BEFORE THE ILLINOIS POLLUTION CONTROL BOARD

IN THE MATTER OF:	)	
PROPOSED AMENDMENTS TO GROUNDWATER QUALITY (35 ILL. ADM. CODE 620)	)	**R2022-018 (Rulemaking - Public Water Supply)**

NOTICE OF FILING

To: ALL PARTIES ON THE ATTACHED SERVICE LIST

PLEASE TAKE NOTICE that I have today electronically filed with the Office of the Clerk of the Illinois Pollution Control Board the attached **Pre-filed Answers of Robyn Prueitt to Pre-Filed Questions of the Illinois Environmental Protection Agency, American Chemistry Council, and Illinois Pollution Control Board,** and a **Certificate of Services**, copies of which are hereby served upon you.

/s/ Sarah L. Lode
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Dated: November 23, 2022

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CERTIFICATE OF SERVICE

I, the undersigned, certify that on this 23rd day of November, 2022, I have electronically served the attached **Pre-filed Answers of Robyn Prueitt to Pre-Filed Questions of the Illinois Environmental Protection Agency, American Chemistry Council, and Illinois Pollution Control Board** upon the individuals on the attached service list. I further certify that my email address is Sarah.Lode@afslaw.com; the number of pages in the email transmission is 31; and the email transmission took place before 5:00 p.m.

/s/ Sarah L. Lode
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Pre-Filed Answers of Robyn Prueitt, Ph.D., DABT to Pre-Filed Questions from the Illinois Environmental Protection Agency, American Chemistry Council, and Illinois Pollution Control Board Regarding the Illinois Environmental Protection Agency's Proposed Amendments to Illinois Administrative Code Title 35, Part 620: Groundwater Quality Standards

Docket Number R22-18

Prepared by

Robyn Prueitt, Ph.D., DABT

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DR. ROBYN PRUEITT'S PRE-FILED ANSWERS TO THE ILLINOIS ENVIRONMENTAL PROTECTION AGENCY (IEPA)

IEPA Question 1
Have the toxicity assessments for each of the proposed PFAS undergone peer-review and public comment prior to the issuance of the final toxicity values?

Answer 1
Yes; however, just because an assessment has undergone peer review and public comment does not indicate that the agencies made the changes suggested by the peer reviewers and public commenters or that the assessments are free from significant issues. Moreover, IEPA did not critically evaluate the toxicity assessments or the toxicity evidence underlying the toxicity values to ensure that the most scientifically supported toxicity values were chosen as the bases for the Proposed PFAS Standards.

IEPA Question 2
With the exception of the toxicity value developed by Illinois EPA to calculate an MTBE (methyl-tertiary-butyl ether) standard, as no oral reference dose in available within the toxicity hierarchy, can you discuss any constituent in Part 620 other than PFAS, with a toxicity value that is not based on a "third-party evaluation"?

Answer 2
I did not review the toxicity values chosen for any constituent other than PFAS in IEPA's proposed Part 620 groundwater standards. Regardless, even if the other constituents are all based on third-party toxicity evaluations using the US EPA Screening Level Hierarchy, IEPA's approach would remain flawed because it chose the toxicity values from the hierarchy without any independent evaluation of their scientific rigor and appropriateness to ensure that the most scientifically supported toxicity values were chosen as the bases for the Proposed PFAS Standards.

IEPA Question 3
Please explain how developing potable resource standards using toxicity values developed for drinking water is considered an inappropriate situation.

Answer 3
My testimony does not indicate that deriving potable resource standards using toxicity values developed for drinking water is inappropriate. However, the toxicity values chosen by IEPA as the bases for the Proposed PFAS Standards were not developed specifically for drinking water; they are either reference doses (RfDs), minimal risk levels (MRLs), or cancer slope factors that were derived by agencies to indicate an exposure level that is safe for humans with an adequate margin of safety. For example, an RfD is defined as "an estimate…of a daily exposure level for a human population, including sensitive populations, that is likely to be without an appreciable risk of deleterious [*i.e.*, adverse] effects during a lifetime"(US EPA, 1989). An MRL is defined as "an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure" (ATSDR, 2021). These types of toxicity values have been used to develop drinking water screening levels and standards, but they are not specifically derived for that use.

Regardless, the issue is not whether these toxicity values can be used to develop potable resource standards (which they can), it is that IEPA chose the toxicity values from the US EPA Screening Level Hierarchy without any independent evaluation of their scientific rigor and appropriateness to ensure that the most scientifically supported toxicity values were chosen as the bases for the Proposed PFAS Standards.

IEPA Question 4
For what reasons do you believe the selection of toxicity values from U.S. EPA's toxicity hierarchy is not appropriate for setting health-based potable resource standards?

Answer 4
The US EPA Screening Level Hierarchy is intended for use in the selection of toxicity values for the derivation of regional screening levels (RSLs). It is not intended to be used for choosing a toxicity value upon which to base an enforceable groundwater standard, and it is not appropriate to use it for this purpose without a careful evaluation of the available toxicity values to ensure that standard practices were used in deriving those values and that the values represent appropriate health endpoints. In fact, US EPA specifically states in its RSL "User's Guide" that "[w]hen using toxicity values other than tier 1," such as is the case here, "users are encouraged to carefully review the basis for the value…" (US EPA, 2022a). The toxicity values at issue are not Tier 1 values.

The US EPA Screening Level Hierarchy represents a highly limited set of evaluations with potential toxicity values, and does not represent the full extent to which these PFAS have been evaluated in the context of risk assessment by other state, federal, and international agencies. A critical review of all available toxicity values would be most appropriate if IEPA does not intend to follow established human health risk assessment practices to derive its own toxicity values. If IEPA's process is to choose from only this limited set of evaluations, then it should conduct an independent assessment of the scientific rigor and appropriateness of each evaluation to ensure that it has chosen the most scientifically supported toxicity values as the bases for the Proposed PFAS Standards.

IEPA Question 5
Do you agree RSL standards, which bases its toxicity selection on the U.S. EPA toxicity hierarchy are health-based standards?

Answer 5
While RSLs are health-based guidance values recommended for screening purposes in the initial evaluation of contaminated sites to determine which substances at the site warrant further investigation (US EPA, 2022a), they are not intended to be cleanup levels or legally enforceable standards (US EPA, 2022a).

IEPA Question 6
Do you agree that ingestion of groundwater is as appropriate health-based endpoint for the calculation of health-based potable resource standards?

Answer 6
Ingestion of groundwater is not a "health-based endpoint" (*i.e.*, health effect); it is an exposure pathway.

IEPA Question 7
Are you aware that Illinois EPA uses the toxicity hierarchy in calculating remediation objectives for 35 Ill. Adm. Code 742 (TACO)?

Answer 7
Whether IEPA uses the US EPA Screening Level Hierarchy to calculate remediation objectives is not relevant. In the context of developing the Proposed PFAS Standards, if IEPA chooses third-party evaluations from the hierarchy, then IEPA should conduct an independent assessment of the scientific rigor and appropriateness of each third-party evaluation to ensure that it has chosen the most scientifically supported toxicity values as the bases for the Proposed PFAS Standards.

IEPA Question 8

Are you aware that Illinois EPA introduced the toxicity hierarchy in its Part 620 R2008-018 updates, which was finalized by the Illinois Pollution Control Board in 2012, with its approval of the use of the hierarchy? Do you disagree with the Board's findings?

Answer 8
Regardless of whether the Board approved the use of the US EPA Screening Level Hierarchy in the Part 620 R2008-018 updates, the Board did not mandate its use, and IEPA should exercise judgment in determining whether the hierarchy is appropriate to use and, if so, how it is applied. In developing the Proposed PFAS Standards, IEPA should not blindly follow the hierarchy and should instead conduct an independent evaluation of the scientific rigor and appropriateness of each toxicity value to ensure that it has chosen the most scientifically supported toxicity values as the bases for the Proposed PFAS Standards.

IEPA Question 9
Do you believe the US EPA Office of Water's 2016 PFOS toxicity evaluation is more scientifically sound than the use of updated toxicity studies for comparison? Please explain your response.

Answer 9
The recency of a toxicity study or a toxicity evaluation does not necessarily indicate whether it is more scientifically sound than studies or evaluations conducted at earlier time periods. Each evaluation should be assessed for its scientific rigor and appropriateness regardless of when it was conducted. IEPA failed to undertake such an assessment before choosing a PFOS toxicity value.

IEPA Question 10
Does RSL use the 2016 toxicity value when developing its health-based standards for PFAS?

Answer 10
No. US EPA uses its Screening Level Hierarchy for RSLs and, therefore, it does not use the RfD from US EPA Office of Water's 2016 PFOS toxicity evaluation for its PFOS RSL because the RfD from such an evaluation is lower in the hierarchy than the Agency for Toxic Substances and Disease Registry (ATSDR) MRL. This does not mean, however, that it is appropriate for IEPA to take the same approach for the Illinois proposed PFOS groundwater standard, because the proposed standard is not a screening level. IEPA should choose the toxicity value used in developing the proposed PFOS groundwater standard only after it engages in an independent evaluation of the scientific rigor and appropriateness of available toxicity values to ensure that the most scientifically supported toxicity value is used. IEPA has failed to undertake such an evaluation.

IEPA Question 11
Did US EPA select the ATDSR MRLs as the noncancer toxicity values for use in developing its RSL health-based screening levels?

Answer 11
US EPA selected the ATSDR MRLs for PFOA, PFOS, PFHxS, and PFNA in developing the RSLs for these four PFAS. However, it is not appropriate for IEPA to take the same approach in developing the Illinois Proposed PFAS Standards because they are not screening levels. IEPA should choose the toxicity values used in developing the Proposed PFAS Standards only after an independent evaluation of the scientific rigor and appropriateness of available toxicity values to ensure that the most scientifically supported toxicity values are used. IEPA has failed to undertake such an evaluation.

IEPA Question 12
Do you believe it is not appropriate for US EPA to utilize the ATSDR MRL toxicity values when calculating health-based screening levels? Please explain your response.

Answer 12
How US EPA chooses its toxicity values for calculating health-based screening levels has no bearing on my testimony, which focuses on how IEPA chose its toxicity values for developing the Proposed PFAS Standards. As noted above, just because US EPA takes this approach for its RSLs does not mean that it is appropriate for IEPA to do the same in developing the Proposed PFAS Standards because they are not screening levels. IEPA should choose the toxicity values used in developing the Proposed PFAS Standards only after an independent evaluation of the scientific rigor and appropriateness of available toxicity values to ensure that the most scientifically supported toxicity values are used. IEPA has failed to undertake such an evaluation.

IEPA Question 13
Do you disagree with US EPA's RSC assessment using its Decision Tree that data is insufficient to allow for a quantitative characterization of different exposure sources? Please explain your response.

Answer 13
Yes, and other states also disagree with using US EPA's default relative source contribution (RSC) of 20% for PFAS. The default value is not scientifically supported and is more stringent than necessary. The default RSC of 20% is the most conservative RSC value used by regulatory agencies, but a higher (and less stringent) RSC value can be determined if information regarding exposure to the specific chemical of interest is known, such as by using the US EPA (2000) "Exposure Decision Tree" for selecting an RSC. Several other states have used this methodology, combined with publicly available data on background concentrations of PFAS in the serum of the general US population, to estimate higher RSC values for several PFAS. For example, the Michigan Department of Health and Human Services (MDHHS, 2019) assumed an RSC value of 50% for PFOA, PFOS, PFHxS, and PFNA in its derivation of public health drinking water screening levels for these PFAS, and the Minnesota Department of Health (MDH) also assumed an RSC value of 50% for deriving its health-based guidance for drinking water for PFOA (MDH, 2020a), PFOS (MDH, 2020b), and PFHxS (MDH, 2020c). There are also multiple studies of dietary, dust, and inhalation exposure to PFOA and PFOS that do not indicate that exposures other than drinking water are likely to add up to 80% of the allowable daily intakes of PFOA and PFOS at their current RfDs or MRLs.

IEPA Question 14
Are products containing PFOA, PFOS or other PFAS present in homes and businesses in Illinois allow for exposure to PFAS?

Answer 14
This question is unclear as asked. To the extent this question seeks to imply that PFAS exposure levels from products containing certain PFAS will add up to 80% of allowable daily intakes for any specific PFAS, the available data do not support that conclusion.

IEPA Question 15
Can these products provide humans, especially young children, a route for exposure to PFAS?

Answer 15
To the extent this question seeks to imply that PFAS exposure levels from products containing certain PFAS will add up to 80% of allowable daily intakes for any specific PFAS, the available data do not support that conclusion.

IEPA Question 16
Is Method 8327 a validated method for analyzing potable resource water? Please explain your response.

Answer 16
US EPA SW-846 Method 8327 is not a validated analytical method for measuring PFAS concentrations in drinking water. According to US EPA's most recent update of this method, it has only been validated for non-potable groundwater, surface water, and wastewater (US EPA, 2021c). Method 8327 is also not listed as an approved method for analyzing PFAS for comparison to drinking water standards (US EPA, 2022b).

Regardless of whether Method 8327 is validated for potable water, however, the lower limits of quantification (LLOQs) for this method are higher than or similar to the IEPA Proposed PFAS Standards for PFOA, PFOS, and PFNA (US EPA, 2019a), so it is unlikely that these PFAS could be reliably measured at concentrations nearing their proposed groundwater standards. Unreliable measurements of PFAS concentrations in groundwater samples cannot be used with any certainty to evaluate compliance with health-based groundwater standards. In fact, US EPA SW-846 Method 8327 specifically advises that "optimally, LLOQs should be less than the desired decision levels or regulatory action levels" for the intended application and the data quality objectives established for the method (US EPA, 2021c).

IEPA Question 17
Is analyzing groundwater based on its use as a potable resource appropriate using a method derived for non-potable uses? Please explain your response.

Answer 17
No. According to US EPA, all test methods used to measure chemicals in drinking water should be approved for nationwide use in all matrices (US EPA, 2022c). As noted above, US EPA SW-186 Method 8327 has not been approved for analyzing PFAS for comparison to drinking water (*i.e.*, potable water) standards (US EPA, 2022b).

IEPA Question 18
Are there potable water methods available to analyze to minimum reporting levels at or below the proposed PFAS potable resource standards?

Answer 18
Yes. US EPA Method 533 and US EPA Method 537.1 are validated methods for analyzing PFAS in drinking water (*i.e.*, potable water) from groundwater sources (US EPA, 2022d). The lowest concentration minimum reporting levels (LCMRLs) for the six PFAS with IEPA proposed groundwater standards for Method 537.1 are all below the proposed standards (US EPA, 2020). US EPA (2021d) will use Method 533 for measuring these PFAS in drinking water for the Fifth Unregulated Contaminant Monitoring Rule (UCMR 5), however. For Method 533, the LCMRL for PFOA (3.4 ng/L) (US EPA, 2019b) is higher than the IEPA proposed PFOA groundwater standard (2 ng/L), so PFOA concentrations cannot be reliably measured for comparison to this proposed standard.

IEPA Question 19
Are there circumstances when a linear model is appropriate for deriving a cancer toxicity value when carcinogens are not demonstrated to act via a mutagen mode of action?

Answer 19
No, although regulatory agencies such as US EPA often use a linear dose-response model as a default if the mode of action has not been ascertained, which is a conservative approach (US EPA, 2005). Such an approach is not necessary or appropriate for PFOA, however, as it is well-documented in the literature that PFOA is not genotoxic or mutagenic (Crebelli *et al*., 2019; Kennedy and Symons, 2015; EFSA CONTAM, 2018; ATSDR, 2021). Rather, the scientific literature indicates that the modes of action for tumors observed in rodents after exposures to high concentrations of PFOA are peroxisome proliferator-activated receptor

alpha (PPARα)-mediated and/or involve sustained increases in cholecystokinin (CCK), and these modes of action involve a threshold (and are not relevant to humans) (Corton *et al*., 2018; Kennedy and Symons, 2015; Biegel *et al*., 2001; Klaunig *et al*., 2003, 2012). Use of a linear dose-response model for a threshold carcinogen is not appropriate, as US EPA cancer guidelines indicate that a non-linear approach should be used when data indicate a lack of linearity (*i.e*., the presence of a threshold) at low doses and the chemical does not have mutagenic activity (US EPA, 2005).

IEPA Question 20
Does Section 5/58.2 of the Illinois Environmental Protection Act define a carcinogen, in part, as classified a category 1 or 2A/2B carcinogen by World Health Organization's International Agency for Research on Cancer (IARC) classify PFOA as a "2B" carcinogen?

Answer 20
My testimony does not dispute whether IEPA used its own definition of a carcinogen; however, it does dispute an interpretation of PFOA as a human carcinogen, as neither animal nor human data support such a conclusion. In its classification of PFOA as a "2B" carcinogen, IARC (2016c) stated that the evidence in humans and experimental animals supporting carcinogenicity was only "limited," and that it could not rule out chance, bias, or confounding in human studies with reasonable confidence. IEPA did not independently evaluate the evidence for the potential human carcinogenicity of PFOA or consider the important uncertainties regarding a causal relationship between PFOA exposure and cancer in humans. Regardless of IEPA's definition of a carcinogen, proposing a groundwater standard based on carcinogenic effects for a chemical that does not have evidence to support human carcinogenicity is not scientifically appropriate.

IEPA Question 21
Would not defining PFOA as a carcinogen violate the Illinois Environmental Protection Act?

Answer 21
This question calls for a legal conclusion. My testimony focuses on the fact that the evidence does not support PFOA as a human carcinogen, and thus, a groundwater standard for PFOA should not be based on carcinogenic effects.

IEPA Question 22
Did you file your concerns regarding the PFOA toxicity assessment with California EPA during its peer-review and Public Comment sessions?
a) If yes, please provide a copy of your comments submitted to California EPA and California EPA's response to your comments.
b) If no, please explain why you are bringing up these concerns during Part 620 rulemaking and did not during the toxicity assessment.

Answer 22
No, I was not engaged to submit comments on California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (CalOEHHA's) PFOA toxicity assessment. However, my testimony focuses on appropriate methodology for setting groundwater standards. If an agency is going to use toxicity values derived by other agencies, such as the PFOA cancer slope factor derived by CalOEHHA, it should first conduct an independent assessment of the scientific rigor and appropriateness of the toxicity values to ensure that it has chosen the most scientifically supported toxicity values as the bases for the proposed PFAS groundwater standards. Instead, IEPA's process for selecting toxicity values blindly follows what other agencies have done and ignores any issues related to the underlying studies and the methods used to derive the toxicity values. Thus, IEPA has assumed no responsibility for ensuring that the toxicity values it chooses are based on sound science and appropriate methodologies, and indeed, IEPA has failed to investigate any criticisms of the various toxicity values it chose.

IEPA Question 23
Did you file your concerns regarding the PFBS toxicity assessment with U.S. EPA during its peer-review and Public Comment sessions during development of its Provisional Peer[1]Reviewed Toxicity Value (PPRTV)?
a) If yes, please provide a copy of your comments submitted to U.S.EPA and U.S. EPA's response to your comments.
b) If no, please explain why you are bringing up these concerns during Part 620 rulemaking and did not during the toxicity assessment.

Answer 23
No, I was not engaged to submit comments on US EPA's PFBS toxicity assessment. However, my testimony focuses on appropriate methodology for setting groundwater standards. If an agency is going to use toxicity values derived by other agencies, such as the PFBS Provisional Peer Reviewed Toxicity Value (PPRTV) derived by US EPA, it should first conduct an independent assessment of the scientific rigor and appropriateness of the toxicity values to ensure that it has chosen the most scientifically supported toxicity values as the bases for the proposed PFAS groundwater standards. Instead, IEPA's process for selecting toxicity values blindly follows what other agencies have done and ignores any issues related to the underlying studies and the methods used to derive the toxicity values. Thus, IEPA has assumed no responsibility for ensuring that the toxicity values it chooses are based on sound science and appropriate methodologies, and indeed, IEPA has failed to investigate any criticisms of the various toxicity values it chose.

IEPA Question 24
Did you file your concerns regarding the PFHxS, PFNA and PFOS toxicity assessments with CDC's Agency for Toxic Substances and Disease Registry (ATSDR) during its peer-review and Public Comment sessions during development of its Minimal Risk Levels (MRLs) for these chemicals?
a) If yes, please provide a copy of your comments submitted to ATSDR and ATSDR's response to your comments.
b) If no, please explain why you are bringing up these concerns during Part 620 rulemaking and did not during the toxicity assessment.

Answer 24
No, I was not engaged to submit comments on ATSDR's toxicity assessments of PFHxS, PFNA, and PFOS. However, my testimony focuses on appropriate methodology for setting groundwater standards. If an agency is going to use toxicity values derived by other agencies, such as the PFHxS, PFNA, and PFOS MRLs derived by ATSDR, it should first conduct an independent assessment of the scientific rigor and appropriateness of the toxicity values to ensure that it has chosen the most scientifically supported toxicity values as the bases for the proposed PFAS groundwater standards. Instead, IEPA's process for selecting toxicity values blindly follows what other agencies have done and ignores any issues related to the underlying studies and the methods used to derive the toxicity values. Thus, IEPA has assumed no responsibility for ensuring that the toxicity values it chooses are based on sound science and appropriate methodologies, and indeed, IEPA has failed to investigate any criticisms of the various toxicity values it chose.

IEPA Question 25
Did you file your concerns regarding the HFPO-DA toxicity assessment with U.S. EPA Office of Water during its peer-review and Public Comment sessions during development of its toxicity value?
a) If yes, please provide a copy of your comments submitted to U.S.EPA Office of Water and U.S. EPA Office of Water's response to your comments.

b) If no, please explain why you are bringing up these concerns during Part 620 rulemaking and did not during the toxicity assessment.

Answer 25

No, I was not engaged to submit comments on US EPA's HFPO-DA toxicity assessment. However, my testimony focuses on appropriate methodology for setting groundwater standards. If an agency is going to use toxicity values derived by other agencies, such as the HFPO-DA RfD derived by US EPA, it should first conduct an independent assessment of the scientific rigor and appropriateness of the toxicity values to ensure that it has chosen the most scientifically supported toxicity values as the bases for the proposed PFAS groundwater standards. Instead, IEPA's process for selecting toxicity values blindly follows what other agencies have done and ignores any issues related to the underlying studies and the methods used to derive the toxicity values. Thus, IEPA has assumed no responsibility for ensuring that the toxicity values it chooses are based on sound science and appropriate methodologies, and indeed, IEPA has failed to investigate any criticisms of the various toxicity values it chose.

DR. ROBYN PRUEITT'S PRE-FILED ANSWERS TO THE AMERICAN CHEMISTRY COUNCIL (ACC)

ACC Question 1

To calculate its proposed groundwater standards for the seven PFAS, IEPA uses US EPA's Screening Level Hierarchy for selecting toxicity values developed by other agencies, which is intended for use in the derivation of screening levels at contaminated sites.

- *Are there issues with using USEPA's Screening Level Hierarchy for choosing toxicity values for use in developing groundwater standards?*

Answer 1

Yes, IEPA inappropriately used the US EPA Screening Level Hierarchy to choose toxicity values. In doing so, IEPA used the US EPA Screening Level Hierarchy without engaging in any independent evaluation of the scientific rigor and appropriateness of the toxicity values and their derivation. The US EPA Screening Level Hierarchy is intended for use in the selection of toxicity values for the derivation of RSLs, which are screening levels for the initial evaluation of a contaminated site and the determination in that context as to which substances detected at the site warrant further investigation (US EPA, 2022a). RSLs are not intended to be legally enforceable standards, but instead are guidance values used for screening purposes. In turn, the US EPA Screening Level Hierarchy is not intended to be used by an agency like the IEPA to select a toxicity value upon which to base an enforceable groundwater standard. It is not appropriate to use the US EPA Screening Level Hierarchy for this purpose without a careful evaluation of the available toxicity values to ensure that standard practices were used in deriving those values and that the values represent appropriate health endpoints. In fact, US EPA specifically states in its RSL "User's Guide" that "[w]hen using toxicity values other than tier 1, users are encouraged to carefully review the basis for the value…" (US EPA, 2022a). The toxicity values at issue are not Tier 1 values.

ACC Question 2

Some of the standards proposed by IEPA are derived from an analysis conducted by the Agency for Toxic Substances and Disease Registry (ATSDR). For its analysis ATSDR only considered studies with animal strains that had pharmacokinetic model parameters to derive its toxicity values for PFAS.

- *What are the concerns with the approach taken by ATSDR to derive toxicity values?*

Answer 2

ATSDR's approach to only consider studies with animal strains that had pharmacokinetic model parameters available for predicting serum concentrations of PFAS in the animals from the administered PFAS doses (ATSDR, 2021) precluded the use of many studies of various endpoints. For example, ATSDR reviewed, but did not consider, several studies of immunological, neurological, and developmental effects in mice and a study of neurodevelopmental effects in rats as a potential basis for its MRL for PFOS because of the lack of pharmacokinetic model parameters for the specific rodent strains used in those studies (ATSDR, 2021). This approach limits the number of studies and endpoints available for consideration as a basis for the MRLs, and the possibility exists that some of the studies that were not considered could have evaluated more scientifically supported and relevant endpoints than the studies that used rodent strains with pharmacokinetic model parameters. IEPA failed to take this limitation of the ATSDR MRLs into account when using the US EPA Screening Level Hierarchy to select which toxicity values to use.

ACC Question 3

IEPA indicates that PFOA meets the definition of a carcinogen because the International Agency for Research on Cancer (IARC) has classified PFOA as "possibly carcinogenic to humans."

- *What does the IARC classification of "possibly carcinogenic to humans" mean?*
- *What other substances are listed by IARC as "possibly carcinogenic to humans?"*

- *Is an IARC listing as possibly carcinogenic an adequate basis for IEPA to conclude that PFOA causes cancer in humans?*

Answer 3

An International Agency for Research on Cancer (IARC) classification of "possibly carcinogenic to humans" (Group 2B) is the lowest possible cancer classification level for IARC, meaning that the evidence of carcinogenicity is very limited and may even be based on evidence from studies in experimental animals alone. In IARC's carcinogenicity classification scheme, Group 2B is just above Group 3, which is the distinction of "not classifiable as to its carcinogenicity to humans" (IARC, 2019). Classification as a Group 2B carcinogen requires the lowest level of evidence of carcinogenicity and is based on either limited evidence of carcinogenicity in humans, sufficient evidence of carcinogenicity in experimental animals, or strong mechanistic evidence of carcinogenicity in any species (IARC, 2019). This means that a substance can be classified as a Group 2B carcinogen based on evidence from studies in experimental animals alone, even if there is no evidence of carcinogenicity in humans.

Several substances that humans commonly seek out, purchase, and ingest or otherwise use have been classified by IARC as Group 2B carcinogens, including pickled vegetables (IARC, 1993) and aloe vera extract (IARC, 2016a). In addition, several substances that humans commonly ingest have been classified by IARC as Group 1 carcinogens ("carcinogenic to humans"), including alcoholic beverages (IARC, 2012), processed meat (IARC, 2018), and salted fish (IARC, 2012), and yet there have been no bans or restrictions on the amount of alcohol, processed meat, or salted fish that consumers ingest. The fact that everyday consumer goods are classified at a higher level of carcinogenicity than PFOA, and yet are not regulated, calls into question the usefulness of IARC cancer classifications as risk assessment tools for setting groundwater standards. In addition, IARC classifications do not account for the dose of a substance that is associated with cancer; under the IARC classification scheme, a substance could still be classified as a carcinogen even if it only causes cancer at extremely high doses that humans would never encounter (IARC, 2019).

The IARC classification of PFOA as a 2B carcinogen is not an adequate basis for concluding that PFOA causes cancer in humans. IARC (2016c) stated that the evidence in humans and experimental animals supporting carcinogenicity of PFOA was only "limited," and that it could not rule out chance, bias, or confounding in human studies with reasonable confidence. Overall, the human data do not support the conclusion that PFOA is a human carcinogen (see, for example, Raleigh *et al*. [2014], Steenland *et al*. [2015], and Steenland and Winquist [2021]).

ACC Question 4

IEPA used a cancer slope factor derived by OEHHA as the toxicity value for its proposed standard for PFOA. In deriving its value, OEHHA uses a linear dose-response model for carcinogenic effects of PFOA.

- *Is a linear dose-response model appropriate for evaluating PFOA carcinogenicity?*

Answer 4

A linear dose-response model is not appropriate for evaluating PFOA carcinogenicity. Such models are used for carcinogens with a mutagenic mode of action or as a conservative default approach when the mode of action has not been ascertained (US EPA, 2005). It is well-documented in the literature that PFOA is not genotoxic or mutagenic (Crebelli *et al*., 2019; Kennedy and Symons, 2015; EFSA CONTAM, 2018; ATSDR, 2021). Rather, the scientific literature indicates that the modes of action for tumors observed in rodents after exposures to high concentrations of PFOA are PPARα-mediated and/or involve sustained increases in CCK, and these modes of action involve a threshold (and are not relevant to humans) (Corton *et al*., 2018; Kennedy and Symons, 2015; Biegel *et al*., 2001; Klaunig *et al*., 2003, 2012). Use of a linear dose-response model for a threshold carcinogen is not appropriate, as US EPA cancer guidelines indicate that a non-linear approach should be used when data indicate a lack of linearity (*i.e*., the presence of a threshold) at low doses and the chemical does not have mutagenic activity (US EPA, 2005).

ACC Question 5

OEHHA's cancer slope factor for PFOA is based on the results of a carcinogenicity study in laboratory rats.

- *Is the rat cancer study scientifically sound?*
- *Does the rat study provide evidence to suggest human carcinogenicity of PFOA?*

Answer 5

The CalOEHHA cancer slope factor for PFOA is based on the observation of increased hepatocellular adenomas/carcinomas and pancreatic acinar cell adenomas/carcinomas (mostly adenomas, however, as there were no statistically significant increases in the incidence of carcinomas) in male rats in a study conducted by the National Toxicology Program (NTP, 2020). The tumors occurred in male Sprague Dawley rats that received PFOA doses of 40 and 80 ppm (2.2 and 4.6 mg/kg-day) in the diet. While the study was generally well-conducted, some of the findings from this study are concerning and may decrease the reliability of the results. The male rats were initially exposed to PFOA doses that were an order of magnitude higher (*i.e*., 150 and 300 ppm), but the authors reported "unanticipated toxicity" after 16 weeks of exposure to these doses and the study was repeated with the lower doses. Another chronic carcinogenicity study with male Sprague Dawley rats conducted by Butenhoff *et al*. (2012) reported no such toxicity with PFOA doses up to 300 ppm, however. Another issue with the NTP (2020) study is the observation of a statistically significant increase in pancreatic acinar cell hyperplasia (which can be a precursor lesion to cancer) in the male untreated control group, indicating a high spontaneous background rate for such lesions, which may have contributed to the increased incidence of pancreatic acinar tumors in the treated rats.

Several agencies have guidelines that require findings of an increased incidence of malignant tumors or a combination of malignant and benign tumors in animal studies before they are able to conclude that there is sufficient evidence of a chemicals' carcinogenicity (see for example, US EPA [2003], NTP [2015], and IARC [2016b]). Apart from the NTP (2020) study, rat carcinogenicity studies of PFOA have reported increases only in benign tumors, and no tumors have been reported in mouse carcinogenicity studies of PFOA (Butenhoff *et al*., 2012; Biegel *et al*., 2001). Thus, the rat tumor findings in the NTP (2020) used by CalOEHHA to derive a cancer slope factor have not been replicated in other rodent studies. Furthermore, the NTP (2020) study reported only small increases in malignant carcinomas that were not dose-dependent or statistically significant, and this does not meet NTP's or other agencies' guidelines for sufficient evidence of carcinogenicity. Overall, the findings in animal studies do not provide sufficient evidence of PFOA's carcinogenicity.

The rat study conducted by NTP (2020) does not provide evidence to suggest human carcinogenicity of PFOA. The scientific literature indicates that hepatocellular and pancreatic acinar tumors purportedly associated with PFOA in rats are likely mediated by modes of action that are not relevant to humans. The liver tumor response in rats is likely mediated by PPARα receptors (Corton *et al*., 2018; Kennedy and Symons, 2015; Biegel *et al*., 2001), the activity of which was elevated in the rats in the underlying NTP (2020) study. PPARα receptor-mediated processes occur much more readily in rats than in humans (Klaunig *et al*., 2003, 2012); therefore, a mode of action for PFOA involving PPARα is likely not relevant to humans (Corton *et al*., 2018). Similarly, pancreatic tumors in rodents may occur by a mode of action that is mediated by downstream events following activation of PPARα receptors, and thus not relevant to humans, and/or by a process involving sustained increases in CCK, a mode of action that is also not relevant to humans (Klaunig *et al*., 2012). In the ATSDR toxicological profile for PFOA that IEPA relied on for a toxicity value for a noncancer groundwater standard for PFOA, ATSDR (2021) agreed that liver effects in animals cannot reliably be extrapolated to humans. IEPA did not consider this finding and did not independently evaluate the evidence and reach its own conclusions regarding the potential human relevance of the results of the NTP (2020) study.

ACC Question 6

In developing toxicity values toxicologists select the dose at which no adverse health effects were observed to occur or are predicted to occur. USEPA considers adverse effects to be those that cause harm to the normal functioning of the test species.

- *Is there evidence that any of the effects used to derive the toxicity values chosen by IEPA should be considered to be non-adverse?*
- *What is the significance of a non-adverse effect?*
- *Is it appropriate to base a toxicity value on a non-adverse effect?*

Answer 6

Yes, there is evidence that the critical effects that form the basis for the toxicity values of PFOS, PFHxS, PFBS, and HFPO-DA chosen by IEPA are not adverse effects.

The critical effects for the ATSDR (2021) MRL for PFOS are delayed eye opening and transient decreased body weight in rat pups that were exposed to PFOS at 0.4 mg/kg-day, as reported by Luebker *et al*. (2005). ATSDR considered 0.4 mg/kg-day to be the lowest observed adverse effect level (LOAEL) and 0.1 mg/kg-day to be the no observed adverse effect level (NOAEL) in this study. In contrast, Luebker *et al*. (2005) considered 0.4 mg/kg-day to be the NOAEL, based on reduced pup survival and reduced weight gain observed at a dose of 1.6 mg/kg-day. The study's authors did not consider the slight delay in eye opening to be an adverse outcome and did not consider the transient decrease in body weight to be toxicologically significant. Thus, IEPA based its groundwater standard for PFOS on a toxicity value that ignores the conclusions of the authors of the underlying study and is based on non-adverse effects.

The critical effect for the ATSDR (2021) MRL for PFHxS is thyroid follicular cell hyperplasia in adult male rats after exposure to PFHxS at 3 mg/kg-day, as reported by Butenhoff *et al*. (2009). Butenhoff *et al*. (2009) noted that this effect was consistent with an increase in liver hypertrophy and induction of liver enzymes (observed in this study) that in turn induce the metabolism of thyroid hormones. The authors did not measure thyroid hormones in this study, however, so the clinical significance (*i.e*., adversity) of the thyroid cell hyperplasia is unknown. ATSDR (2021) concluded that the liver effects observed in the only other candidate study it selected for deriving an MRL for PFHxS (a mouse study reporting liver effects) were *not* considered to be adverse.

The critical effect for the PFBS RfD derived by US EPA (2021a) is decreased serum thyroid hormone (thyroxine [T4]) levels in mouse pups exposed to PFBS at doses above 50 mg/kg-day, as reported by Feng *et al*. (2017). Observations in the study by Feng *et al*. (2017) indicate that there is uncertainty as to whether the decrease in T4 levels was a toxicologically relevant, adverse effect in this study. For example, there was no increasing dose-response for the T4 effects or other reported effects (Feng *et al*., 2017). In addition, the authors did not compare the T4 values to the range of normal values, did not indicate if the T4 values were low enough to constitute hypothyroidism, and did not indicate whether there were any changes in thyroid histology.

The critical effect for the HFPO-DA RfD derived by US EPA (2021b) is a "constellation of liver lesions" in mice, as reported in an unpublished reproductive and developmental study that was submitted to US EPA by DuPont under a Toxic Substances Control Act (TSCA) Consent Order. There is uncertainty as to the adversity of some of the reported liver effects. Some of the effects, such as single-cell and focal necrosis, are adverse, but other effects are either adaptive changes (*i.e*., hepatocellular hypertrophy, or enlargement of liver cells) or of unclear adversity (*i.e*., alterations in the cytoplasm of liver cells). There was no clear increase in incidence of the adverse effects of necrosis; it is only when the incidences of all of the adverse

and non-adverse effects were combined together that there was a clear increase in incidence compared to the unexposed control group.

A non-adverse effect of a substance does not represent toxicity. Some substances can induce adaptive or compensatory effects that are responses to stressors in the environment that maintain homeostasis (*i.e*., the body's normal function), and these effects are not adverse (Lewis *et al*., 2002; Goodman *et al*., 2010). Effects that are transient and not sustained during the complete period of exposure, or those that are completely reversible after exposure has ended, are also not likely to be adverse (Lewis *et al*., 2002; Goodman *et al*., 2010). It is not appropriate to base a toxicity value on a non-adverse (*i.e*., non-toxic) effect, as this goes against established practice for developing toxicity factors for use in determining regulatory standards. For example, US EPA risk assessment guidance notes that the purpose of a toxicity assessment (in which toxicity values are derived) is to "weigh available evidence regarding the potential for particular contaminants to cause adverse effects in exposed individuals," and the definition of a chronic RfD is "[a]n estimate…of a daily exposure level for a human population, including sensitive populations, that is likely to be without an appreciable risk of deleterious [*i.e*., adverse] effects during a lifetime" (US EPA, 1989). Similarly, ATSDR defines an MRL as "an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure" (ATSDR, 2021).

ACC Question 7

Most of the toxicity values on which the IEPA proposed standards are based, including the values for the seven PFAS, are derived from studies in laboratory mice and/or rats. While it is often assumed that the effects seen in the laboratory studies are relevant to humans, available evidence indicates that some observed effects are unique to the rodent species and not of human relevance.

- *Is there evidence that any of the critical effects that form the basis for the toxicity values chosen by IEPA are not relevant to humans?*
- *Is it appropriate to base a toxicity value on a health effect that is not relevant to humans?*

Answer 7

Yes, there is evidence that the critical effects that form the basis for the toxicity values of PFOA, PFHxS, PFNA, PFBS, and HFPO-DA chosen by IEPA are not relevant to humans. Such evidence for PFOA is discussed above in the answer to Question 5.

The thyroid follicular cell hyperplasia in adult male rats that was used as the critical effect for the ATSDR (2021) MRL for PFHxS was noted by the study authors to be "consistent with the known effects of inducers of microsomal enzymes where the hepatocellular hypertrophy results in compensatory hypertrophy and hyperplasia of the thyroid" (Butenhoff *et al*., 2009). This refers to PPARα activity, which ATSDR (2021) agrees is a mechanism that is not relevant to humans.

The critical effect for the ATSDR (2021) MRL for PFNA is decreased body weight and developmental delays in mouse pups exposed to PFNA at 3 mg/kg-day, as reported in the study by Das *et al*. (2015). PFNA activates PPARα (Wolf *et al*., 2008; Vanden Heuvel *et al*., 2006) and induces PPARα-dependent gene expression (Rosen *et al*., 2017). There is direct evidence that PPARα mediates many of the reported effects of PFNA in experimental animals, including developmental effects (Rosen *et al*., 2017; Wolf *et al*., 2010). Delayed eye opening and reduced pup body weight in PFNA-exposed mice have been shown to be dependent on PPARα activity (Wolf *et al*., 2010), which calls into question the relevance of these endpoints to humans.

The decreased serum T4 levels in mouse pups that was used as the critical effect for the PFBS RfD derived by US EPA (2021a) is of uncertain relevance to humans, because rodents are highly susceptible to thyroid hormone perturbations when compared to humans (NRC, 2005; Bartsch *et al.*, 2018; Parker and York,

2014; Brown-Grant, 1963), due to their smaller reserve capacity of thyroid hormones (NRC, 2005; Lewandowski *et al*., 2004; Hayes, 2014).

The constellation of liver lesions used as the critical effect for the HFPO-DA RfD derived by US EPA (2021b) are likely mediated by PPARα and thus is of limited relevance to humans (Chappell *et al*., 2020; Thompson *et al*., 2019). The involvement of PPARα in the mode of action of the liver effects of HFPO-DA and the lack of relevance of this mode of action to humans was even acknowledged by US EPA (2021b).

It is not appropriate to base a toxicity value for human populations on a health effect that is not relevant to humans. US EPA risk assessment guidance indicates that if experimental animal data are to be used for identifying the critical effect of a substance as a basis for a toxicity value, the relevance of the effect to humans must be considered (US EPA, 1989).

ACC Question 8

The toxicity values for the seven PFAS selected by IEPA include several uncertainty factors that add an additional level of conservatism to the calculation.

- *Is the use of uncertainty factors in the derivation of the toxicity value chosen by IEPA appropriate for each PFAS?*

Answer 8

The use of uncertainty or modifying factors in the derivation of the toxicity values for PFOS, PFNA, PFBS, and HFPO-DA chosen by IEPA is not appropriate. IEPA did not independently evaluate whether the derivation of each toxicity value was scientifically appropriate.

In deriving the MRL for PFOS, ATSDR (2021) used an unnecessary extra modifying factor of 10 to reduce the MRL 10-fold based on the concern that immunotoxicity may be a more sensitive endpoint than developmental toxicity. This modifying factor is inappropriate and results in an overly conservative MRL, as the occurrence of immunological effects at such low doses of PFOS is not supported by the science. For example, ATSDR (2021) cited a study by Peden-Adams *et al*. (2008) as evidence for immunological effects occurring at low doses of PFOS. However, the findings from this study have not been replicated in other studies (see, for example, Qazi *et al*. [2010]), and a dose-response relationship was not observed for the most sensitive endpoint cited by ATSDR (2021).

As noted above for Question 7, there is direct evidence that PPARα mediates many of the reported effects of PFNA in experimental animals, including developmental effects such as the decreased body weight and developmental delays that are the critical effect for the ATSDR MRL for PFNA. PPARα-mediated events are less relevant to humans than to rodents. Therefore, the uncertainty factor (UF) of 3 for interspecies differences that ATSDR (2021) included in its derivation of an MRL for PFNA, which decreased the MRL value by 3-fold, is overly conservative. An interspecies UF is generally applied when a toxicity value is based on an animal experiment, as an added protection in case humans are more sensitive than the test animals to the adverse effect. Because PPARα-mediated processes are less active in humans than in mice, it is likely that humans are *less* sensitive than mice to the effects of PFNA, making the interspecies UF unnecessary.

As noted above for Question 7, US EPA's (2021a) choice of thyroid hormone changes in mice as a critical effect is overly conservative, because rodents are highly susceptible to thyroid hormone perturbations when compared to humans, due to their smaller reserve capacity of thyroid hormones. This suggests that the UF of 3 for interspecies differences that US EPA (2021a) included in its derivation of the RfD for PFBS is unnecessary, and that the RfD could be higher and still protective of human health. US EPA (2021a) also included a database UF of 10 based on lack of neurodevelopmental and immunotoxicity data, noting that

immunotoxicity is an effect of concern for other PFAS. This database UF is unnecessary because of the large number of studies on PFBS reproductive and developmental toxicity, the fact that a toxicity value that protects against thyroid hormone effects will also protect against developmental effects (as indicated by US EPA [2021a]), and the lack of data indicating potential immunotoxicity of PFBS.

In its derivation of the HFPO-DA RfD, US EPA (2021b) used a database UF of 10, based on concerns of reproductive and developmental effects. This UF is unnecessary, as there are multiple reproductive and developmental studies of HFPO-DA that were reviewed by US EPA (2021b), and these studies reported effects at doses similar to or higher than those associated with the critical effect of liver lesions, indicating that an RfD based on liver lesions is applicable to all life stages and is protective of reproductive and developmental effects.

ACC Question 9

Several different toxicity values have been published since the IEPA first released its proposal more than a year ago.

- *Should IEPA consider those more recent toxicity values?*
- *Can the more recent values be viewed to either support or conflict with the IEPA's proposal?*

Answer 9

Yes, in addition to all other available toxicity values, finalized toxicity values published since IEPA's release of its proposed groundwater standards should be considered by IEPA. IEPA should evaluate the scientific soundness of each value before choosing the toxicity values to use in the development of the groundwater standards, keeping in mind that the recency of a toxicity study or a toxicity evaluation does not necessarily indicate whether it is more scientifically sound than studies or evaluations conducted at earlier time periods.

DR. ROBYN PRUEITT'S PRE-FILED ANSWERS TO THE ILLINOIS POLLUTION CONTROL BOARD

Board Question 7

On Page 4, you note, "IEPA followed its own process of choosing toxicity values by relying on values developed by other agencies to use in its calculations of the Proposed PFAS Standards" instead of developing toxicity values based on traditional human health risk assessment practices. Please clarify whether you are suggesting that IEPA must be developing toxicity information rather than relying on information developed by other agencies. If so, are you aware that IEPA generally relies on toxicity values developed by federal agencies to derive standards?

Answer 7

Established human health risk assessment practice for developing health-based standards is to derive toxicity values after a thorough review of the literature. To the extent IEPA is to rely on toxicity values derived by other agencies, IEPA should not blindly choose those values from the US EPA Screening Level Hierarchy. IEPA should instead conduct an independent evaluation of the scientific rigor and appropriateness of the available toxicity values to ensure that the most scientifically supported toxicity values were chosen as the bases for the Proposed PFAS Standards. This practice is consistent with the guidance associated with US EPA's Screening Level Hierarchy, as US EPA specifically states in its RSL "User's Guide" that "[w]hen using toxicity values other than tier 1," such as is the case here, "users are encouraged to carefully review the basis for the value…" (US EPA, 2022a).

Board Question 8

On page 4, you refer to IEPA's response that concerns brought up by the American Chemistry Council regarding the Agency for Toxic Substances and Disease Registry's (ATSDR's) interpretation of the data from the study used as the basis for its PFOS minimum risk level (MRL) (which was chosen as the PFOS toxicity value by IEPA) should be directed to ATSDR (citing IEPA, 2022a, Agency Answer 7).

a) Please explain for the record the process ATSDR follows in establishing MRL for a hazardous substance.

b) Does the process of establishing MRL involve public comment, including an external peer review by experts in subjects related to content of Toxicological Profile?

c) *Considering the expertise and resources available at the state level, please comment on why it is unreasonable for IEPA to rely on toxicity data developed by federal agencies responsible for developing health-based values to protect health of general population.*

Answer 8

a) The process that ATSDR follows in establishing MRLs is to identify "the most sensitive substance-induced endpoint considered to be of relevance to humans" for noncancer effects observed after oral or inhalation exposure and to apply uncertainty factors to the point of departure for that endpoint (*i.e*., the level of exposure that is below the level that might cause adverse health effects in the most sensitive individuals) (ATSDR, 2021).

b) Yes, the proposed MRLs that result from the process described above undergo peer review and public comment; however, just because an assessment has undergone peer review and public comment does not indicate that the agencies made the changes suggested by the peer reviewers and public commenters or that the assessments are free from significant issues.

c) My testimony does not indicate that it is unreasonable for IEPA to rely on toxicity values derived by other agencies; the issue is that IEPA did not critically evaluate the toxicity assessments or the toxicity

evidence underlying the toxicity values to ensure that it chose the most scientifically supported toxicity values as the bases for the Proposed PFAS Standards.

Board Question 9

On page 5, you state that ATSDR's interpretation of the underlying study used for its PFOS MRL results in an overly conservative toxicity value because ATSDR chose a nonadverse effect as the critical effect for the MRL.

a) *Please comment on what you would consider as an appropriate critical effect that should have been considered in establishing the MRL.*

b) *Was the issue of critical effect raised during the development of the MRL's public comment process?*

c) *If so, how did ATSDR address the concerns regarding the conservative nature of toxicity values.*

Answer 9

a) The PFOS MRL is based on a study by Luebker *et al.* (2005) that reported delayed eye opening and transient decreased body weight in rat pups that were exposed to PFOS at 0.4 mg/kg-day. While ATSDR considered 0.4 mg/kg-day to be the LOAEL and 0.1 mg/kg-day to be the NOAEL, the study authors did not consider the slight delay in eye opening to be an adverse outcome and did not consider the transient decrease in body weight to be toxicologically significant. Luebker *et al.* (2005) considered 0.4 mg/kg-day to be the NOAEL, based on reduced pup survival and reduced weight gain observed at a dose of 1.6 mg/kg-day. The value of 0.4 mg/kg-day (based on reduced survival) is a more scientifically supported NOAEL than the value of 0.1 mg/kg-day used by ATSDR in the derivation of its PFOS MRL.

b) Comments submitted by Crouch and Green (2018) during the public comment period also noted that Luebker *et al.* (2005) did not consider the delay in eye opening to be adverse and did not consider the body weight decrease to be toxicologically significant, and these commenters stated that ATSDR made a "questionable choice" in basing the PFOS MRL on these effects. In addition, comments submitted by 3M Co. (2018) included a discussion of the critical effects from the Luebker *et al.* (2005) study and their lack of relevance to humans and noted that the PFOS MRL was conservative and not scientifically justified.

c) ATSDR did not address the concerns of Crouch and Green (2018) or 3M Co. (2018) regarding the lack of adversity and toxicological significance of the critical effects and the conservative nature of the PFOS MRL because ATSDR (2021) still chose delayed eye opening and transient decreased body weight in rat pups from the study by Luebker *et al.* (2005) as the critical effects for the final PFOS MRL.

Board Question 10

On page 5, you note, "ATSDR only considered studies with animal strains that had pharmacokinetic model parameters available for predicting serum concentrations of PFAS in the animals from the administered PFAS doses (ATSDR, 2021), which precluded the use of many studies of various endpoints."

a) *Please comment on whether the reason for relying on studies with pharmacokinetic model parameters is because they help in predicting human toxicity to contaminants more so than studies without such parameters.*

b) *Provide citations of the studies that were precluded by ATSDR with different endpoints.*

c) *Comment on the endpoints in the precluded studies in terms of whether they were higher or lower than ATSDR's determined MRLs for PFAS.*

Answer 10

a) Pharmacokinetic model parameters for certain animal strains can help in the prediction of serum concentrations of PFAS in those animal strains; however, some of the studies reviewed by ATSDR (2021)

actually measured serum PFAS concentrations in the animals, precluding the need for estimation of serum concentrations using pharmacokinetic modeling. Some of the studies not considered by ATSDR (2021) in the derivation of the PFOS MRL included measured serum PFOS concentrations (*e.g*., Dong *et al*., 2009, 2011; Guruge *et al*., 2009; Peden-Adams *et al*., 2008), so the fact that there were no pharmacokinetic modeling parameters available for the animal strains in those studies is a moot point. In addition, other agencies, such as US EPA, do not limit the studies considered as the basis for PFAS toxicity values to those that only used animal strains for which pharmacokinetic parameters are available.

b) ATSDR (2021) listed several studies that were not considered in the derivation of the PFOS MRL because of a lack of pharmacokinetic modeling parameters for the animal strains, including a study with neurotoxicity as the critical effect (Long *et al*., 2013), four studies with immunotoxicity as the critical effects (Dong *et al*., 2009, 2011; Guruge *et al*., 2009; Peden-Adams *et al*., 2008), and three studies with developmental toxicity as the critical effects (Wang *et al*., 2014; Onishchenko *et al*., 2011; Yahia *et al*., 2008). ATSDR (2021) did not consider whether some of these studies could have evaluated more scientifically supported and relevant endpoints than the studies that used rodent strains with pharmacokinetic model parameters. While this may not necessarily be the case for all of the studies not considered in the derivation of the PFOS MRL (*e.g*., the findings of the immunotoxicity study by Peden-Adams *et al*. [2008] have not been replicated in other studies and a dose-response relationship was not observed for the most sensitive endpoint reported in the study), ATSDR's approach of not considering all available studies limits the number of endpoints available for consideration as a basis for the MRLs.

c) In the immunotoxicity studies that were not considered by ATSDR (2021), the LOAELs were lower than the LOAEL selected by ATSDR as the basis for the PFOS MRL, whereas the LOAELs from the neurotoxicity and developmental toxicity studies were similar to or higher than the LOAEL selected by ATSDR. ATSDR (2021) did calculate a "candidate" MRL from the measured serum PFOS concentration reported in one of the immunotoxicity studies (Dong *et al*., 2011), and this MRL (3×10^{-6} mg/kg-day) was slightly higher than the final PFOS MRL (2×10^{-6} mg/kg-day).

Board Question 11

Also on page 5, regarding RSC for noncancer effects, you note that Michigan and Minnesota have used methodology described by USEPA in its "Exposure Decision Tree", combined with publicly available data on background concentrations of PFAS in the serum of the general US population to select an RSC value of 50% for several PFAS.

a) Please explain how the data on background concentrations of PFAS in general population was used in the decision tree.

b) *Please submit the Michigan Department of Health and Human Services, and Minnesota Health Department publications cited on page 5 of your testimony into the record.*

Answer 11

a) The Michigan Department of Health and Human Services (MDHHS, 2019) and the Minnesota Department of Health (MDH, 2020a,b,c) selected RSC values of 50% for several PFAS using the subtraction method suggested by US EPA in its "Exposure Decision Tree" (US EPA, 2000). The subtraction method involves subtracting all non-drinking water exposures (*i.e*., background exposures) from the toxicity value to determine the amount of the toxicity value available for drinking water exposure, and the remaining percentage is applied as the RSC (US EPA, 2000). For each PFAS, MDHHS (2019) and MDH (2020a,b,c) subtracted background concentrations in serum in the general US population from the serum concentrations associated with the toxicity values and determined that the remaining percentage of serum PFAS that could be apportioned to ingestion of drinking water was at least 50% for each PFAS.

b) The document in which MDHHS (2019) selected an RSC of 50% for PFOA, PFOS, PFHxS, and PFNA is publicly available and can be accessed at the following link: https://www.michigan.gov/documents/pfasresponse/MDHHS_Public_Health_Drinking_Water_Screening_Levels_for_PFAS_651683_7.pdf

The document in which MDH (2020a) selected an RSC of 50% for PFOA is publicly available and can be accessed at the following link: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfoa.pdf

The document in which MDH (2020b) selected an RSC of 50% for PFOS is publicly available and can be accessed at the following link: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf

The document in which MDH (2020c) selected an RSC of 50% for PFHxs is publicly available and can be accessed at the following link: https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf

Board Question 12

On page 7 regarding carcinogenic of PFOA, you state that "it is well-documented in the literature that PFOA is not genotoxic or mutagenic (Crebelli et al., 2019; Kennedy and Symons, 2015; EFSA CONTAM, 2018; ATSDR, 2021)". Please comment on whether the research has ruled out mutagenicity of PFOA or the chemical is still being studied to evaluate the carcinogenic effects.

Answer 12

The literature cited in my testimony indicates that it is unlikely that PFOA is mutagenic and also that the results of available animal studies of PFOA do not meet agency guidelines for sufficient evidence of carcinogenicity. In addition, the available human data do not support the conclusion that PFOA is a human carcinogen. The current evidence that does not support mutagenicity or carcinogenicity of PFOA cannot be ignored.

Board Question 13

Also on page 7, you state that "PPARα {peroxisome proliferator-activated receptor alpha} receptor mediated processes occur much more readily in rats than humans."

a) Please elaborate on how PPARα mechanisms is less relevant in humans.

b) Are the PPARα mechanisms nonexistent or occur less often in humans?

c) If they do occur in humans, please comment on the extent of their occurrence.

Answer 13

PPARα-mediated processes, particularly with respect to induction of liver tumors, are less relevant to humans than to rats or mice because of differences in the expression and activation of PPARα between species (Klaunig *et al*., 2003, 2012; Corton *et al*., 2018). Thus, while humans do express PPARα, the levels of PPARα gene and protein expression are approximately 10-fold lower in the human liver than the rodent liver (Klaunig *et al*., 2003, 2012). Human PPARα is also less sensitive to activation by PPARα activators such as PFOA, indicating that humans would be less responsive to such activators than rodents (Klaunig *et al*., 2012; Corton *et al*., 2018). In contrast to rodents, human PPARα does not regulate genes involved in liver cell growth, and activation of human PPARα has not been shown to induce liver cell proliferation (Corton *et al*., 2018). After an extensive review of the weight of the evidence for PPARα as a mode of action (MOA) for liver tumors in rodents, Corton *et al*. (2018) concluded that "[t]here is overwhelming evidence that humans are not responsive to the carcinogenic effects of PPARα activators." Further, Corton

et al. (2018) stated: "Over the last 40 years, a large body of data has been generated involving many academic, government and industry labs on a diverse array of chemicals that strongly supports the MOA for PPARα liver tumorigenesis in the rodent and provides equally strong evidence for the lack of relevance to the human."

Board Question 14

On pages 11, you note that USEPA relied on an unpublished DuPont reproductive and developmental study to derive the RfD for HFPO-DA where the critical effect used was a "constellation of liver lesions" rather than a "single liver effect". Please elaborate on why a "constellation" of liver lesions and/or effects is not appropriate to derive the RfD by considering adversity as a whole.

Answer 14

The "constellation of liver lesions" relied upon by US EPA (2021b) is a combination of several individual liver effects, some of which are not considered adverse or are of unclear adversity. Only when the incidence of all of these effects were combined together did the animals exposed to 0.5 mg/kg-day HFPO-DA (the dose level that US EPA [2021b] considered to be the LOAEL) showed a clear increase in incidence compared to the unexposed control group. This approach is not appropriate for deriving the RfD because it goes against standard risk assessment practice of basing a toxicity value on the dose level at which there is a clear increase in a single adverse effect.

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