disparate slope estimates for PFOA and PFOS or provide a description for how PFOA and PFOS exposures mixed to generate a single economic benefit model. The CVD risk reduction model is not described in a way that allows for transparent reproducibility of the approach or evaluation of sensitivity of the model to changes in estimated serum TC responses. It cannot be determined, based on the reported information, whether EPA is accurately accounting for the differences in exposure-response slopes for PFOA and PFOS. Moreover, it is impossible to determine from the record provided by EPA what benefit would be expected from the reduction of PFOA or PFOS alone. Sufficient information should be provided for the model to be independently verified.

Additionally, EPA does not evaluate the sensitivity of the CVD risk reduction model to changes in the estimated slope. As shown in Tables F-2 and F-3 of the Economic Analysis (USEPA 2023c), the estimated slopes for PFOA and PFOS are heavily dependent on the studies included in the meta-analytic models, with ranges changes in serum TC of 0.002 to 1.632 mg/dL per ng/mL PFOA and 0.0003 to 0.40 mg/dL per ng/mL PFOS. EPA acknowledges in its discussion of modeling limitations and uncertainties (USEPA 2021c; Table 7) that "*the derivation of PFOA/PFOS exposure-response functions for the relationship between PFOA/PFOS serum and TC levels assumes that the six studies used in meta-analysis capture the majority of PFOA/PFOS effects on serum TC levels*." EPA further states that the included studies "*may not represent all possible relationships between PFOA/PFOS and serum TC levels*" and describes the impact of this uncertainty as "uncertain." However, EPA does not further address or describe the potential impact of study inclusion or exclusion. EPA neither established that its selection of "linear models only" for meta-analysis was reasonable, nor did it evaluate the impact of other reasonable models (such as the US/Canada-population models) on CVD risk reduction estimates. It is best practice to consider a range of modeling options, especially given the uncertainties attributable to study inclusion and selection. Even if EPA were to select the linear models only, as a conservative estimate assuming a significant dose-response, the 95% CIs for the pooled estimate for PFOA are broad (e.g., 1.57 mg/dL per ng/mL PFOA [95% CI 0.0177, 3.13]) and the 95% lower limit for the pooled estimate for PFOS is negative (i.e. -0.005), indicating a reduction in serum TC (a beneficial effect) with increasing serum PFOS. Therefore,

the Economic Analysis may not be appropriately representing the accurate risk/benefit of reduction in PFOA/PFOS exposures. Uncertainties in the underlying slope estimates used as the basis for the economic benefits model translates into uncertainties in the estimated economic benefit for PFOA/PFOS reduction. Because the confidence interval produced by the studies chosen by EPA for PFOS includes both negative and positive slopes in the 95% confidence interval, the interpretation of the economic benefit is uncertain as to whether reductions in PFOS could be beneficial or harmful. Therefore, because of the uncertainties and lack of statistical significance, use of serum TC as the basis for Economic Benefit Analysis is likely not accurate, informative, or appropriate. EPA should provide uncertainty analyses to evaluate the range of impacts on CVD risk based on variations in slope assumptions and show its confidence in the underlying estimate of economic benefit.

In summary, the meta-analysis presented by EPA fails to follow best practice for meta-analyses (*e.g.* The Cochrane Handbook for Systematic Reviews of Interventions) and does not sufficiently account for underlying uncertainties in the dose-response relationships between serum PFOA/PFOS and serum TC. These uncertainties cannot be evaluated due to the complexity and lack of transparency in EPA's modeling documentation. Additional information regarding the impact of model selection and model uncertainty is needed to provide confidence in EPA's CVD risk reduction model.

IX. THE SDWA REQUIRES A COST-BENEFIT ANALYSIS FOR EACH MCL

The SDWA was amended in 1996 to specifically require cost-benefit analysis as part of the regulatory process. Id. § 300g-1(b)(3)(C), (4)(C). For each drinking water standard and each alternative standard being considered by EPA, § 1412(b)(3)(C)(i) provides that EPA must publish and seek public comment on an analysis of the health risk reduction benefits and costs associated with the proposed MCL. Id. § 300g-1(b)(3)(C)(i). The purpose of the cost-benefit analyses is to determine whether the benefits of the MCL justify, or do not justify, the costs of the proposed regulation.

EPA failed to determine whether the benefits of the HI-MCL justify the costs of the proposed regulation as it did not quantify benefits for any health point for PFHxS (USEPA 2023i). Because there is no quantitative benefit analysis for the HI portion of the rule, there cannot be a cost-benefit analysis for that portion of the rule. This violates the SDWA.

In the cost analysis EPA did conduct, documented in the *Economic Analysis for the Proposed Per- and Polyfluoroalkyl Substances National Primary Drinking Water Regulation* (USEPA 2023i), EPA uses opaque methodological approaches, fails to document the assumptions it applies, and fails to provide an adequate and transparent description of the analytical approaches, models, and tools that it uses to estimate costs. These omissions impose substantial uncertainty on many steps of this convoluted cost analysis. That uncertainty propagates and compounds throughout the analysis and imposes biases on various intermediate calculations. These biases subsequently yield potentially highly uncertain cost estimates of questionable accuracy.

EPA is missing critical data and is forced to use category-wide and/or nationwide estimates for baseline and compliance characteristics in the selection of treatment technology or non-treatment alternative. The absence of this data negates EPA's ability to present cost analysis results at the PWS-level. Instead, EPA collapses the more than 66,000 PWSs and summarizes nationwide cost and benefit estimates for 36 general PWS categories.[95] This generalization and reporting opacity prevent an evaluation of the potential distributional impacts of the proposed NPDWR.

a. EPA Did Not Account for the Fact that Costs Incurred are "Solely the Result of the" NPDWR, but Purported Benefits are Not.

EPA's analysis of the benefits of the proposed MCLs does not comply with SDWA §1412(b)(3)(C)(i)(I)'s requirement to analyze "[q]uantifiable and nonquantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits *are likely to occur as the result of treatment to comply with each level.*" And while the costs of the Proposed Rule are "solely as a result of compliance" with the Rule, the purported benefits are not.[96]

The first step in assessing the benefits of the Proposed Rule is to analyze the baseline conditions of the population in the United States. Average blood levels of PFOA and PFOS in the U.S. population have decreased by more than 70% and 85% respectively since 2000.[97] Moreover, based on the latest NHANES biomonitoring data from the 2017-2018 timeframe, average blood levels of PFAS such as PFHxS and PFNA also decreased significantly during that time.[98] In short, the baseline conditions of PFOA and PFOS exposure and blood serum levels, as well as PFAS subject to the HI, have decreased significantly in the past two decades, and there is no evidence indicating they will not continue to do so in the absence of the Proposed Rule.[99] The SDWA requires that EPA demonstrate the incremental decrease in illness or morbidity is meaningful and associated with the NPDWR itself, not other actions such as decreased exposure through voluntary cessation of manufacturing or use.[100]

The SDWA requires EPA to evaluate how the small fraction of any purported benefit of reduced PFOA and PFOS exposure would result from EPA establishing a NPDWR as opposed to

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[95] The Bayesian model EPA used to establish a national distribution of PFAS concentrations as part of the benefit-cost analysis did not include important covariates including distance from the PFAS source, topography, number of private drinking water wells in the area or state, climatology, distance to nearest large water and river systems, and other environmental factors. EPA's Bayesian model outputs are clearly not representative of the PFAS exposure distribution on a national level. Therefore, any benefit-cost conclusions drawn based on these data and model outputs do not represent the expected PWS concentrations across the US and cannot be used to support a MCLG. EPA does not provide details of the Bayesian model that are commonly included in the description by practicing statisticians. Therefore, evaluation of adequacy and believability of the model outputs cannot be understood, as required by EPA's QC practices.

[96] SDWA §1412(b)(3)(C)(i)(I).

[97] *See* https://www.atsdr.cdc.gov/pfas/health-effects/us-population.html

[98] The CDC stopped analyzing for PFBS since 2014 as part of its NHANES monitoring program because of the lack of detection in general population blood.

[99] *See* Biomonitoring Data Tables for Environmental Chemicals | CDC

[100] *See* SDWA §1412(b)(3)(C)(i)(I).

the myriad other factors already greatly reducing exposure over time. Under the SDWA, EPA must also show that the small incremental reduction in exposure is meaningful or even measurable in terms of benefit as compared to reductions from other means. Unless EPA can demonstrate an incremental benefit based solely on a NPDWR that outweighs the associated cost, which in fact would derive from the NPDWR, then the proposed NPDWR does not comply with the mandates of the SDWA.

b. EPA Improperly Inflated the Purported Benefits of the Rule

i. EPA improperly quantified benefits of co-removed substances rather than co-occurring substances

EPA quantified benefits of a co-removed substance (THM4) (USEPA 2023i, p. 6-108). This is inappropriate as it artificially inflates the benefits of the MCL. The SDWA contemplates quantifying benefits from co-occurring substances but **not** quantifying the benefits of all co-removed substances.[101] If EPA were to weigh the benefits of all co-removed substances as a result of treatment, every NPDWR would have its benefits inflated because any treatment technique will remove more than the targeted substance. For example, THM4 is not a PFAS and EPA did not make a determination that it is a co-occurring substance. EPA's inclusion of the purported benefits of THM4's removal in the cost-benefit analysis violates the SDWA's clear direction on considerations to be included in that analysis.

1. EPA's failure to clearly analyze the benefits of the PFOA and PFOS proposed standards separately overstates the benefits of the PFOS standard and precludes appropriate analysis of the individual MCLs.

EPA's failure to separately analyze the benefits of the PFOA and PFOS MCLs violated the SDWA directive that EPA analyze "quantifiable and non-quantifiable health risk reduction benefits for which there is a factual basis in the rulemaking record to conclude that such benefits are likely to occur as the result of treatment to comply with each level."[102] For example, CVD reduction is a major element of EPA's benefit analysis for PFOA and PFOS. CVD reduction depends on EPA's calculation of the impact of reduction of total cholesterol (TC). There are numerous issues with EPA's calculation of a dose-response relationship between serum PFOS and TC, including that they do not demonstrate what is normally considered a statistically significant relationship between those two factors. Even ignoring those issues, and assuming the accuracy of EPA's analysis, the impact on TC from reducing PFOS is nearly two orders of magnitude less than the reduction in TC that EPA calculated for PFOA.[103]

EPA has not provided enough information in the record to allow for replication of the benefit analysis. This lack of transparency with respect to the benefits of the proposed standards prevents meaningful comment on an aspect of the proposed rule with a very significant impact

[101] See SDWA §1412(b)(3)(C).
[102] SDWA §1412(b)(3)(C)(i)(I).
[103] EPA stated that "[w]hen using studies reporting linear associations between total cholesterol and serum PFOA or PFOS, EPA estimated a positive increase in TC of 1.57 (95% CI: 0.02, 3.13) mg/dL per ng/mL serum PFOA (p-value=0.048), and of 0.08 (95% CI:-0/01, 0.16) mg/dL per ng/mL serum PFOS (p-value=0.064.)" 88 FR 18709.

on EPA's analysis of whether the proposed standards meet the SDWA requirements that the benefits outweigh the costs.

c. The Benefit-Cost Model is New and Unvalidated

EPA previously developed a generalized tool known as the SafeWater Cost-Benefit Model (CBX) analysis tool to automatically estimate costs and benefits of drinking water standards. EPA indicates that CBX was designed to evaluate the impacts of a single proposed MCL and incorporates uncertainty in both input and output values to generate best-guess estimates of the impacts of proposed drinking water regulations. The single MCL CBX model was peer-reviewed.

For the proposed NPDWR, EPA developed a new model called the SafeWater Multi-Contaminant Benefit Cost Model (MCBC), which can track multiple substances and compare those to proposed MCLs developed for individual substances or mixtures of substances. EPA states that MCBC modifies the "structure of the occurrence data input to the model…to not only handle multiple contaminants, but to incorporate all information from the PFAS occurrence model on the predicted co-occurrence of contaminants," allows the assignment of more than one compliance technology, and estimates the costs and benefits associated with estimated reductions in multiple contaminants (USEPA 2023i).

Unlike the CBX model, the MCBC model has not been validated, approved for use via a public review and comment process, or peer-reviewed by independent third-party experts. The absence of a peer review process casts doubts on the validity, reliability, and accuracy of the cost estimates derived from its use. Peer review is particularly necessary because the modifications of the MCBC model relative to CBX are significant. For example, the estimation of statistical uncertainty is calculated differently when two or more uncertain variables are considered simultaneously relative to just one uncertain variable. The resulting uncertainty propagates and compounds throughout the analysis. The impact of the modifications of the MCBC model relative to its CBX counterpart is unknown and is not explained in sufficient detail. This issue is further complicated by the opacity of the analysis, which does not allow stakeholders and members of the public to evaluate whether the uncertainty is being appropriately addressed. Without peer review, expert validation, and a public comment process allowing for input from stakeholders of the PWS community, the MCBC model and its resulting cost estimates cannot be considered validated, reliable, or accurate.

d. Significant Data are Missing and Insufficient Detail is Provided Regarding Imputation

EPA lacks complete PWS-specific data across the 49,193 community water systems (CWSs) and 17,337 non-transient non-community water systems (NTNCWSs) in the Safe Drinking Water Information System (SDWIS/Fed) for many of the baseline and compliance characteristics necessary to estimate costs and benefits. Data are incomplete for design, average daily flow rates, water quality characteristics, treatment in-place, and labor rates, among other factors. EPA does not explain 1) the number of CWSs for which data are missing, 2) the number of each baseline and compliance characteristic for CWSs that are missing by CWS category, 3)

the number of NTNCWSs for which data are missing, or 4) the number of each baseline and compliance characteristic for NTNCWSs that are missing by NTNCWS category. EPA states that "[i]n some cases, the categorical data are simple point estimates. In this case, every model PWS in a category is assigned the same value" (USEPA 2023f, p. 18691). Consequently, many characteristics necessary to estimate costs and benefits—such as design, daily flow rates, water quality characteristics, among others—may be simple category-wide or nationwide averages. It appears that, in estimating the costs and benefits of the proposed NPDWR, EPA makes assumptions that are themselves based on assumptions.

The baseline and compliance characteristics are critically important to the cost analysis. For example, the SafeWater Multi-Contaminant Benefit-Cost Model (MCBC) uses the baseline and compliance characteristics as input values for a decision tree model. The decision tree model then selects the treatment technology or non-treatment alternative in response to estimated occurrence/co-occurrence estimates. These treatment technologies or non-treatment alternatives form the foundation of all costs and benefits estimated in response to the proposed rule. As EPA notes, "there are nearly 3,500 individual cost equations across the categories of capital and operation and maintenance (O&M) cost, water source, component level, flow, bed life (for GAC and ion exchange), residuals management scenarios (for GAC and ion exchange), and design type (for GAC)" (USEPA 2023f, p. 18692). These assumptions and imputation processes have a significant impact on the overall cost estimates, and EPA fails to transparently adequately describe them in detail or justify their use.

X. THE PROPOSED RULE DOES NOT PERMIT MEANINGFUL NOTICE AND COMMENT IN VIOLATION OF THE SDWA AND THE APA

The APA requires notice-and-comment rulemaking for agency rules, 5 U.S.C. § 553(b)-(c). This notice-and-comment process is a "crucial" rulemaking requirement to ensure that "regulations are tested via exposure to diverse public comment" and "affected parties [have] an opportunity to develop evidence in the record to support their objections to the rule and thereby enhance the quality of judicial review." *Daimler Trucks N. Am. LLC v. EPA*, 737 F.3d 95, 100 (D.C. Cir. 2013); *see Miami-Dade Cty. v. EPA*, 529 F.3d 1049, 1058 (11th Cir. 2008) (the purposes of notice requirements in notice-and-comment rulemaking under the APA are "(1) to ensure that agency regulations are tested via exposure to diverse public comment, (2) to ensure fairness to affected parties, and (3) to give affected parties an opportunity to develop evidence in the record to support their objections to the rule and thereby enhance the quality of judicial review"), quoting *Envtl. Integrity Project v. EPA*, 425 F.3d 992, 996 (D.C. Cir. 2005).

The D.C. Circuit has explained that an agency must "allow for meaningful commentary" not only as to the requirements that a proposed rule adopts, but also on the "technical basis for a proposed rule." *N. Am.'s Bldg. Trades Unions v. OSHA*, 878 F.3d 271, 301 (D.C. Cir. 2017); *see also Owner-Operator Indep. Drivers Ass'n v. FMCSA*, 494 F.3d 188, 199 (D.C. Cir. 2007) (the notice-and-comment requirement applies not only to the text of a rule but also to the "technical basis for a proposed rule" and the "critical factual material that is used to support the agency's position"). And the methods relied on by the agency must be made "available during the rulemaking." *Am. Radio Relay League, Inc. v. FCC*, 524 F.3d 227, 237 (D.C. Cir. 2008). An

agency cannot withhold key elements of its analysis—methods and data—until the final rule, because that defeats the purpose of the notice and comment process.

Unless the agency promulgates a revised proposal in which it fully discloses the data and methods on which it relies, so that interested parties may comment on them, the public will learn of that "uncommented upon data and calculations," *Am. Radio Relay League, Inc. v. FCC*, 524 F.3d 227, 237 (D.C. Cir. 2008), only when the "final rule reveal[s]" them. *CSX Transp. v. STB*, 584 F.3d 1076, 1081 (D.C. Cir. 2009). That is not a permissible way to conduct rulemaking governed by the APA.

Here, basic transparency requirements have been blatantly violated, as demonstrated above. See Scientific Integrity Fast-Track Action Committee (2022), which states, "development of Federal regulations follows strict procedures that support transparency, e.g., through issuance of Notices of Proposed Rulemaking that solicit public input and establishment of regulatory dockets containing related information that are open for public inspection. Continued vigilance is necessary to ensure these procedures are followed and that all underlying documentation—including related scientific information—is made publicly available." The Agency's numerous failures to disclose underlying data and methods for its analysis are described throughout these comments.

3M has been prejudiced by the agency's non-disclosure of these key bases for the Proposed Rule. While it comments here on the errors in EPA's analysis, and on the gaps in the data and methods EPA used, what these comments cannot address is the substance of the missing material. *See Horsehead Res. Dev. Co. v. Browner*, 16 F.3d 1246, 1268 (D.C. Cir. 1994) ("While we have noted that insightful comments may be reflective of notice and may be adduced as evidence of its adequacy, we have rejected bootstrap arguments predicating notice on public comments alone. Ultimately, notice is the agency's duty because comments by members of the public would not in themselves constitute adequate notice. Under the standards of the APA, notice necessarily must come—if at all—from the Agency"). The only way to cure this serious procedural defect is for the agency to issue a new proposed rule in which it discloses all the data and methodology underlying its conclusions, on which interested parties may then comment.

XI. CONCLUSION

As detailed in the above comments and the attached appendices, EPA's Proposed Rule does not comply with either the SDWA or the APA. The Proposed Rule is not based on best available, peer-reviewed science, as required by the SDWA, nor does it comport with EPA's own guidance on how to conduct the analyses underlying the Proposed Rule. These numerous failures are identified in detail in 3M's comments.

3M appreciates the opportunity to comment on the Proposed Rule.

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3M Company

3M Center
St. Paul, MN 55144-1000
651 733 1110

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Appendix B to 3M Comments on EPA Proposed National Primary Drinking Water Standard

EcoStat Comments on the United States Environmental Protection Agency's Proposed Per- and Polyfluoroalkyl Substances National Primary Drinking Water Regulation

By: William Warren-Hicks, Ph.D., Donald Catanzaro, Ph.D.

EcoStat, Inc.

Mebane, NC 27302

May 30, 2023

Introduction

The United States Environmental Protection Agency (EPA) has published a series of quality control (QC) and best practice guidelines for program development and project development (USEPA 1992, 2002), data quality objectives (USEPA 2003, 2006), and good statistical practice (USEPA 2006). EPA has also published approved methods and software for calculating benchmark doses (BMD) and their uncertainty (USEPA 2012, 2022) which have been developed into an interactive web site. These guidelines are intended to ensure that the resulting decisions made by EPA meet standards based on the best available science, including reproducibility of results, appropriate data treatment, ensuring representative data, and accurate identification and quantification of true risk to human populations and environmental metrics.

However, the methods and procedures used by EPA to support the National Primary Drinking Water Regulation Rulemaking (the "Proposed NPDWR") did not follow these established procedures, and lack good data practice, good statistical analysis practice, consistency of methods and models, and the ability to replicate analytical results.

In the following sections we provide specific examples of where EPA is lacking good practice in its selected quantitative approaches and provide examples of inappropriate practices and issues not addressed by EPA in the proposed rule.

Below, we demonstrate key statistical issues in the Proposed NPDWR using references to the rulemaking and supporting documents, describe how the issues impact the validity of the Maximum Contaminant Level (MCL), reference EPA support documents with examples, explain that EPA is required to meet its own guidance and specifications, and provide examples from National Health and Nutrition Examination Survey (NHANES) illustrating the issue.

Background on NHANES

NHANES is a program of studies administered by the Centers for Disease Control and Prevention (CDC) to produce vital and health statistics for the United States. Since 1999, this cross-sectional survey has been a continuous program that examines a nationally representative sample of about 5,000 different people each two-year sampling period (located in 15 counties across the country). NHANES collects demographic, socioeconomic, dietary, and health-related data and conducts a comprehensive medical examination which consists of blood work, dental, and physiological measurements. Beginning with NHANES 1999–2000, PFAS and associated compounds have been measured in some (but not all) NHANES participants. NHANES employs a multiyear, stratified, clustered design to create a nationally representative sample of the US civilian, noninstitutionalized US population; however, NHANES purposely oversamples certain demographic groups to increase the reliability and precision of health status indicator estimates for those groups. This survey design results in each sampled person not having an equal probability of selection and thus sample weighting is needed to produce correct population estimates of means, percentiles, and other descriptive statistics.

Lack of appropriate analytical techniques when using NHANES data

As described above, proper analysis of NHANES data requires the use of sample weighting variables to produce correct estimates of means, percentiles, and other descriptive statistics. EPA

acknowledged in its supporting document "Economic Analysis for the Proposed Per- and Polyfluoroalkyl Substances National Primary Drinking Water Regulation Appendices" (see (USEPA 2023b), page F-23) that many of the papers forming the foundation of EPA's analysis of the relationship between PFAS and serum cholesterol did not clearly indicate whether the required sampling weights were used in their analyses. Despite acknowledging this fact, EPA did not give these publications appropriate classifications for study quality (*see e.g.* Figure 3-34 on pages 3-159 through 3-161 of (USEPA 2023d)). EPA chose studies where data analyses did not meet EPA guidance and good practice guidelines. Therefore, these studies were of low quality. Subsequent analyses by EPA in the support documents use the number of studies with study quality (high/medium/low) as a metric of certainty of the relationship (*see e.g.* Table 3-8 on pages 3-185 through 3-189 of (U.S, 2023d)), giving an incorrect sense of the relationship between PFOS concentrations and cholesterol.

We highlight these misclassification errors of study quality for cholesterol but the same issue applies to any and all analyses that include NHANES data without confirming use of appropriate sample weighting variables and must be corrected.

1. **Lack of consistent quality control practice by EPA in the Proposed Rule and supporting documents negates the validity of key findings.**

EPA has not proposed data quality objectives (DQOs) or Quality Assurance Project Plans (QAPP) for any data source chosen and associated findings used to establish the MCLG. EPA and National Institutes of Health (NIH) National Institute of Environmental Health Sciences (NIEHS) program offices, are required to generate quality assurance/quality control (QA/QC) plans that include the derivation of analysis-specific, and data-specific DQOs. Under standard quality control practices, DQOs are required for any research initiative in order to document and ensure that data are collected properly, data are treated using good statistical practice, and any findings can be replicated by scientists and data analysts not working at EPA. EPA's own documents provide guidance on DQOs, program planning, good data practice, and good statistical practice. (*See e.g.* USEPA 2003, 2006, 2014).

EPA has not followed its own requirements and guidance for collecting and analyzing data. Rather, for the MCLG and associated analyses, EPA has largely relied on previously published studies conducted by non-EPA employees for which EPA has no control over data collection, data treatment, outlier detection, variance estimation, elimination of records, or good statistical practice. For example, EPA has selected papers where the data used to calculate BMDs and other measures of risk, were not publicly available or difficult and time-consuming to obtain (*e.g.,* Budtz-Jørgensen & Grandjean, 2018; Shearer et al., 2021). EPA has violated a key principle of statistical analysis, which requires that all studies and findings be available to the outside public and the findings replicated.

EPA did not address the inconsistent methods and approaches to BMD calculation in the selected papers and documents used to support the MCLG. This lack of consistency severely limits EPA's ability to reliably and accurately assess potential risk. Note the calculation approach used in (Budtz-Jørgensen & Grandjean, 2018) is completely different than that used by (Dong et al., 2019) (which incorrectly references (Liu et al., 2016)). Different statistical models will, simply based on different mathematics, provide differing results. This uncertainty, and the possible inaccuracy it would cause in the final rule, was not addressed by EPA. For example, EPA has accepted the slope produced by (Dong et al., 2019) when rerunning its BMD calculations yet

ignores the fact that the slope is calculated with an incomplete data set, and data weights are not consistent with NHANES guidance. This is clearly a violation of EPA's quality principles and guidance.

EPA has established guidance that it should use DQOs as an insurance to create analyses of high caliber that are scientifically defensible. Here, EPA failed to establish DQOs, contrary to its own guidance.

2. EPA does not provide evidence that the study data sets used for BMD calculation represent the US population and even when appropriate datasets are selected, they are improperly analyzed.

(2A) EPA did not verify the representational nature of datasets selected for its BMD calculation

The data underlying several key studies EPA relies as the basis for its Proposed NPDWR are unavailable for review and evaluation (see for example Budtz-Jørgensen & Grandjean, 2018). Moreover, even where data is available, EPA did not address the representativeness of the data with respect to US national level populations.

Unless individual study findings can translate directly to the US population at large, the findings cannot be used to anticipate the impact of the rulemaking on human health risk in the US. Also, without a clear and quantitative understanding of how studies based on various non-representative data sets were analyzed and treated, the costs and benefits of the proposed rule cannot be assessed properly.

(2B) Lack of appropriate analytical techniques when using NHANES to create population metrics

As described above, proper analysis of NHANES data requires the use of sample weights to produce correct estimates of means, percentiles, and other descriptive statistics. As acknowledged in an EPA supporting document (*see e.g.* page F-23 of USEPA 2023b) many of the papers forming the foundation of the potential association between PFOA/PFOS and serum cholesterol did not clearly indicate whether the required NHANES sampling weights were used in their analyses. Despite EPA acknowledging this fact, EPA did not appropriately classify these publications for study quality (*see e.g.,* Figure 3-34 on pages 3-159 through 3-161 of USEPA, 2023d). Subsequent analyses use a number of studies with study quality (high/medium/low) as a metric for the degree of confidence that can be attributed to the study finding (*see e.g.* Table 3-8 on pages 3-185 through 3-189 of USEPA 2023d). EPA, for example when reviewing the Dong et al. 2019 study, ignored good data and statistical practice when assigning quality scores. An independent analysis of Dong et al. indicates the analysis approaches and data practices used by Dong were flawed and the findings unsupportable. See Section 6.5).

(2C) EPA's removal of important modeling co-variates is not accepted practice and is inconsistent with study authors' conclusions.

EPA's improper analyses and lack of justification for alterations of previously published models lacks statistical rigor, are problematic, and leads to incorrect conclusions. An important modeling approach for assessing population phenotypes that aid in the assessment of representative models, is to include at least some basic population information like ethnicity, age, gender, socioeconomic status, and other components in the model. Here, EPA's failure to adjust BMD calculations for key co-variates results in incorrect BMD model generation which led to incorrect BMDL values.

In fact, the Budtz-Jørgensen & Grandjean (2018) study reveals, both in the SAS output and as clearly stated in the original paper (at 7), when co-variates like gender, age, and type of booster are included in the model, the relationship of PFOS or PFOA blood concentrations are shown to have a non-significant relationship with antibody titer changes (see Table 1, below reproduced from Table 1 of Budtz-Jørgensen & Grandjean, 2022). We provide other examples where models are developed without inclusion of important statistically significant covariates arises later in the comments. For example, we will demonstrate that the PFOA and PFOS blood concentration relationships to selected response variables are very weak to non-existent when using US nationally representative data such as NHANES.

Table 1. PFOS Model Non-Adjusted Copied from Output Sent to EPA

PFOS Model Non-Adjusted	
Variable	Pr > t
Intercept	0.510
PFOS Parameter	*0.120*
sex	0.006
Age at 7 years	0.388
Booster type at age 5	0.860
From Table 1 of (Budtz-Jørgensen & Grandjean, 2022)	

In addition, EPA has not explained when or why co-variates are either included or excluded from the statistical models used by EPA to support the MCLG. This lack of scientific rigor in model development is clearly a violation of good statistical practices (Harrell 2016). When key population metrics are included in the model, these metrics dominate any relationship between the response variable and the model parameters. In such models, the parameter associated with either PFOA or PFOS is generally statistically insignificant.

3. NHANES data important to PFAS and Health Outcomes are frequently changed and/or modified.

NHANES regularly updates datasets which have PFAS concentration variables, changing the values or excluding data that do not meet program standards. Some of these changes occur relatively soon after the datasets have been released and are posted on the NHANES news website (see https://www.cdc.gov/nchs/nhanes/new_nhanes.htm and https://www.cdc.gov/nchs/nhanes/archive_new_nhanes.htm). In 2021 and 2022 the NHANES Biospecimen Program processes were reevaluated to monitor quality control after a procedural error was identified. Following a comprehensive review of all surplus sample datasets generated between 1999 and 2018, NHANES modified certain data files to remove records that were initially included in error and did not meet program standards and revised files were released in April 2022 (Source: Update to Tables Associated with Revised NHANES Biospecimen Program Data Files see https://www.cdc.gov/exposurereport/whats_new_121522_1.html)

> From https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/SSPFAC_H.htm
>
> Note: The NHANES Biospecimen Program processes were reevaluated in 2021 and 2022 to monitor quality control after a procedural error was identified. This error did not pose

any risk of participant disclosure. Addressing this error resulted in the removal of some records from various stored biospecimen data files between 1999 and 2018 that did not meet program standards. After a comprehensive review of all stored specimen datasets, this data file was modified to remove records (15-<20% of records) that were initially included in error. No data values were altered. However, survey weights were adjusted. For each analyte included in this data file, it was determined that overall and for stratified sex, age, and race/Hispanic origin groups, the updated file using the new sample weights resulted in an estimate within the 95% confidence limit calculated using the original file and sample weights. However, not all possible analyses were performed. For any queries related to this dataset please email the Biospecimen Program at serumplasmaurine@cdc.gov.

While EPA notes the possibility of NHANES data updates, EPA does not provide details on the data used in its analyses, or the year class of the data. Additionally, EPA ignores that papers published prior to any updates must have used the incorrect values in their analyses and thus the conclusions are at a minimum inaccurate and at worst incorrect. EPA must provide details on whether and how data updates were incorporated into its models.

NHANES Cycle	PFAS Data First Published	PFAS Data Last Revised
1999-2000	Oct-06	Dec-22
2001-2002	-	-
2003-2004	Jul-07	Dec-22
2005-2006	Aug-09	Sep-12
2007-2008	Oct-10	Oct-13
2009-2010	Dec-11	Oct-13
2011-2012	Feb-14	Oct-14
2013-2014*	Jul-16	-
		Apr-22
2015-2016	Sep-18	-
2017-2018	Nov-20	-
*For 2013-2014, PFAS were in two different NHANES tables		

EPA does not provide sufficient detail on the data used in its analyses; therefore, it is difficult to know whether EPA is using outdated data. However, given the frequency of the updates in NHANES data, any and all publications that EPA is relying on and using NHANES PFAS data that have been previously published analyses contain an unknown number of errors. The ramification is that the analyses, the generated models, and conclusions based on uncorrected NHANES data are most certainly flawed. EPA must provide details on how the NHANES data updates were incorporated into its models, if they were incorporated at all and must update its analyses to use the most accurate datasets supplied by NHANES.

4. NHANES cholesterol values changed significantly due to non-PFAS factors

NHANES determined that a change in assay methods was most likely responsible for changes in HDL cholesterol values in the NHANES cycles from 1999-2008 (Source: National Health and

Nutrition Examination Survey, 1999-2000 Data Documentation, Codebook, and Frequencies Cholesterol - Total & HDL (Lab13) https://wwwn.cdc.gov/Nchs/Nhanes/1999-2000/LAB13.htm). NHANES developed a formula to correct HDL values and re-posted the corrected data. It is very rare that papers document when data extracts were downloaded but it is not uncommon for papers to take more than two years from publication to data analysis and papers published with data prior to corrections will have inaccurate findings. The following table shows the original dates of data published for cholesterol as well as prescription drugs.

NHANES Cycle	Prescription Drugs		TC & HDL		LDL	
	First Published	Last Revised	First Published	Last Revised	First Published	Last Revised
1999-2000	-	-	Jun-02	Apr-10	Jun-02	Mar-07
2001-2002	-	-	Sep-04	Apr-10	Jun-05	Mar-07
2003-2004	Aug-07	Jun-09	Jun-06	Apr-10	Sep-06	May-08
2005-2006	Sep-08	Jun-09	Nov-07	Apr-10	Mar-08	
2007-2008	Apr-10		Sep-09	Feb-10	May-10	Sep-10
2009-2010	May-12		Sep-11		Dec-11	
2011-2012	Jul-14		Sep-13		Jan-14	
2013-2014	Dec-16		Oct-15	Mar-16	Mar-16	
2015-2016	Jan-19		Sep-17		Jan-19	
2017-2018	Mar-20		Feb-20		Dec-20	Mar-21
2017- Pre 2020	Sep-21		Aug-21		Oct-21	

Again, any and all analyses that EPA is relying on that included NHANES data must use the most accurate datasets supplied by NHANES.

5. Dong et al., 2019, a key study upon which EPA relies, has serious methodological issues that render it unreliable.

EPA repeatedly cites Dong et al. (2019) in estimating Point of Departure (POD), reference dose (RfD), and benchmark dose (BMD) (USEPA 2023b, 2023d). The importance of this paper in EPA's analysis can be seen in particular on:

- Page F-10 of USEPA 2023b states "Although the datasets and models were not exactly the same in all NHANES-based studies, to avoid estimate dependency issues due to overlapping populations in the meta-analysis, EPA also performed a sensitivity analysis including only the data from the study covering the broadest range of NHANES cycles (2003–2014) (Dong et al.,2019)."
- Page K-4 of USEPA 2023b states "The use of single study-based TC effect estimates, rather than EPA meta-analysis-based effect estimates. To this end, EPA used estimates from a large NHANES study (Dong et al., 2019) …"
- Page E-298 of USEPA 2023c states that EPA re-analyzed the data using the regression models from the Dong et al., 2019 study, together with updated NHANES data, applied to a modified hybrid model to develop BMD and BMDL estimates for various time periods and assumptions.

Methodological issues with Dong et al.(2019) that seriously impact the veracity of the statistical associations found and alter the fundamental representational aspects of NHANES data include:

1. Dong et al. (2019) did not analyze the full NHANES dataset but rather excluded certain cholesterol and PFAS values. On page 463 the authors state, "to ensure no influential points heavily impact on the analysis results, the outliers for PFASs and cholesterol (data points more than 1.5 interquartile ranges (IQRs) below the first quartile or above the third quartile) were excluded."
2. Not only did the authors exclude portions of the original data for outliers, they also excluded based on age on page 464. The authors state, "The regression analysis was also conducted for adults [20-80 years] since most correlations observed for adolescents were insignificant." Data should only be excluded when they are known to be incorrect, due to laboratory measurement errors, etc. When data exclusion changes the results of the study or misrepresents the study, exclusion of the data is improper (Resnick 2000). EPA has not justified data exclusions by any of the outside authors, and EPA has not internally rigorously evaluated data treatment nor established good data treatment guidelines that are consistent with DQOs.
3. The final regression models for BMD calculations published by the authors did not adjust for gender nor age despite the fact that these co-variates were found to be significant by their own analyses.
4. As recognized by EPA, Dong et al. (2019) did not explicitly state that the models generated used the appropriate NHANES weighting.
5. Dong et al. (2019) used custom code within a statistical software package (Matlab) to conduct a hybrid BMD calculation rather than using EPA approved BMD modelling software (e.g. BMDS (USEPA 2022))

Given these serious statistical and methodological issues, rating the Dong et al. (2019) study as a medium quality study, as EPA did here, is inconsistent with EPA statements on how it judged the merits of specific studies for the purpose of assigning a quality score. Additionally, given that the exclusion done by the authors removes the national representative nature of the NHANES dataset and introduces strong bias into the analysis, it is inconsistent with sound science and EPA's own guidance to use it as a basis for calculating BMDs.

Despite these significant issues with Dong et al., (2019) EPA retained the slope estimates and used these flawed estimates to calculate BMD and BMDL (see page E-298 of U.S, 2023c "where m is the slope, β, (from the Dong regression model) and b is the intercept."). It is not proper statistical practice to realize that a previous analysis used flawed methodologies and verify that with your own analyses as EPA did here, only to go ahead and use the incorrect values.

EPA has not followed its own QC guidelines when using findings from outside sources. EPA has not questioned many of the selected author's findings or taken steps to replicate them, nor has EPA reviewed the original author's poor data treatment. Given the deviation from sound practice and EPA guidance with respect to EPA's treatment of Dong et al. (2019), it is likely this lack of quality control and poor statistical practice has carried over to other data and statistical modeling activities throughout the technical portion of the Proposed NPDWR.

6. EPA's approaches to Benchmark Dose (BMD) are insufficient and inconsistent with accepted statistical standards.

EPA's approach to BMD calculations is lacking in appropriate sensitivity testing, choice of equation, and in some cases inappropriate use of information from the original publications. We discuss below the inappropriate information use and practice utilized by EPA for BMD calculations.

(6A) EPA does not properly address statistical significance

In Appendix E, Table E-1 (USEPA 2023c, e) displays BMDs in the Budtz-Jørgensen & Grandjean (2018) paper. In Table E-1, the slope coefficient which is used to calculate the BMD is clearly not significant, nor even close to significant. EPA states that the non-significant parameter can be used to calculate the BMD and BMDL. What is not shown is that the models in Table E-1 are poor representations of the original data (which are not available for review and testing) and fit the data poorly (they have a non-significant t-statistic). Therefore, the resulting non-significant slope is not correlated with the original data, and therefore is inconsistent with the underlying science inferred by the model. We note that the unavailability of the data negates the ability to rerun the model and thereby ensure the published results are reproducible and precise. No practicing statistician would agree that a BMD or a BMDL estimated from a non-significant model including a non-significant model parameter should be used to set a standard. EPA repeats this mistake throughout the BMD calculation process.

(6B) EPA's choices regarding statistical and/or biological properties of analyzed data are inconsistent with accepted practice.

EPA clearly states that selection of the BMR for the purpose of estimating a BMD involves making judgements about the statistical and biological properties of the data set. Yet, EPA provides no analysis of the sensitivity that these choices may have on the final BMD. The choice of BMR and the choice of "extra risk" (the p(0) term in the BMD calculation) simply will not withstand scientific review without a clear association back to clinical effects on the US population. As noted in the EPA QAPP guidelines, it is bad statistical practice to make judgement calls and subsequently calculate costs and benefits, without exploring the ramifications of and sensitivity of the results to these decisions in practice.

In summary (1) EPA has not conducted a sensitivity analysis of these arbitrary BMR and p(0) terms; (2) EPA provides no scientific basis for the choice of model equation; (3) EPA provides no scientific justification for (or against) specific BMR and p(0) choices, other than to state what EPA believes is commonly used; and most importantly,(5) EPA provides no explanation or examples of how the BMD calculations relate to actual human health risk. EPA must scientifically support how these calculations result in reduced mortality on a national scale.

For example, in the below table we demonstrate BMD and BMDL outcomes using two different BMD model equations (the Budtz-Jørgensen & Grandjean (2018) model, and the EPA Hybrid method used in Dong et al.(2019)). Models with three different sets of co-variates are fit (rows of the table) for NHANES total cholesterol data. (Dong et al., 2019). The appropriate NHANES weighting functions are used to generate the model estimates (there is no mention of weights in Dong et al. 2019). The choice of the extra risk term, and the choice of BMR make a significant difference in the resulting BMD and BMDL and could highly influence the final reference dose and ultimately the MCLG. Key co-variates that possibly affect the model parameter estimates

should be included in all BMD calculations, which many of the papers selected by EPA do not do. These co-variates include the presence of a cholesterol lowering drug, age, ethnicity, gender, and BMI. Note in the analysis below the wide range of BMD and BMDL values found with relatively small changes in the BMR and p(0) terms. Also note that the slope parameter (the parameter multiplied by the total cholesterol concentration) is non-significant in every model. We supply this table only to show the range of BMD and BMDL values that can occur with arbitrary values of BMR and p(0). Good statistical and scientific practice requires EPA to relate the selected BMR and p(0) terms to the endpoints of interest, which according to EPA are severe disease or mortality estimates for the US population on a national basis. We also note that EPA claims the Dong et al. (2019) model included key co-variates like those above; however, this is not noted in the actual paper.

There are many BMD model forms and analytical approaches to choose from (Budtz-Jorgensen, Keiding, & Grandjean, 2001; Crump, 1995; Liu et al., 2016; USEPA 2012, 2022; Wheeler, Cortinas, Aerts, Gift, & Davis, 2022; Wheeler et al., 2023), including regression approaches, maximum likelihood approaches, and Bayesian approaches. How EPA chose from these differing approaches was not explained. Additionally, EPA did not robustly compare results from the various model forms and statistical paradigms. Without these explanations and comparisons, EPA's decision-making and the scientific basis for its Proposed NPDWR are not transparent and prevent meaningful comment and analysis by reviewers.

Table 2 (below) provides an examination of the sensitivity of the BMD and BMDL calculations using two different model equations, and various values of BMR and p(0). Note that for any specific model and set of co-variates, the BMD and BMDL values vary tremendously. This results in a large variance in the resulting RfD. The equations are associated and follow a specific set of progressive calculations. Uncertainty at any specific level of the calculation hierarchy results in a compounded uncertainty in the final reference dose and ultimately the MCLG. EPA has not addressed this compounding of uncertainty in any of the technical documents or appendices. This issue is critical, because the cascading uncertainty sheds light on the lack of scientific integrity of the EPA proposed rule.

Table 2. Demonstration of range of BMD values with arbitrary choice of BMR and p(0): Total Cholesterol. Dong et al. (2019) reports BMD=10.5 mg/dL, BMDL=5.6 mg/dl.

Co-variates	(Budtz-Jørgensen & Grandjean, 2018) Method				Liu et al., 2016 Method			
	BMR=0.05		BMR=0.1		p(0)=.1 BMR=0.05		p(0)=.20 BMR=0.05	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
None	55.8	30.8	109.0	60.3	152.4	83.9	504.4	204.4
Age (<20, 21-80) Taking cholesterol drug (yes, no)	150.3	60.9	293.6	118.9	387.8	157.1	341.9	150.1
Age (<20, 21-80) Taking cholesterol drug (yes, no) Ethnicity Gender	102.7	45.4	200.6	88.6	262.0	115.2	341.9	150.1
Age (<20, 21-80) Taking cholesterol drug (yes, no) Ethnicity Gender BMI Category (healthy, obese, overweight, underweight)	103.6	45.0	202.5	87.8	262.0	113.7	345.9	150.1

The following comments (6C – 6F) are specific to USEPA 2023c, but likely also apply to USEPA 2023e.

(6C) EPA made repeated statistical mistakes contrary to accepted practice

In Table E-2 (page E-274) EPA repeats the mistake of excluding important co-variates and acknowledges in Table E-2 that no information is available to ascertain model fit. Again, without the ability to replicate the Budtz-Jorgensen results and identify if the model from which the BMDL was derived has statistical validity, these results are invalid.

The fundamental statistical mistakes noted above continue with Table E-3 (E-275).

(6D) Inappropriate calculations to reproduce and/or calculate model parameters

(1) Note that EPA in "Selection of Benchmark Response" (following Table E-3) attempts to calculate a pooled variance using Log base 2 of the 25th and 75th percentiles, and uses these percentiles in an attempt to calculate a pooled variance. This calculation is unsupported. EPA acknowledges it does not have the original data, and therefore, it is not mathematically possible calculate a pooled variance. There are many distributions that could result in the same 25th and 75th percentile, but a pooled estimate based on actual data could be very different than what was calculated by EPA. This attempt to overcome lack of actual data is statistically inappropriate. In addition, EPA has no knowledge of

how the 25th and 75th percentiles were generated, and cannot replicate these values without the original data set. Also, because the authors make no mention of it, EPA presumably does not know how the original authors treated issues with non-detected values, possibly dropped records, or dealt with sampling issues and weights. Again, EPA cannot use mathematical calculations to overcome the non-available data issue where the results cannot be repeated by the general public or other scientists. The outputs in Table E-4 are unsupported. Even EPA admits there is low confidence in the results, yet EPA continues to use the information. For example, in Section E.71 EPA states "[t]he Agency notes that the estimated models are potentially subject to omitted variable bias from other sources, such as income level, but EPA does not have adequate information to evaluate the impacts of this bias…"

(2) On page E-278, EPA seems to not have the original data for Timmermann et al. (2021) and attempts to back out a regression slope in order to calculate the BMD. This practice is mathematically indefensible, and could easily result in a wrong answer. Also, EPA is required under its own guidelines (USEPA 2003, USEPA 2006) to ensure that, consistent with the data, the original authors did not incorrectly treat the data (i.e., removal of outliers, etc.) prior to using the results for standard setting.

(3) The above inappropriate mathematical and statistical comments also apply to Section E.1.1.4, Modeling Results for Decreased Diphtheria Antibody Concentrations (page E-279).

(4) In Section E.1.2.1. EPA again makes unsupported assumptions as to the mean and sigma estimates based on the 25th and 75th percentiles in Chu et al. (2020). EPA needs to obtain the original data, examine the original data using good data practices, and then calculate mean and sigma values. Using the ratio of percentiles reported in a paper is not in line with best statistical practice, and will most likely not represent values obtained using actual data.

(5) See sections E.1.2.2 – E.1.2.7 for continued statistical issues as described above.

(6) In each of the six high confidence studies for which EPA uses to calculate BMD/BMDLs (Sections E.1.2), EPA inappropriately uses the regression coefficients published in the paper, ignoring the fact that the published models incorporate co-variates in their final model. For instance in Chu et al.(2020) the paper published in Table 2 adjusted regression coefficients for "gestational age, maternal age, maternal occupation, maternal education, family income, parity, and infant sex" (see page 4). When these types of adjustments are made, they are part and parcel of the final and the regression coefficient of interest. For example, b in Table 2 is only statistically valid *in the presence of the co-variates* (also known as confounding variables). In this, and other sections of the report, EPA has repeatedly ignored the full model specification and instead only used the regression coefficient of interest, violating standard statistical principles.

(6E) Single variable regression models can overinflate the relationship to PFAS

Table E-9: EPA states that PFOS is significant in the single-PFAS model. As noted above, when a single variable regression model is applied to a larger data set, the basic tenants of hypothesis testing theory results in significant parameter estimates, simply due to sample size. However, we have showed in our comments that when critical co-variates like gender and age are included in the regression models, the coefficients on PFOA and PFOS are generally non-significant. This is a "signal and noise" problem, with the co-variates easily showing they are much more important to the endpoint (i.e., antibody titer) than PFOS and PFOA blood concentrations.

(6F) EPA's attempts to overcome missing information are inconsistent with accepted scientific practice

EPA's calculation of the "extra risk" in E.1.2.7 is not consistent with sound scientific practice. First, EPA does not know what the true background percentage of PFOS or PFOA is in the US. EPA has not evaluated a national-level exposure of these substances, which would vary tremendously on a national basis. Therefore, EPA's attempts to calculate an "alternative control group" response is not appropriate, and simply represents a statistical calculation that EPA has not defined explicitly. Without an exact understanding of background values (which EPA has not adequately addressed in this rule making), statistical calculations such as those in E.1.2.7 are inconsistent with sound and acceptable practice.

7. Ignoring of the totality of NHANES immune and vaccine data

The Bulka, Avula, & Fry (2021) study used NHANES data to investigate the relationship between PFAS and possible immune effects investigated eight different pathogens (cytomegalovirus (CMV), Epstein Barr virus (EBV), hepatitis virus types C and E (HCV, HEV), human immunodeficiency virus (HIV), herpes simplex virus types 1 and 2 (HSV-1, HSV-2), Toxoplasma gondii (T. gondii), and *Toxocara canis* and *Toxocara cati* (*Toxocara* spp.)). No relationships between PFAS and these pathogens were found, until the authors constructed a composite measure to sum across all these pathogens. However, in 2020 these same authors, using NHANES data proposed lead exposures increased the risk of CMV infection and impair immune control of the virus in young adults. The usage of the same dataset to support radically different pathways for impairment represents p-hacking which is a form of data exploitation to discover patterns which would be presented as statistically significant, when in reality, there is no underlying effect.

8. EPA is overly conservative in the calculation of RfDs.

EPA employs a series of highly conservative uncertainty and safety factors to generate an RfD. These values are not consistent with best practice for selection of such factors. EPA did not use robust statistical uncertainty techniques, as is expected as part of best available science, in order to replace the arbitrary safety and uncertainty factors with data-based measures of uncertainty. Model-based prediction uncertainty (for both statistical and toxicological models) approaches are available and should be used by EPA in place of overly conservative and subjective factors.

Classic safety factors and uncertainty factors are generally not based on models or data, which, as noted above does not meet EPA's own quality assurance guidelines. Any uncertainty used by EPA should be peer-reviewed, and based on actual data (e.g., uncertainty in BMD dependent on choice of model, BMR, p(0), etc.). Safety factors should be based on true data, and in particular,

reflect the ability of others replicate EPA's results. EPA does not have actual data sets for many of the endpoints addressed in the rulemaking, and EPA did not oversee the work ensuring good quality control of the author's findings.

Without proper uncertainty analysis based on EPA's guidance on good statistical practice, the uncertainty and safety factors employed by EPA do not result in a scientifically defensible RfD value.

9. Comments on Framework of a Bayesian Hierarchical Markov Chain Monte Carlo Occurrence Model (Appendix A, (U.S, 2023b))

(9A) EPA introduced bias in establishing PFOA/PFOS water concentrations

EPA states that small PWSs were selected using a population-weighted stratified random sampling design, in part because the data from these systems have lower detection limits. EPA states that non-detects are less informative than reported values. EPA states that if state data met certain specifications, then the data were comparable to UCMR 3 and could be used to inform the national occurrence model. Further, the state data were limited to those PWS already in the UCMR 3 data set.

The above approach by EPA is inconsistent with standard methods for selecting random samples for establishing an un-biased estimate of PFOA and PFOS water concentrations across the US. Limiting the state data to only those PWS selected by UCMR 3 imposes an artificial geographic restraint on the drinking water exposure distribution. EPA's logic results in only 17 states, which is likely unrepresentative of PFOS and PFOA water concentrations across the US. In fact, Table A-1 indicates that not only are few states selected, the number of systems included for each state are highly inconsistent. For example, only 1 PWS is available for the states of ME, GA, and ND; which effectively gives these states no influence on the final results, even though these states have many small communities representing a large number of populations and geographic factors.

Also, to generate an exposure distribution on a national level, a representative sample must be derived using metrics other than state population totals. The actual concentrations of PFOA or PFOS are a function of many factors, including distance from the PFAS source, topography, number of private drinking water wells in the area or state, climatology, distance to nearest large water and river systems, and other environmental factors. EPA's state data are clearly not representative of the PFAS exposure distribution on a national level. Therefore, any conclusions drawn based on these data do not represent the expected PWS concentrations across the US and cannot be used to support a MCL.

EPA does not explain what it means when it says that "… if the state data met certain specifications, EPA assumed that they were statistically comparable with the UCMR 3 data…" EPA must define what "certain specifications" means. For example, did EPA remove all PFOA or PFOS concentrations that were non-detects?

EPA uses a natural log of the PFAS concentrations. Many state-level data sets, especially those with a large number of non-detects, set the value to zero. Ln(0) is undefined. The results indicate that EPA removed all zero values from the data set because the use of a natural logarithm of zero

does not exist. This approach arbitrarily deletes small values from the data set. According to best scientific practices, EPA should be using Ln(x+1) rather than the Ln(x) so as to not introduce bias into the analysis.

(9B) Conceptual Model Structure

EPA uses something called a "fixed factor shift" for small systems. This approach seems to increase the influence of small system data on the overall population mean. EPA does not explain why this adjustment is necessary (equation A-2). If the data are indeed representative of the US, no adjustment would be necessary. Equation A-2 seems to be an admission by EPA that the state data were not obtained using a pre-specified data collection plan containing DQOs, as required by EPA guidance documents. EPA must explain the degree to which equation A-2 influences the final answers.

EPA's use of small-system specific standard deviations is not clear, and it is not clear how EPA mathematically used these standard deviations. EPA states it uses within-system standard deviations pooled across size categories for PFHxS and PFHpA. Note, a within-system variance component for those systems with small sample sizes (and in particular when the small sample is composed predominately of non-detects) is unreliable at best. EPA must provide insight into the relative influence of this issue on the final results in order to assuage worries of veering from statistical best practices.

A Bayesian model is fully capable of estimating both within- and between- small system variances if the model is constructed correctly. There is no reason, outside of the model, to create covariance matrices or evaluate variance components independent of the full model. The beauty of a correctly constructed Bayesian Hierarchical Model is that the data inform the parameters and associated variance components at each level of the hierarchy. Therefore, EPA's approach as described in this section appears to be invalid.

As noted above, EPA did not include key geographic co-variates when building the Bayesian model (e.g., distance from the source, environmental metrics, climatology, etc.). These values should have been included in the model in an effort to correctly account for geographic variability among the water systems. Without these terms, or an attempt to build a model that explicitly accounts for geographic variance components, the outputs from the model are inaccurate and cannot be used to establish an exposure distribution for the US population.

EPA used "weakly informative prior distributions." EPA must provide the mathematical details of the prior distributions, and how the prior distributions were constructed. If indeed they are fully non-informative, EPA must provide the basis for using non-informative distributions. If the prior distributions do not account for natural geographic variability, then the prior distributions are incorrectly constructed and the resulting marginal predictive distributions are incorrectly constructed. Without this additional information, it is unclear whether EPA followed best available practices in the creation of its model.

EPA must provide the mathematical details of its calculations within the Bayesian model. EPA needs to provide mathematical equations showing the construction of the marginal mean distributions at each level of the hierarchy, the construction of marginal predictive distributions,

the construction of the joint likelihood and prior distributions, etc. Without an explicit mathematical statement of the model, the model and its components cannot be fully evaluated.

10. Comments on Effects of Reduced Birth Weight on Infant Mortality (Appendix E, (USEPA 2023b))

(10A) Data Sources

EPA describes a data set with only two years of data. Given the discussion about changes over time in infant mortality described by EPA, a data set with only two years of data is insufficient to build the regression models described in Appendix E. Natural changes over time must also be included in the model. Otherwise, any correlation of birth weight and infant mortality will be erroneous and could easily be due to other time-dependent factors not included in the model.

EPA must make the data set described in E.3.1 available to the public under the EPA's quality assurance and good statistical practice guidelines. It has failed to do so in the supporting documents for the Proposed NPDWRs.

(10B) E.7.1 Mortality Regression Models

Figure E-1 indicates that EPA has built a series of models, generating different model coefficients for various factors that influence birth weight and infant mortality including gender and ethnicity. This approach is inconsistent with scientific best practice. The proper approach is to build a single model with key co-variates like gender and ethnicity included in the single model (Harrell 2016). Otherwise, the model error term (which is the basis for hypothesis testing) is biased and not representative of the entire population included in the data set. EPA could use linear contrast or estimate methods to evaluate differences in gender and ethnicity, but the error term must result from a single model fit.

EPA does not show the significance of each of the regression and logistic model parameters. In other parts of the technical appendices supporting the MCLG, EPA has ignored the fact that many co-variates (e.g., gender or ethnicity) are the variables highly associated with the model response variable, and either PFOS and PFOA are not significant or are minor parameters relative to the key phenotype co-variates. EPA must demonstrate a strong relationship, considering the entire data set and scientifically derived and supported co-variates in the statistical models. As the presentation currently stands, the lack of information provided by EPA negates the ability of the public to evaluate the validity of the models.

EPA must show which co-variates are included in the models generating the odds ratios of Table E-4, including their statistical significance. Otherwise, the validity of the models cannot be examined from a scientific perspective.

11. Comments on Figure 6-10 Overview of Analysis of Co-Removal Benefits ((U.S, 2023a))

In a decision tree like that seen in Figure 6-10, each step of the decision analysis is comprised of models with uncertain predictions, decisions based on subjective judgement, value-based judgements, and uncertain cost estimates and cost expectations. This graphic represents the decision process EPA has both implicitly and explicitly used to generate the MCL. At issue is the

level of uncertainty a multi-branched decision analysis actually represents. In practice, EPA has not identified nor quantified the measurable uncertainty in each step of the decision process used by EPA. EPA must provide the public with an honest estimate of the degree to which the MCGL will result in a benefit to human health, including the actual costs which the public must incur for these indeterminate benefits. A rigorous uncertainty analysis of the Figure 6-10 decision tree will result is such a large uncertainty in the total value of reduced bladder cancer, that any positive benefit will not be quantifiable.

Conclusion

The methods and procedures used by EPA to support the Proposed NPDWR did not follow EPA's own established procedures and guidance, including those for good data practice, good statistical analysis practice, consistency of methods and models, and the ability to replicate analytical results. Therefore, the analytical findings by EPA and outside sources cannot be validated, and EPA's proposed standard lacks scientific and statistical merit. EPA's reliance on non-national data bases, work by external authors, inability to quality control the data, models, and outputs is shown to be a major criticism of the underlying statistical approaches EPA has used to support the MCLG and MCL.

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William Warren-Hicks, Ph.D.

Phone: (919) 628-2064 Email: billwh@ecostat-inc.com

Education:

1990 Ph.D., Environmental Statistics, Duke University
1979 M.S., Environmental Toxicology and Statistics, University of Texas School of Public Health
1976 B.S., Magna cum laude, Biology with Honors, University of Houston

Professional Associations:

American Statistical Association
Society of Environmental Toxicology and Chemistry

Positions:

EcoStat, Inc., Mebane, NC

2004 – ongoing **Chief Executive Officer.** EcoStat Inc. is a small women-owned business specializing in the quantitative environmental and human health sciences. Areas of expertise include environmental risk assessment in air, water and terrestrial environments; statistics and data analysis in both human health and environmental sciences; data base development and management; computer programming; water and air quality permitting; quantitative toxicity test evaluation; terrestrial and water quality modeling and model validation; and chemical exposure modeling and model validation.

Example Clients: 3M, Dow Chemical, Syngenta Crop Science, private clients through attorneys, British Petroleum, US EPA Clean Air Markets Division, US EPA Office of Water, US EPA Office of Groundwater and Drinking Water, Bayer Crop Science, Department of Energy, Water Environment Research Foundation (WERF), Florida Power and Light, California Wind Energy Association (CalWEA), and NextEra Energy.

Social and Scientific Systems, Durham, NC

2015 – 2016 **Director of Biostatistics.** Provide senior leadership in the statistical sciences and related quantitative disciplines applicable to public health research. These areas include (1) public and private clinical trials of new and existing pharmaceutical products, (2) analysis of epidemiological data including –omics studies, (3) statistical analysis of laboratory derived assay data, and (4) oversight of data operations and data management for clinical studies. Manage a group of approximately 40 individuals, in the areas of statistics, modeling, statistical programming, data base management, and analytics.

Clients: National Institute of Health, Center for Disease Control, Coast Guard, National Institute of Environmental Health Sciences, private biotech firms, and private pharmaceutical companies.

Cardno ENTRIX., Raleigh, NC

2011 – 2015 **Principal/Vice President/Technical Director/Biostatistics Practice Leader.** Responsible for Cardno-wide intellectual leadership and business development in the quantitative sciences. Lead statistician for BP Gulf Oil Spill (Clean Water Act litigation, National Resource Damage Assessment litigation). Incrementally managed over 25 statisticians and scientists in the role of biostatistics practice leader.

Other clients: US Fish and Wildlife Service, Upper Neuse River Basin Association, Mosaic Fertilizer, Inpex Oil (Australia), Sidley Austin (Washington), Arnold and Porter (New York), and Duke Energy.

The Cadmus Group, Chapel Hill, NC

2003 - 2004 **Vice President for Strategic Science Initiatives**: Member of the Cadmus executive committee that provides overall business oversight and direction for the company; responsible for business management and development in human health and environmental sciences, strategic company planning, market forecasting, and intellectual leadership at the corporate level. Technical areas of responsibility include human health and environmental risk assessment, modeling and statistics in the air quality sciences, and exposure and effects assessment in both human and ecological risk sciences.

Example clients: **Government:** EPA Office of Research and Development, EPA Office of Water, EPA Office of Air and Radiation, EPA Clean Air Markets Division, EPA Office of Ground Water and Drinking Water, Department of Energy, Corps of Engineers. **Industry:** 3M, Syngenta Crop Science, Bayer Crop Science, Aventis Crop Science, City of Cary, NC, Weyerhaeuser Pulp and Paper, American Chemistry Council, CEFIC, Water Environment Research Foundation (WERF), American Metropolitan and Sewage Association (AMSA), Utility Water Act Group.

1997 - 2003 **Vice President and Group Manager**: Responsible for business development, business management, and personnel management in the ecological risk sciences, statistics, and engineering; manager of the Cadmus North Carolina office; responsible for offices in Ottawa, Ontario, Canada, Oak Ridge, TN, Laramie, WY, Springfield, MA, and Cincinnati, OH; Managed over 60 scientists, statisticians, and engineers; developed both a government and private client practice; responsible for group-level contracts, budgets, legal issues, and personnel issues. Responsible for

over 100 projects in the human and environmental risk sciences, and air quality.

1991 - 1997 **Principal Scientist**: responsible for business development and personnel management in the ecological risk sciences, statistics, and engineering; manager of the Cadmus North Carolina office and four other offices in the US and Canada.

Kilkelly Environmental Associates, Raleigh, NC

1988 - 1991 **Senior Scientist**: responsible for data analysis and statistical assessments of environmental exposure and effects data; worked with EPA's Corvallis Laboratory to develop EPA's first risk assessment documents including the development of assessment and measurement endpoint concepts; published well received papers on toxicity test variability; worked with EPA's Acid Rain Division to develop the Acid Rain rules for utility emissions of SO_2, NO_x CO_2, and particulates.

Carolina Power and Light Company, Raleigh, NC

1982 - 1988 **Senior Statistician**: supported over 60 biologists in the assessment of impacts to biota at CP&L's nuclear and coal-fired power plants; generated survey designs, performed statistical analyses, participated in on-site sample collection activities, and generated reports to State and Federal agencies; developed thousands of lines of code in SAS and Fortran for the statistical assessment of environmental data.

TRW Environmental, RTP, NC

1980 - 1982 **Engineer:** supported EPA's Office of Air Quality Policy and Standards (OAQPS) in running air quality models, setting of NAAQS values, and PSD permit development.

Duke University Center for Demographic Studies

1977 - 1985 **Programmer and Statistician**: developed maximum likelihood statistical models of longitudinal cancer trends over various demographic groups and geographical areas of the US; developed program code in Fortran, IBM assembly language, and Basic.

Professional Highlights

- Over 35 years of experience supporting industry, government programs, academic institutions, and research initiatives in water, air, and terrestrial environments. Areas include development of statistical analysis of water, air, biota, and groundwater data; NRDA studies; exposure and effects data analysis, risk assessment methods and procedures development in both human health and environmental sciences, evaluation of toxicity data for both terrestrial and aquatic species, criteria development, development

and implementation of regulations, overall support of programmatic goals and objectives, formal research activities, analysis of avian survey measurements, development collision risk assessment methods and models for the wind industry.

- Manager of over 400 projects for industry and government resulting in numerous reports, conference proceedings, and peer-reviewed publications in the areas of NRD litigation, wind power, water quality, air quality, environmental statistics, epidemiology studies, human health risk assessment, probabilistic risk analysis, watershed assessment, bioassessment, and Bayesian decision and inference.

- Initiated and developed four individual businesses within existing firms: (1) air quality division The Cadmus Group, (2) risk assessment division The Cadmus Group, (3) statistics group Cardno ENTRIX, (4) Biostatistics Center within Social and Scientific Systems.

- Originated, managed, and maintained EcoStat, Inc., a small business working with both industry and government.

- Science Advisory Board: Restoration of the Missouri River (ongoing).

- EPA Science Advisory Board: Ecological Risk Assessment of PCB Impacts, Kalamazoo River, Michigan.

- Statistician: Evaluation of airborne risk from radioactive nuclides. Hunters Point, CA Superfund Site.

- Statistical support to Dow Chemical: Tittabawassee River Risk Assessment. Evaluation of risk to avian species.

- Fish and Wildlife Service Science Advisory Board: Evaluation of PCB toxicity on the Hudson River, NY: Evaluation of Laboratory Toxicity Tests.

- Fish and Wildlife Service Science Advisory Board: Evaluation of PCB toxicity on the Hudson River, NY: Evaluation of PCB Effects on Mink.

- Fish and Wildlife Service, State of Michigan, EPA- Science Advisory Board: Evaluation of PCB toxicity to avian species on the Hudson River, NY.

- Invited panel member of the National Wind Coordination Committee (NWCC), Risk Assessment Workgroup.

- Invited speaker and associated lead chapter author of six SETAC Pellston Conferences including Sediment Risk Assessment, Multiple Stressors (steering committee member), Probabilistic Risk Assessment of Pesticides, Whole Effluent Toxicity Testing,

Uncertainty Analysis In Ecological Risk Assessment (chair, lead editor, lead conference organizer, and creator), and Pesticide Risk Assessment for Pollinators.

- Instructor and creator of a continuing education course sponsored by the Duke University School of the Environment entitled *New Advances in Quantitative Ecological Risk Assessment*. Invited speaker in the School of the Environment at Duke University in the areas of risk assessment, data analysis, probability, and ecological modeling.

- Invited panel member and reviewer of the EPA Framework Document For Ecological Risk Assessment, The Superfund Risk Assessment Guidance Document, and the Canadian Risk Assessment Guidance Document for New Substances.

- Lead consulting statistician supporting the majority of the EPA Acid Rain Division's (now the Clean Air Markets Division) regulatory development activities under the 1990 Clean Air Act Amendments.

- Project manager for major research initiatives including: ecological risk assessment methods and software (WERF), assessments of whole effluent toxicity test variability (WERF), site-specific nutrient criteria, development of risk assessment methods for DOE sites (DOE EM-6), state-of-the-science in ecological risk assessment uncertainty methods (American Chemical Society), and case studies in ecological risk assessment (CEFIC Long-term Research Initiatives).

- Lead statistician for British Petroleum on the Deepwater Horizon Oil Spill in the Gulf of Mexico.

- Developer of *Using Monte Carlo Analysis In The Probabilistic Risk Assessment of Pesticides*, a course in uncertainty analysis methods that was given multiple times to EPA's Office of Pesticide Programs (OPP), individual chemical companies, and industry coalitions. Created courses in statistics and probability for Environment Canada's Priority Substances Assessment Program. Developer of courses at Duke University and SETAC in decision sciences, statistics, and probabilistic risk assessment.

- Lead statistician to the Federal Insecticide, Fungicide and Rodenticide Act Environmental Model Validation Task Force (FEMVTF) Statistics Committee in conducting an uncertainty analysis of the PRZM3.12 model.

- Lead statistician supporting 316(b) studies for the assessment of fish entrainment at the Brunswick nuclear power plant, Duke Energy.

- Over 50 platform and poster presentations at NWCC, SETAC, and SOT annual meetings. Frequent invited session chair and speaker at conferences, symposium, and ASTM meetings.

CLASSES TAUGHT

Decision-Making Under Uncertainty – Bayesian Inference. 2016. Seminar Series. Law Seminars International.

New Advances in Ecological Risk Assessment: July 2008. Duke University, School of the Environment, Durham, NC.

Statistical Methods for Water Quality Data Analysis. March 2008. U.S. EPA Region 5. Chicago, Ill.

Bayesian Statistics for Dummies. With Tom Aldenberg. November 2004. Portland, Oregon.

Statistics MTH 112. Fall Semester. 2004. Elon University, Elon, NC.

New Advances in Ecological Risk Assessment: June 2004. Duke University, School of the Environment, Durham, NC.

Methods (Old and New) in Probabilistic Ecological Risk Assessment. April 2004. SETAC Europe Annual Meeting Short Course, Prague, Czech Republic.

Methods (Old and New) in Probabilistic Ecological Risk Assessment. November 2003. SETAC Annual Meeting Short Course, Austin, TX.

Technical Approaches to Setting Site-specific Nutrient Criteria. September 2002. Water Environment Federation, Chicago, IL.

Using Monte Carlo Analysis in the Probabilistic Risk Assessment of Pesticides. June 2002. Syngenta, Jealott's Hill Research Station, Jealott's Hill, England.

Uncertainty Analysis. Duke University School of Engineering. Spring Semester 2001. Durham, NC.

Using Monte Carlo Analysis in the Probabilistic Risk Assessment of Pesticides. November 2001. Syngenta, Greensboro, NC.

Using Monte Carlo Analysis in the Probabilistic Risk Assessment of Pesticides. July 2001. American Crop Protection Association, Baltimore, MD.

Using Monte Carlo Analysis in the Probabilistic Risk Assessment of Pesticides. January 2001. EPA Office of Pesticide Programs, Washington, DC.

Using Monte Carlo Analysis in the Probabilistic Risk Assessment of Pesticides. March 2000. EPA Office of Pesticide Programs, Washington, D.C.

New Advances in Ecological Risk Assessment: April 2002. Duke University, School of the Environment, Durham, NC.

Advanced Topics in Ecological Risk Assessment: March 1999. Duke University, School of the Environment, Durham, NC.

Uncertainty Analysis in Ecological Risk Assessment. 1998. SETAC Annual Meeting, Charlotte, NC

Advanced Topics in Ecological Risk Assessment: March 1998. Duke University, School of the Environment, Durham, NC.

Statistics Course. April,1997. Priority Substances Assessment Program. Environment Canada. Hull, Ontario, Canada.

Advanced Topics in Ecological Risk Assessment: March 1997. Duke University, School of the Environment, Durham, NC.

Uncertainty Analysis in Ecological Risk Assessment. 1996. SETAC Annual Meeting, Washington, DC.

Aquatic Ecological Risk Assessment: Methods for Screening-Level and Probabilistic Risk Assessments. November 1996. Sponsored by the Water Environment Federation. Washington, DC.

Advanced Topics in Ecological Risk Assessment: February 1996. Duke University, School of the Environment, Durham, NC.

Invited Lectures: Overview of Ecological Risk Assessment. Spring 1995. Course title: Environmental Risk Assessment and Decision Making. Duke University, School of the Environment, Durham, NC.

Aquatic Ecological Risk Assessment: April 1995. Duke University, School of the Environment, Durham, NC.

Invited Lectures: Risk Assessment Methods in Water Quality. Spring 1993. Course title: Environmental Risk Assessment and Decision Making. Duke University, School of the Environment, Durham, NC.

Invited Lectures: Risk Assessment Methods in Water Quality. Spring 1992. Course title: Environmental Risk Assessment and Decision Making. Duke University, School of the Environment, Durham, NC.

Invited Lectures: Risk Assessment Methods in Water Quality. Spring 1992. Short course: Environmental Risk Assessment. Duke University Continuing Education Series, Duke University, Durham, NC.

Invited Lecture: Variability of Biological Endpoints and Effects on Standard Setting. Fall 1991. Course title: Environmental Toxicology. Duke University, School of the Environment, Durham, NC.

Regression Analysis, With Laboratory. Spring Semesters 1986-1988. Duke University, School of Environmental Sciences, Durham, NC.

Graduate Student Committee Assignments

Eric Thirolle, M.S.: Thesis title: Guidance for the selection and use of exposure models in ecological risk assessment. Duke University School of the Environment. 1996.

Tom Stockton, Ph.D. Thesis title: Using Bayesian MARS methods for assessing acid deposition. Duke University School of the Environment. 1998.

Molly Haviland. M.S. Thesis title: Soil carbon and dryland spring wheat yield response to a one-time compost application. Montana State University. Ongoing.

PRESENTATIONS

Warren-Hicks, W. J. Role of Statistics in Litigation. 2019. Law Seminars Institute. Albuquerque, New Mexico.

Warren-Hicks, W. J., Bohrmann, T., Robbins, K., 2013. Geospatial Modeling: Don't Take Your GIS Statistics Software for Granted. SETAC National Conference. Nashville, TN.

Warren-Hicks, W. J. and S. Bartell. 2009. Models Versus Data. Invited Presentation. SETAC Debate Series. SETAC National Conference. New Orleans, LA.

Kravits, M., Eskew, D., Warren-Hicks, W. J. 2008 Application of the Stressor Identification (SI) Methodology to a Contaminated Floodplain and Adjacent Irrigated Meadows – Upper Arkansas River, Colorado Case Study. SETAC Annual Meeting, Tampa, Fl.

Zillioux, E. J., Newman, J. R., Warren-Hicks, W. J. 2008. Ranking Wildlife Risks from Multiple Anthropogenic Stressors. SETAC Annual Meeting, Tampa, Fl.

Giddings, J., and Warren-Hicks, W. J. 2008. Developing a plant-based chronic water quality standard for acetochlor. SETAC Annual Meeting, Tampa, Fl.

Warren-Hicks, W. J. 2006. Chair: The Future of Environmental Statistics and Ecological Modeling. SETAC Annual Meeting, Montreal, Canada.

Arnold, R.W, and Warren-Hicks, W. J. Site-specific, Regional, or National Metals Criteria? – A Case Study With Cu In San Francisco Bay. 2005. SETAC Annual Meeting, Baltimore, MD.

Warren-Hicks, W. J., Parkhurst, B. R. 2003. Whole Effluent Toxicity Tests: Using Bayesian Methods To Calculate Model-Based Endpoint Variability. SETAC Annual Meeting, Austin, TX.

Parkhurst, B. R., Warren-Hicks, W. J. 2003. Alternatives to EPA's Methods for Calculating Reasonable Potential for WET: Case Studies. SETAC Annual Meeting, Austin, TX.

Giddings, J. M., Gonzalez-Valero, J. F., Warren-Hicks, W. J. 2003. Exposure Duration and Effects of Atrazine on Aquatic Plant Communities in Mesocosms. SETAC Annual Meeting, Austin, TX.

Giddings, J. M., Gonzalez-Valero, J. F., Warren-Hicks, W. J. 2003. Integrating Dose-Response With Species Sensitivity Distributions. SETAC Annual Meeting, Austin, TX.

Warren-Hicks, W. J. 2003. Statistical Methods and Approaches in Risk Assessment: Lessons Learned. Invited Address. SETAC European Congress, Hamburg, Germany.

Warren-Hicks, W. J., Parkhurst, B.P., Beach, S., Butenhoff, J., Giesy, J. 2002. Understanding the Global Distribution and Environmental Effects of PFOS. Society of Toxicology Annual Meeting. Salt Lake City, Utah.

Warren-Hicks, W. J., Qian, S., Dobbs, M. 2002. Species Sensitivity Distributions in Non-Target Plant Risk Assessments. Society of Toxicology Annual Meeting. Salt Lake City, Utah.

Dobbs, M. G., Ramanarayanan, T. S., Warren-Hicks, W. J., Qian, S., Giddings, J. M., Kelly, I.D., Allen, R., Fischer, R.W. 2002. Assessing the risk to non-target crops through irrigation water. Society of Toxicology Annual Meeting. Salt Lake City, Utah.

Parkhurst, B. P., Warren-Hicks, W. J., Bartell, S., Smart, M. 2002. Site-Specific Nutrient Criteria: An Alternative To US EPA Nutrient Criteria. Society of Toxicology Annual Meeting. Salt Lake City, Utah.

Parkhurst, B. P., Warren-Hicks, W. J., Bartell, S., Smart, M. 2002. Site-Specific Nutrient Criteria: An Alternative To US EPA Nutrient Criteria. Water Environment Federation Annual Meeting. Chicago, IL.

Warren-Hicks, W. J., Santoro, M., Bacon, D., Parkhurst, B. P., Moore, D. J. 2001. Ecological Risk Assessment of PFOS. Invited Address. Society of Toxicology and Chemistry World Congress. Baltimore, Maryland.

Warren-Hicks, W. J., Carbone, J.P., Havens, P. 2001. Using Monte Carlo Techniques to Judge Model Prediction Accuracy: Validation of PRZM 3.1. Society of Toxicology and Chemistry World Congress. Baltimore, MD.

Carbone, J. P., Havens, P., Warren-Hicks, W. J. 2001. Validation of a Complex Fate and Transport Model. Model Accuracy and Regulatory Criteria. Society of Toxicology and Chemistry World Congress. Baltimore.

Salvito, D. T., Allen H. E., Parkhurst, B. R., Warren-Hicks, W. J. 2001. Comparison of Trace Metals in the Intake of Discharge Water of Power Plants Using "Clean" Techniques. Water Environment Research. Vol 73, No. 1, 24-29.

Dobbs, M., R, Ramanarayanan, T., Warren-Hicks, W. J. 2001. The Risk of Balance To Non-Target Plants. Society of Toxicology and Chemistry World Congress. Baltimore, Maryland.

Warren-Hicks, W. J., Santoro, M., Bacon, D. Parkhurst, B.P., Moore. D.J. 2000. Understanding the Global Distribution and Environmental Effects of PFOS. SETAC Annual Meeting. Nashville, TN.

Warren-Hicks, W. J., Wolpert, R. L. 2000. Estimating national distributions of *Giardia* and *Cryptosporidium* in the U.S. with Hierarchical Bayesian models. Third SETAC World Congress. Brighton, United Kingdom.

Warren-Hicks, W. J. 2000. Propagating Uncertainty In Non-Hierarchal Models. SETAC Annual Meeting. Nashville, TN.

Warren-Hicks, W. J., Moore, D. 2000. Uncertainty Analysis In Ecological Risk Assessment: American Chemistry Council and CEFIC Long-Range Research Initiatives. SETAC Annual Meeting. Nashville, TN.

Warren-Hicks, W. J., Biddinger, G. 1999. Debates In Ecological Risk Assessment. Chair. Society of Toxicology and Chemistry World Congress. Philadelphia, PA.

Warren-Hicks, W. J., Moore, D. 1999. Beyond Monte Carlo. Invited Address. Society of Toxicology and Chemistry World Congress. Philadelphia, PA.

Warren-Hicks, W. J., Parkhurst, B. R., Moore. D. R. J. 1999. Whole Effluent Toxicity Test Variability: A Variance Components Analysis. Water Environment Federation Annual Meeting.

Moore, D. R. J., R. S. Teed, W. J. Warren-Hicks, B. R. Parkhurst, R. B. Berger, J. J. Pletl, D. L. Denton, R. B. Baird. 1999. Intra- and Inter-treatment variance in reference toxicant tests. 20th Annual Society of Environmental Toxicology and Chemistry Conference.

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DONALD G. CATANZARO, PHD

Contact Information
16144 Sigmond Lane
Lowell, Arkansas 72745
479-721-2533
dgcatanzaro@gmail.com

Dr. Catanzaro is a Project Scientist and Project Manager that has over 20 years of experience working in statistics, human and ecological health, internet technologies, and Geographic Information Systems (GIS). I have devoted my career to turning large data systems into information and eventually into knowledge. I have developed skills over the long-term using several different GIS, remote sensing, CAD, and GPS software and hardware systems. Dr. Catanzaro's previous employment has been with County Planning Agencies, Federal Agencies, and private firms where his clients have included Federal, State, Tribal, Local, Non-Government organizations as well as private companies. I have a broad Biogeographical and Computer Science background and am well grounded in data analysis including survival, uni/multi-variate, nonparametric, and spatial statistics. My career has been multi-disciplinary in approach, wide in scope, and international in scale.

I have the ability to move seamlessly between large relational databases (multi- million rows) and several computer languages and have analyzed large datasets such as forest inventory data for bioenergy assessments; risk analysis of invasive species to the Great Lakes based on shipping data and habitat niche models; analysis of NO_2 and SO_2 National Ambient Air Quality Standards (NAAQS) for the EPA; analysis of long term monitoring of air quality monitors within California; creating interactive graphical libraries to explore the scientific literature, and conceptual models of nitrogen and phosphorus flows through ecosystems; analyzing pollution attenuation through ground water with spatial statistics; genetic determinates of Extensively Drug-Resistant Tuberculosis (XDR-TB); and; creating population models using multiple US Census Bureau products. I am also currently investigating the effects of air pollution on TB patients (California and Viet Nam), long-term mortality trends in Moldova TB patients, and the use of Artificial Intelligence (Google's TensorFlow) to detect tuberculosis in chest x-rays.

Education

PhD, Biology, University of Arkansas, 1998
BA, Geography, University of California – Los Angeles, 1991

Additional Training

Human Subjects Training (CITI and NIH)
McGill Infectious Diseases and Global Health (2016)
- Course I: Tuberculosis Research Methods
- Course II: Advanced TB Diagnostics Research

Good Clinical Practice (GCP)
Curry International Tuberculosis Center (2015)
- Course I: Focus on LTBI
- Course II: Tuberculosis Clinical Intensive

Specialized Computer Applications

Microsoft Office
Excel (expert), Word, PowerPoint, Access
Business Intelligence
PowerBI
Relational Databases
MS SQL Server/Azure, MySQL, PostgresSQL, Oracle, Informix

Statistics
R, MatLab/Octave, SAS , SAS JMP, SPLUS
Programming
SQL, Python, Visual Basic for Applications, Java, JavaScript, HTML, XML, Flash / Flex, UNIX
GIS/Remote Sensing
ESRI ArcPro/GIS/View/Info, CAD, GRASS 6.4, ERMapper, GeniePro, PCI, ERDAS

Other Technical Skills

Univariate, Multivariate Parametric and Non-Parametric Statistics, Artificial Intelligence/Machine Learning, Regression, Geostatistics, Time Series, Survival Analysis
Database Theory and Management
Integration of data collection hardware and software - mobile computers, depth sounder, GPS
Remote Sensing Application and Theory (aerial photography and digital systems)

Professional Experience

University of Arkansas, Fayetteville, Department of Biological Sciences
Dates Employed: 2014 - Present

Research Assistant Professor: I am the lead Data Analyst & Statistician for a large group researching various aspects tuberculosis diagnostics and treatment. My core responsibilities includes installing & managing REDCap (a browser-based clinical data system), developing and implementing data capture/entry systems (paper, computer, mobile), and creating web-enabled databases which drive project related analysis. As leader of the Data Core, I develop SQL code (and other languages) to support project management by displaying analytics of disparate datasets and creating unique data visualizations. I have used Artificial Intelligence (Google's TensorFlow) to detect tuberculosis in chest x-rays; combined Python & SQL to ingest data from REDCap to MS SQL Server and display information in MS PowerBI, implemented a bioinformatics pipeline to process whole genome sequencing data; developed SQL code which ingests and processes XML data created by a tuberculosis diagnostic device; performed statistical analysis (e.g. trend, regression) for several scientific papers; served as SQL developer to use the common cellphone to provide a simple/easy way to monitor adherence to anti-tuberculosis therapy; performed spatial analysis combining coccidioidomycosis natural history, epidemiology, and global climate change data to predict areas where coccidioidomycosis may increase over time; and used SQL and R to analyze Arkansas All Payer's Claim Database (APCD) investigating age/gender relationships and nontuberculous mycobacterial infection.

Sustainment & Restoration Services (SRS) / Oneida Total Integrated Enterprises (OTIE)
Dates Employed: Jan 2006 - Present

Landscape Ecologist: I have been both a Project Manager (PM) and Project Scientist (PS) for OTIE for the last 16 years. On work assignments where I was PM, I was responsible for developing work plans and budgets, ensuring the overall quality of project work, supervising work performed by other PS and staff members, writing monthly reports and summaries, and preparing final project report(s). On work assignments where I was a PS, I was responsible for assembling data sources, analyzing spatial and temporal patterns, running statistical analysis, reviewing and writing reports.

Projects I have been involved in over the last 16 years include: providing technical support to the EPA National Center for Environmental Assessment (NCEA) and National Exposure Research Laboratory (NERL) who provide guidance to regions, states and tribes on how tools and science to support implementation of the Clear Water Act & Clean Air Act. Both offices in particular are working to develop metrics that define a relationship between specific ecosystem service and one (or more) aspects of community health.

I have worked with Census 2010, 2000, and 1990 as well as American Community Survey (ACS) data and recreational user data (e.g. USFWS National Survey of Fishing, Hunting, and Wildlife-Associated Recreation).

Selected Project Experience

- **Lyme Disease -** Over three Work Assignments served as the statistical analyst and GIS support for determining the generalized applicability of a model to predict Lyme disease incidence across Maryland and Pennsylvania from landscape variables such as population and forest cover. An online interactive viewer was developed tying ArcGIS for Server Javascript API to logistic regression predictive equations and assisted users as they explore models by the usage of interactive sliders to vary disease rate thresholds and risk probabilities and examine the consequences
- **CADStat** – Served as QA/QC Manager for two EPA Work Assignments to develop CADStat, a menu-drive statistical package of several data visualization and statistical methods. CADStat is currently deployed on EPA's server (http://www.epa.gov/caddis) and is a Java Graphical User Interface to R (R is an open source statistical software). Methods in CADStat include: scatter plots, box plots, correlation analysis, linear regression, quantile regression, conditional probability analysis, and tools for predicting environmental conditions from biological observations
- **CCAT** – I developed an HTML5/Javascript application for the EPA called the Community Cumulative Assessment Tool (CCAT)

which combines EPA's Environmental Justice, Risk Assessment, and Community Involvement concepts to address multiple stressors within the EPA's cumulative risk assessment framework.

- **C/T-FERST** – Performed data development, integration and deployment of the EPA's Community/Tribally-Focused Exposure and Risk Screening Tool (C/T-FERST) which supports EPA's integration with other decision-support tools for communities and tribes. C/T-FERST is intended to assist community partners with the challenge of identifying and prioritizing community environmental health risk issues.

EcoStat, Inc
Dates Employed: Feb 2010 - Present

Statistician Provided data quality, processing and statistical analysis for multiple projects including in the development of Data Quality Objectives (DQOs) for the EPA's NO_2 and SO_2 National Ambient Air Quality Standards (NAAQS). NAAQS are designed to provide requisite protection of public health as appropriate under section 109 of the Clean Air Act (CAA). The interacting effects of precision, bias, and completeness were investigated using hourly measurements at over 300 monitoring stations across the country. Other projects include developing an interactive data exploration tool (using MS Excel) for pesticide risk assessment, data processing and analysis of MTBE contamination of private wells, spatial and time series analysis of pollutant inputs into Puget Sound ,exploratory data analysis and model development between Carbon Dioxide emissions and measurements of other power plant variables.

San Diego State University, Bioinformatics & Medical Informatics Department
Dates Employed: May 2012-May 2013

Adjunct Faculty: Data Core leader, lead statistician, and member of the Leadership Team for a NIH sponsored project to test new genetic-based diagnostics tools to detect XDR-TB (U01-AI082229). The project enrolled over 1,110 subjects in three international sites to investigate common mutations which confer drug-resistance. I provided technical oversight of data collection systems (both web and laptop/netbook based), quality assurance, as well as liaison support between the Health Information Technology Group and the clinical staff.

The complexity of project components required several staff members input into how to most efficiently store, manage, query, analyze, and visualize the large quantity of data collected. I played a major role in many of these activities, using expert knowledge to maintain a high level of data collections efficiency and quality. I provided statistical analysis, geographic analysis, and data visualizations to other project staff working with epidemiological and genetic data.

BioEnergy Systems LLC
1726 N Charlee Fayetteville, Arkansas 72703
Dates Engaged: 2007-2012

As a consultant to BioEnergy Systems, I worked on natural resource evaluations, project site assessments (desk studies), renewable energy systems, and data visualizations of complex issues for clients. I compiled the data to support an assessment of agricultural and forest biomass resources in the mid portion of the Mississippi River Alluvial Valley, an area that included 98 counties in Arkansas, Kentucky, Mississippi, Missouri and Tennessee)

Co-developed a high-resolution user-interactive tool for analyzing biomass feedstock supplies (BioFeedStAT® see http://www.biomass2.com/fsa/fsa.html). The tool is used to determine quantities vs. distances (in 0.5-mile increments -- actual road miles, not air miles) and transport costs of any combination of target feedstocks. Source data for BioFeedStAT® is a combination of large databases housing data from the US Forest Service Forest Inventory Data, USDA Cropland Data Layer, and USDA Census of Agriculture.

US Census Bureau / Census Coverage Measurement, Kansas City Regional Census Center
Dates Employed: May 2009- July 2011

Regional Technician (Grade GG-0301-12): As a Regional Technician for 2010 Census, provided technical assistance to the Kansas City Regional Census Center (KC-RCC) for all five Census Coverage Measurement (CCM) operations. CCM operations have three primary objectives: (1) to inform the public about the quality of the census counts; (2) to help identify sources of error to improve census taking, and (3) to provide alternative counts based on information from the coverage measurement program.

As a Regional Technician, I worked under specific direction from the regional office to provide technical and administrative support for all recruitment, personnel, payroll, field data collection, group quarters, office and evaluation operations, automation activities, postal liaison activities, map/geography problems.

Served as a Master Trainer and trained Field Operation Supervisors, Crew Leaders, and Enumerators in all CCM operations in Arkansas, Oklahoma, Missouri, and Minnesota. I trained over 350 employees in small group settings (classes of 10-20). I served as trouble shooter in all five CCM operations and backfilled Field Operation Supervisors, Crew Leaders, and/or Enumerators when field staff quit or not available to work.

Enercon Services, Inc
Dates Employed: Mar 2006 – May 2007
Project Scientist: Provided training to subordinate employees on how to conduct a Severe Accident Mitigation Alternatives (SAMA) for the Nuclear Regulatory Commission (NRC). Oversaw work of subordinate employees, and performed quality checks to ensure high quality work was submitted.

Provided project work, Quality Assurance, and Technical Review for several different nuclear license renewal applications from Entergy Corporation to the NRC. Project works included using GIS to collect, analyze, and support the writing of reports to support the construction of a SAMA for submittal to the NRC. Used US Census Bureau Summary File (SF) 1 and SF3 (for general and environmental justice populations) and Agricultural Census, and local sources of data (e.g. tourism, tax assessment, population growth) to investigate how a severe accident at a nuclear power plant may affect the surrounding communities.

Quality reviews included ensuring all calculations and methodologies follow NRC guidance, performing independent checks on data, reviewing all written materials and sources to ensure accuracy and veracity.

FTN Associates, LTD
Dates Employed: Oct 2002 – Dec 2005
Landscape Ecologist: Provided GIS, biological and statistical expertise for industrial, governmental, and non-governmental clients for a water resources environmental consulting company. Wrote proposals (technical and cost), analyzed data, wrote monthly and final report(s) and recruited and supervised subordinate employees (as necessary).

Created socio-economic and agricultural datasets (data sources were Census 2000 SF1 and SF3 and Census of Agriculture 1997 and 2002) to support Severe Accident Mitigation Alternatives (SAMA) and NEPA analyses for nuclear power industry; providing global climate change research on coral reefs of American Samoa; used GIS to model a new framework for sustainable water resources management; remote sensing and wildlife assessment for Columbian Sharp-Tailed Grouse; organizing and facilitating a 30 person workshop to address multiple stressors to aquatic ecosystems; synthesizing and reviewing the results of the EPA STAR Ecosystem Indicator Program; conducting literature review and analysis on nitrogen phosphorus-algae dynamics; and used GIS to model pollution attenuation through groundwater.

National Park Service, Virgin Islands / South Florida Cluster – Long Term Ecological Monitoring
Dates Employed: Oct 1999 - Oct 2002

Inventory & Monitoring Coordinator (Grade GS-0401-12): Number of Employees: 3

Budget: $350,000Supervised employees, responsible for purchasing major/minor equipment, develop and tracked

budgets for a brand new Inventory & Monitoring Program. Responsible for developing and implementing a statistically defensible program to inventory and monitor six marine natural resources found in the 98,000 acres of natural resources at three National Park Service (NPS) units: Virgin Islands National Park, Buck Island Reef National Monument, and Dry Tortugas National Park. These six resources were: water quality, coral reefs, seagrass, seabirds, fish, and sea turtles. Infused several technological improvements in the monitoring program which reduced field time and data transcription such as: obtaining remote sensing datasets (multispectral and hyperspectral), creating several park-wide fully functional GIS, using SONAR technology to locate monitoring sites for coral reefs and seagrass beds, standardizing underwater digital photography and videography, use of digital field data recorders, and storage of field data in relational databases. During my tenure, I was able to infuse several technological improvements in the monitoring program which reduced field time and data transcription by at least 30%. Developed and maintain a comprehensive GIS and Relational Database Management System (RDMS) for spatial and biological data to link coral reef, seagrass, fish population, seabird, water quality and sea turtle datasets together into one cohesive unit. Created interactive programs to ensure correct data entry into computerized systems, served as primary statistical consultant for data analysis, and presented results of data analysis to NPS management.

National Park Service
Virgin Islands / S Florida Cluster – Long Term Ecological Monitoring
Dates Employed: Apr 1999 – Oct 1999

Ecologist/Data Manager (Grade GS-0401-11): Primary duties were to develop and maintain a comprehensive Relational Database Management System for spatial and biological data associated with the Virgin Islands-LTEM program. I was responsible for the upkeep of computer systems and linking previously collected datasets together into one cohesive unit. As the lead individual for the VI-LTEM program, I provided oversight for the construction of statistically defensible I & M protocols that are consistent with current policies and guidelines. Hired new employees, tracked budgets and projected budgetary needs into the future. I increased the visibility of the Virgin Islands-LTEM program by increasing communication and information flow to the national NPS I&M Program, higher level management in each park, and division managers within each park.

National Park Service
Prairie Cluster-Long Term Ecological Monitoring Program
Wilson's Creek National Battlefield
Dates Employed: Sep 98 – Apr 99

Ecologist/Data Manager (Grade GS-0401-11 (Term Position)): Primary duties were to develop and maintain a comprehensive Relational Database Management System for spatial and biological data associated with the Prairie Cluster LTEM program. As Data Manager, I met with Principal Investigators which were writing monitoring protocols and worked to standardize data collection procedures while ensuring contracted work fulfilled NPS I&M goals. I constructed digital databases using geographically registered data, analyzed and derived new data themes to interpret long-term monitoring data, ensured that documentation of these datasets was maintained and that long-term archiving, integration, and retrieval of data sets produced by the Prairie Cluster LTEM program and supporting cooperators occurred. I was program liaison with GIS providers to ensure appropriate development of spatial layers and integration of Prairie Cluster LTEM datasets into GIS themes. I provided technical support with respect to accuracy, precision and completeness of all resultant datasets of Prairie Cluster LTEM work. Other duties included interpreting aerial photographs, satellite and other types of data using knowledge of geography, physical and biological resources and wrote a scope of work for an adjacent land use study using historic aerial photographs dating to 1936. I installed and integrated GIS and data management software programs and provided training on new software applications.