

**BEFORE THE ILLINOIS POLLUTION CONTROL BOARD**

IN THE MATTER OF: )  
)  
PROPOSED AMENDMENTS TO ) R2022-018  
GROUNDWATER QUALITY ) (Rulemaking – Public Water Supply)  
(35 Ill Adm. Code 620) )

**NOTICE**

TO: SEE ATTACHED CERTIFICATE OF SERVICE LIST

PLEASE TAKE NOTICE that I have today electronically filed with the Office of the Clerk of the Illinois Pollution Control Board the AMERICAN CHEMISTRY COUNCIL'S RESPONSE to the PRE-FILED QUESTIONS submitted by the Board, the Illinois Environmental Protection Agency, and 3M in the matter of the Illinois Environmental Protection Agency's proposed amendments to groundwater quality, a copy of which is herewith served upon you.

Dated: November 23, 2022

Respectfully Submitted,

**AMERICAN CHEMISTRY COUNCIL**

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**RESPONSE TO PRE-FILED QUESTIONS  
TO THE AMERICAN CHEMISTRY COUNCIL'S PRE-FILED TESTIMONY**

Response to Pre-Filed Questions from the Illinois Pollution Control Board

37. *On pages 5 through 8, you raise several concerns regarding USEPA's 2021 Assessment of HFPO-DA and PFBS. Please clarify whether you are referring to the updated toxicity assessments published in April 2021.*

The referenced portions of my pre-filed are based on the final USEPA assessment for PFBS released on April 2021 (EPA/600/R-20/345F) and the USEPA final assessment for HFPO-DA issued in October 2021 (EPA Document 822R-21-010).

38. *Please comment on whether USEPA's toxicity assessment process allows for public comment and expert peer review prior to final publication.*

USEPA conducted letter peer reviews of the draft PFBS and HFPO-DA Human Health Toxicity Value (HHTV) assessments in the summer of 2018 and released the draft assessments for public comment in November 2018. USEPA conducted a subsequent letter peer review of a revised HHTV for PFBS in 2020; a peer review of the revised assessment for HFPO-DA was conducted in 2021. USEPA subsequently released a final assessment for PFBS in January 2021 and a revised final assessment for the chemical in April 2021. USEPA released the final assessment for HFPO-DA in October 2021.

Despite making some changes to the 2018 public drafts of the documents before issuing the final assessments, USEPA did not make the revised documents available for review by the public. In the case of the April 2021 PFBS assessment, USEPA revised its approach to calculating the human equivalent dose (HED) and removed the lower end of the range of toxicity values. For its final assessment of HFPO-DA, USEPA used a health effects metric that it has never used before and increased the total uncertainty factor to 3000 - despite having received additional data from public commenters.

- a. *If so, did ACC or any other researchers/groups raise the "underlying" concerns noted in your testimony (pages 5-8) during the public comment/peer review process?*

ACC was among several groups who submitted comments on the public drafts of the PFBS and HFPO-DA assessments in January 2019. The issues raised in my pre-filed testimony on the IEPA proposal address the changes made to the assessments subsequent to the closing of the public comment period. ACC and other stakeholders did not have an opportunity to comment on the changes prior to the release of the final assessments.

*b. If concerns noted in your testimony were raised, how did USEPA respond to them. Please submit any relevant documents from the USEPA toxicity assessment process into the record.*

Although USEPA has released its response to comments from the peer reviewers, its response to comments on the HHTV for PFBS submitted by ACC and other stakeholders have not been made publicly available. ACC did not have an opportunity to review the changes made to the HHTV for HFPO-DA prior to its finalization.

I have attached ACC's comments on the public drafts of USEPA's PFBS and HFPO-DA assessments. I also have attached a request for correction of the final HFPO-DA assessment filed pursuant to the Information Quality Act.

39. *On pages 9 through 13, you raise several concerns regarding ATSDR minimum risk levels (MRLs) for PFHxS, PFNA and PFOS that were used by IEPA to propose Class I/II standards.*

*a. Please comment on whether the process for developing MRLs at ATSDR allows for peer review and public comment prior publication of the MRL.*

The MRLs for PFHxS, PFNA, and PFOS are contained in ATSDR's Toxicological Profile for Perfluoroalkyls which was finalized in May 2021. The Toxicological Profile did undergo peer review and was made available for public comment.

*b. If so, did ACC or any other researchers/groups raise the concerns noted in your testimony (pages 8-13) during the public comment/peer review process of MRL development?*

ACC submitted written comments on the draft Toxicological Profile in August 2018. The concerns expressed in my pre-filed testimony on the IEPA proposal are consistent with the ACC's August 2018 comments to ATSDR.

*c. If concerns noted in your testimony were raised during MRL development, how did ATSDR respond to them. Please submit any relevant documents from the ATSDR MRL development process into the record.*

ATSDR has not made its response to stakeholder comments publicly available. In addition, the comments of the peer reviewers and ATSDR's response to those comments, are not publicly available.

40. *On page 4, you state, “the calculation of an acceptable daily exposure (ADE) for a child between the ages of 0 and 6 years of age is similarly not appropriate for PFNA and PFOS for which the ATSDR MRL is based on developmental effects among laboratory animals in utero.”*

a. *Please elaborate on why the use of ATSDR MRLs are inappropriate.*

As noted in my pre-filed testimony, ATSDR based its derivation of MRLs for PFNA and PFBS on developmental effects in laboratory animal studies resulting from *in utero* exposures. In the case of PFNA, the key effect was decreased body weight and developmental delays in the offspring; for PFOS, the key effects were decreased body weight and delayed eye opening in the pups. Since these effects result from exposure during gestation, the MRL should be based on daily exposures to the pregnant female, not on exposures to the child after birth. This approach is consistent with the approach taken by USEPA in deriving its 2016 lifetime Health Advisory (LHA) for PFOS.

b. *What would you recommend that the Board consider as the bases for establishing groundwater standards for PFNA and PFOS that would be protective of children between ages of 0 to 6 years instead of ATSDR MRLs?*

I do not believe that sufficient data are available to derive a groundwater standard for PFNA. In the animal study selected by ATSDR for deriving the MRL, the researchers reported toxic effects in the pregnant females that make it difficult to interpret the effects in the offspring.<sup>1</sup> In addition, there is evidence from another study that the developmental effects used by ATSDR result from a mechanism that is unique to the laboratory animals that may be of limited relevance to humans.

For PFOS, ATSDR's analysis ignored the conclusions of the authors of the study selected for deriving the MRL when identifying the dose at which adverse effects were seen in the animal offspring.

As noted above, the calculation of the groundwater standard also should be based on exposure to the pregnant female not on the fetal animal's exposure.

#### Response to Pre-Filed Questions from the Illinois Environmental Protection Agency

1. *Do you disagree with U.S. EPA's RSC assessment using its Decision Tree that data is insufficient to allow for a quantitative characterization of different exposure sources? Please explain.*

I believe that sufficient data are available to more definitively characterize exposure to the PFAS included in the proposal, as described in USEPA's Decision Tree. Data from the Centers for Disease Control and Prevention (CDC) demonstrate that blood levels of

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<sup>1</sup> USEPA. Guidelines for Developmental Toxicity Risk Assessment. Risk Assessment Forum. EPA/600/FR-91/001 (December 1991). (USEPA Developmental Toxicity Guidelines)

PFOA and PFOS have declined precipitously as a result of the decision by US manufacturers to phase out production of these two substances in the early 2000s. Levels of PFNA and PFHxS also have declined as these substances are no longer produced in the US. This decline in serum levels signals a significant drop in exposure to these substances – as manufacturers have switched to the use of other substances. As other sources of exposure have declined, the contribution of drinking water to total exposure has increased. As a consequence, the default assumption of an RSC of 0.2 – is no longer applicable for these legacy PFAS. Several state agencies including those in MI, NH, NY, and PA have reached this same conclusion.

2. *Are products containing PFOA, PFOS or other PFAS present in homes and businesses in Illinois that allow for exposure to PFAS?*

PFAS are a broad class of substances with vastly different physical and chemical properties. Although there are many uses of PFAS in products manufactured for homes and businesses, it is wholly inappropriate to suggest that all PFAS present an equivalent level of concern. For the six PFAS for which IEPA has proposed groundwater standards, exposure in product present in homes and businesses is likely to minimal.

Before PFOA manufacture ceased, it was used as a processing aid in the production of various fluoropolymers. It was not used in the production of products for homes and businesses. The same is true for HFPO-DA which replaced PFOA as a processing aid in fluoropolymer production.

US production of PFOS ceased nearly two decades ago. While it was widely used before being phased out, exposures have declined dramatically as evidenced by the CDC serum data. The same is true for PFNA and PFHxS, which while not as widely used as PFOS, have been phased out as well.

3. *Can these products provide humans, especially young children, a route for exposure to PFAS?*

Given the context of this rulemaking, the ACC assumes this question asks about potential groundwater exposure from PFAS-containing products. The ACC is not aware of such an exposure route. Moreover, as noted above, it is inappropriate to suggest that exposure to all PFAS presents a health concern.

4. *What do you consider the “applicable adult population” for calculating the HTTAC?*

The selection of an applicable adult population is dependent on the health endpoint on which the assessment of hazard is based. For example, as noted above, for effects resulting from *in utero* exposure, females of child-bearing age are the appropriate population.

5. *What would the appropriate daily water intake of liters per kilogram body weight per day be for an applicable adult population?*

As indicated above, the applicable population is dependent on the health endpoint of concern. According to USEPA's Exposure Factors Handbook,<sup>2</sup> the 50<sup>th</sup> percentile of water intake for adults is between 0.012 and 0.015 L/kg per day. The 95<sup>th</sup> percentile ranges from 0.037 to 0.047 L/kg per day.

6. *Is the applicable adult population daily water intake protective of sensitive populations, such as pregnant or lactating females, and young children?*

The selection of applicable adult population is dependent on the health endpoint on which the assessment of hazard is based. For example, as noted above, for effects resulting from *in utero* exposure, females of child-bearing age are the appropriate population for which USEPA assumes a daily water intake of 0.043 l/kg per day.

7. *Section 620.410 – Groundwater Quality Standards, discusses concerns with the PFAS toxicity assessments. Did you file your concerns regarding the PFOA toxicity assessment with California EPA during its peer-review and Public Comment sessions?*

IEPA's proposed groundwater standard for PFOA is based on an analysis conducted by California's Office of Environmental Health Hazard Assessment's (OEHHA) as part of its recommendation to the State Water Resources Control Board (SWRCB) for a Notification Level for PFOA in drinking water.<sup>3</sup> The OEHHA recommendation document was not made available for public comment and, to the ACC's knowledge, was not subject to peer review.

ACC submitted comments on the study that was basis for its recommendation to the SWRCB in response to OEHHA's call for information for the development of a Public Health Goal (PHG) for PFOA in January 2020. OEHHA released a draft PHG in July 2021 that used a different key study as a basis for its analysis. ACC submitted comments on the draft PHG in October 2021. OEHHA has not yet finalized the PHG or released a second draft for public comment.

- a. *If yes, please provide a copy of your comments submitted to California EPA and California EPA's response to your comments.*

A copy of ACC's response to the call for information for the development of a PHG for PFOA is attached. (See Attachment 1.)

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

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<sup>2</sup> <https://www.epa.gov/expobox/about-exposure-factors-handbook>

<sup>3</sup> OEHHA. Notification Level recommendations: perfluorooctanoic acid and perfluorooctane sulfonate in drinking water. California Environmental Protection Agency (August 2019).

8. *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-Reviewed Toxicity Value (PPRTV)?*

ACC submitted comments on the public draft of the toxicity assessment for PFBS in January 2019. USEPA released a final assessment in January 2021 and a revised assessment in April 2021. It did not seek comment on the changes that were made as part of the April 2021 revision.

- a. *If yes, please provide a copy of your comments submitted to U.S.EPA and U.S. EPA's response to your comments.*

A copy of ACC comments on the public draft of the toxicity assessment for PFBS are attached. (See Attachment 2.)

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

9. *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?*

ACC submitted comments on the public draft of the Toxicity Profile for Perfluoroalkyls in August 2018.

- a. *If yes, please provide a copy of your comments submitted to ATSDR and ATSDR's response to your comments.*

A copy of the ACC's August 2018 comment to ATSDR is attached. (See Attachment 3.)

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

10. *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?*

ACC submitted comments on the public draft of the toxicity assessment for HFPO-DA in January 2019. USEPA released a final assessment in October 2021 that contained significant changes to its 2018 draft, including the use of a controversial health endpoint that USEPA had never used before. USEPA did not release a revised draft for public comment to seek input on the changes.

- 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.*

A copy of the ACC's comments on the public draft of the toxicity assessment for HFPO-DA is attached. (See Attachment 4.)

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

11. *On what Method is the U.S. EPA's MRLs based?*

In presentations to drinking water utilities in June 2022,<sup>4</sup> USEPA's Office of Water indicated that the minimum reporting level (MRL) for PFOA and PFOS in drinking water is 4 parts per trillion (ppt). These MRLs are based on the requirement for the Fifth Unregulated Contaminant Monitoring Rule (UCMR 5) to use EPA Analytical Method 533 to measure the six PFAS included in IEPA's proposal. Under UCMR 5, public water systems in Illinois and throughout the country will be required to sample for 29 PFAS between 2023 and 2025 using Method 533.<sup>5</sup>

According to USEPA, the MRL is the minimum quantitation level that, with 95 percent confidence, can be achieved by a capable analyst at 75 percent or more of the laboratories using the specific analytical method.

12. *Does Method 537.1 have MRL of 0.000002 mg/L for each of the proposed PFAS?*

No. Method 537.1 provides single "laboratory lowest concentration minimum reporting levels" (LCMRLs) for the six PFAS in drinking water between 0.82 and 6.3 nanograms per liter (ng/L).<sup>6</sup> These LCMRLs values are not equivalent to the MRLs which EPA has determined can be reliably measured for the purposes of the UCMR 5 national survey. A copy of Method 537.1 is attached. LCMRLs are typically used to help develop MRLs but are not, and cannot be used as, MRLs.

13. *Does Method 537.1 provide the lowest concentration minimum reporting levels in potable water for PFAS?*

The reported LCMRLs for Method 537.1 are lower than those reported for Method 533, the other USEPA-validated method for analyzing potable water. The LCMRLs for Method 533 are reported to range from 3.4 to 4.8 ng/L. As noted above, USEPA will require public water systems in Illinois to use Method 533 for the six PFAS as part of the UCMR 5 survey.

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<sup>4</sup> <https://www.epa.gov/sdwa/drinking-water-health-advisories-pfoa-and-pfos>

<sup>5</sup> <https://www.epa.gov/dwanalyticalmethods/method-533-determination-and-polyfluoroalkyl-substances-drinking-water-isotope>

<sup>6</sup> <https://www.epa.gov/pfas/epa-pfas-drinking-water-laboratory-methods>

Response to Pre-Filed Questions from 3M

1. *IEPA chose toxicity values for each PFAS from toxicity assessments conducted by other agencies according to a specific hierarchy. Did IEPA adequately consider the strengths and limitations of the underlying data for these toxicity assessments?*

No. IEPA's selection of toxicity values appears to be based solely on the hierarchy of human sources of toxicity information health toxicity values data sources outlined by USEPA's Office of Solid Waste and Emergency Response (OSWER). IEPA has not provided information suggesting that it conducted an independent review of the underlying data.

2. *IEPA emphasizes relying on the most recent data when selecting toxicity values. Do the most recent studies always represent the most reliable and relevant data?*

No. Although it is important to include the most recent data in an assessment of toxicology, the data must be viewed in the context of all of the available data to evaluate the weight of the scientific evidence. A study, whether new or old, may have methodological limitations that diminish its value to the assessment.

IEPA's dependence on the OSWER hierarchy has resulted in its failure to consider more recent data and more recent assessments that incorporate these newer data. This is a major shortcoming of IEPA's use of the hierarchy that should be corrected. A rigid dependence on the hierarchy for selection of toxicity values may lead to use of older, less comprehensive assessments. This is a particular concern given the slow pace at which USEPA updates IRIS assessments.

3. *IEPA uses the default relative source contribution of 0.2 for calculating the proposed standards for five of the PFAS. Is the use of this default value appropriate, and if not, why not?*

Sufficient data are available to more definitively characterize exposure to the PFAS included in the IEPA's proposal. Data from the CDC demonstrate that blood levels of PFOA and PFOS have declined precipitously as a result of the decision by US manufacturers to phase out production of these two substances in the early 2000s. Levels of PFNA and PFHxS also have declined as these substances are no longer produced in the US. This decline in serum levels signals a significant drop in exposure to these substances – as manufacturers have switched to the use of other substances. As other sources of exposure have declined, the contribution of drinking water to total exposure has increased. As a consequence, the default assumption of an RSC of 0.2 is no longer applicable for these legacy PFAS. This is the conclusion of several state agencies, including those in MI, NH, NY, and PA.

4. *IEPA uses the U.S. EPA's HFPO-DA toxicity value. Are there issues with the endpoint selected as the basis for the HFPO-DA toxicity value?*

Yes. These concerns are summarized in the attached request for correction filed by Arnold & Porter of USEPA's final assessment for HFPO-DA issued in October 2021. The concerns include:

- the use of health effects in animals that are of limited relevance,
- use of a new and unprecedented toxicological endpoint,
- misapplication of scientific criteria in identifying adverse effects,
- use of evaluation criteria that have not been peer reviewed, and
- use of improper and significantly inflated uncertainty factors.<sup>7</sup>

These changes to USEPA's October 2021 final assessment resulted in a significant lowering of the toxicity value. They were not included in the public draft of the assessment and were not made available for public comment prior to finalization of the assessment.

5. *The toxicity values that IEPA chose to use for calculating the proposed standards for HFPO-DA, PFBS, PFNA, and PFOS all used database uncertainty factors or modifying factors due to concerns that there is a lack of information regarding whether other effects, such as reproductive and developmental toxicity or immunotoxicity, are observed at lower exposure levels than the critical effects upon which the toxicity values were based. Are these database uncertainty factors appropriate?*

The uncertainty factors applied to derive the toxicity values selected by IEPA include the following:

	Uncertainty Factor				
	Animal to Human (UFA)	Human Variability (UFH)	Subchronic to Chronic (UFS)	Database Uncertainty/ (UFD)	Total
HFPO-DA	3	10	10	10	3000
PFBS	3	10	1	10	300
PFHxS	3	10	1	10	300
PFOS	3	10	1	10	300
PFNA	3	10	1	10	300

Although the application of a UFA of 3 and a UFH of 10 is consistent with standard practice, use of a UFD (or modifying factor) of 10 is not. Guidance developed by USEPA explains that a UFD is to be applied when reproductive and developmental toxicity studies are missing since they have been found to provide useful information for

<sup>7</sup> See Attachment 5.

establishing the lowest no adverse effect level.<sup>8</sup> USEPA guidance also notes that, for a reference dose (RfD) based on animal data, a factor of 3 is often applied if either a prenatal toxicity study or a two-generation reproduction study is missing, or a factor of 10 may be applied if both are missing.<sup>9</sup> In deciding whether to apply an UFD, the guidance advises that the assessor should consider both the data lacking and the data available for particular organ systems as well as life stages.

Because robust data is available on the reproductive and developmental effects of PFOS, PFBS, and HFPO-DA, IEPA's application of a UFD of 10 is wholly inconsistent with USEPA guidance (which, again, posits that a UFD should be used in the absence of reproductive and developmental toxicity studies). Although studies of the reproductive/developmental effects of PFHxS and PFNA are lacking, their absence is reflective of a larger general dearth of information on these substances. USEPA is currently developing IRIS assessments for these two substances. IEPA should defer the development of groundwater standards for at least these two substances until the assessments are available and peer reviewed.

For all five substances, the reviewing agency (USEPA or ATSDR) also suggests concerns about immunotoxicity as a basis for applying a UFD or modifying factor reflects. These concerns appear based on equivocal data available for PFOA and PFOS. Certainly, in the case of PFOS, there are data available to evaluate immunotoxicity. For the other four substances, in the absence of chemical-specific data to suggest immune effects, applying an uncertainty factor on the basis of this health effect is inappropriate.

It is worth noting that the total uncertainty factor of 3000 used to derive the toxicity value for HFPO-DA is the maximum value that USEPA could have conceivably used. USEPA has previously stated that any greater factor is considered too uncertain for toxicity assessment and for calculation of a reference dose.<sup>10</sup>

6. *The IEPA proposal mentioned both critical effects and adverse effects.*
  - a. *Are all of the critical effects that form the bases for the toxicity values chosen by IEPA considered adverse effects?*

According to USEPA, adverse effects are those that cause harm to the normal functioning of a plant or animals due to exposure to a substance. For the reviews chosen by IEPA for PFOS, HFPO-DA, and PFNA, the effects considered critical by the reviewing agency (USEPA or ATSDR) should not be considered adverse.

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<sup>8</sup> EPA Risk Assessment Forum. A review of the reference dose and reference concentration processes. EPA/630/P-02/002F (December 2002). <https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>

<sup>9</sup> Ibid, at 4-45.

<sup>10</sup> Ibid, at 4-41.

For PFOS, ATSDR ignored the conclusion of the authors of the key study that the effects seen at the lowest dose were transient and not considered adverse. In ignoring this conclusion, ATSDR selected a significantly higher dose as the no observed adverse effect level (NOAEL), which significantly impacted its calculation of the toxicity value.

For PFNA, the adverse effects seen in the offspring of female mice occurred at a dose that also caused maternal toxicity. As noted by USEPA guidance, “at doses that cause excessive maternal toxicity (that is significantly greater than the minimal toxic level), information on developmental effects may be difficult to interpret and of limited value.”<sup>11</sup>

As explained in greater detail in the attached correspondence from Arnold & Porter, USEPA’s use of a “constellation of liver effects” is unprecedented and misapplies scientific criteria in determining whether the observed effects should be considered adverse.

*b. Are the stated critical effects considered relevant to humans?*

In addition to the questions about whether the observed effects in laboratory animal studies should be considered adverse, there is also a concern about whether the animal effects are relevant to humans. Many of the effects observed in the rodent studies, particularly liver and developmental effects, involve the activation of the peroxisome proliferator activated receptor (PPAR $\alpha$ ) or other nuclear receptors. Activation of the PPAR $\alpha$  receptor in rodents initiates a characteristic sequence of morphological and biochemical events, principally, but not exclusively, in the liver.<sup>12</sup> The proliferation of peroxisomes has been associated with a variety of effects, including hepatocellular hypertrophy, alterations in lipid metabolism, and decreased pup survival and immune effects. Since humans and non-human primates have been found to be less responsive to PPAR $\alpha$  agonists than rodents,<sup>13</sup> the relevance of the rodent findings to humans is highly questionable.

*c. Do you have any concerns with using non-adverse, non-human-relevant effects as the bases for toxicity values used in calculating groundwater standards? If so, what are they?*

Yes. The use of observed effects in laboratory animal studies that are non-adverse and/or of limited, or no, relevance to humans can lead to incorrect toxicity assessments. Selection of non-adverse effects of little relevance to humans can lead to overly conservative toxicity values that can result in public confusion, greater effort and additional, unnecessary costs.

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<sup>11</sup> USEPA Developmental Toxicity Guidelines, at 6.

<sup>12</sup> Kennedy GL *et al.* The toxicology of perfluorooctanoate. *Crit Rev Toxicol* 34(4):351-384 (2004).

<sup>13</sup> Corton JC *et al.* Mode of action framework analysis for receptor-mediated toxicity: the peroxisome proliferator-activated receptor alpha (PPAR $\alpha$ ) as a case study. *Crit Rev Toxicol* 44(1):1-49 (2014).

7. *What did the 2019 National Toxicology Program (NTP) 28-day toxicity studies of various PFAS show with respect to the human relevance of the reported effects of these substances?*

NTP's 28-day study exposed Sprague-Dawley (SD) rats to various concentrations of seven PFAS by gavage – PFBS, PFHxA, PFHxS, PFOA, PFOS, PFNA, and PFDA. An additional group of animals was exposed to Wyeth-14,643 (a PPAR $\alpha$  agonist) for qualitative comparison to the PFAS-exposed groups. The researchers evaluated clinical pathology, thyroid hormones, expression of PPAR $\alpha$  and another nuclear receptor CAR, liver enzymes, blood concentrations, and histopathology. They reported that many of the effects observed in the liver of the PFAS-exposed animals were also observed in the rats administered Wyeth-14,643 – indicating that these effects are likely mediated by PPAR $\alpha$  and thus may not be of relevance to humans.

8. *IEPA chose a cancer toxicity value for PFOA from an assessment of PFOA carcinogenicity by OEHHA, which was based on a carcinogenicity study conducted by NTP.*

The NTP bioassay study reported liver adenomas in male SD rats and pancreatic adenomas in male and female rats exposed to PFOA in food.<sup>14</sup> In the study, male rats were exposed post-weaning to up to 80 parts per million (ppm) while females were exposed to up to 1000 ppm.<sup>15</sup> The study also reported significant increases in hepatocyte cytoplasmic alteration and hypertrophy in the males in all the exposure groups. The study also noted a significant increase in pancreatic hyperplasia - a potentially preneoplastic lesion - in all the male groups, including the control group in which hyperplasia was reported in 36 percent of the animals.

The high background rate observed in this study is consistent with the historical sensitivity of the Sprague-Dawley rats compared to other rat strains – and more significantly when compared to humans.

*a. Are the results of this study reliable?*

According to the report, the male portion of the study was repeated using significantly lower exposures after “unanticipated toxicity” was observed in male rats exposed to 150 and 300 ppm after 16 weeks. In light of the fact that male SD rats tolerated doses as high as 300 ppm in a previous chronic study,<sup>16</sup> the reports of unanticipated toxicity at

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<sup>14</sup> NTP. Technical report on the toxicology and carcinogenesis studies of perfluorooctanoic acid administered in feed to Sprague-Dawley rats. Technical Report 598. Department of Health and Human Services. Research Triangle Park, North Carolina (2019).

<sup>15</sup> The study included groups of animals exposed to PFOA perinatally and post-weaning to assess the potential impact of gestational and lactational exposure but reported very few significant differences between the response in animals exposed post-weaning only to those with both perinatal and post-weaning exposure.

<sup>16</sup> Butenhoff JL *et al.* Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. *Toxicol* 298(1–3): 1–13 (2012).

comparable levels in the male rats in the NTP study raise concerns about the overall confidence in the study.

*b. Are the tumors observed in this study relevant to humans?*

Likely not. The tumor types observed in the NTP study – liver, pancreas – have been observed with other substances that are PPAR $\alpha$  agonists. Because of key toxicodynamic and biological differences in responses between rodents and humans, PPAR $\alpha$  activators are considered unlikely to induce liver and pancreatic tumors in humans.

For liver tumors, this conclusion is based on minimal or no effects observed on growth pathways, hepatocellular proliferation and liver tumors in humans and/or species (*e.g.*, hamsters, guinea pigs and *Cynomolgous* monkeys) that are more appropriate animal model surrogates than mice and rats. The relevance of the liver tumor data from laboratory studies is further called into question as a result of a clinical study of a subpopulation of cancer patients with normal liver function exposed to weekly PFOA doses as high as 1,200 milligrams which reported no differences in clinical hepatic measures.<sup>17</sup>

For the induction of rat pancreatic tumors by PFOA, the available mechanistic data are less robust, but also point to the importance of PPAR $\alpha$  activation in the liver. The high background rate observed of pancreatic hyperplasia in the NTP study is consistent with the historical sensitivity of the Sprague-Dawley rats compared to humans.

*c. Is there any evidence to indicate that PFOA is carcinogenic to humans?*

PFOA has been reported to cause liver tumors in laboratory animal studies, but the available epidemiology evidence does not support an association with liver cancer in humans. Reports of kidney cancer in epidemiology studies are conflicting, and not supported by the results of the animal bioassays.

9. *IEPA's proposal uses the terms "minimum reporting level," "quantification limit," and "method detection limit."*

*a. What is the method detection limit (or MDL)?*

USEPA defines the MDL as the minimum measured concentration of a substance that can be reported with 99% confidence that the measured analyte concentration is distinguishable from method blank results. This is a statistical determination of precision, and accurate quantitation is not expected at this level.

*b. What is a minimum reporting level?*

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<sup>17</sup> Convertino M *et al.* Stochastic pharmacokinetic-pharmacodynamic modeling for assessing the systematic health risk of perfluorooctanoate (PFOA). *Toxicol Sci* 163(1) 293-306 (2018).

According to USEPA, the minimum reporting level, or MRL, is the minimum quantitation level that, with 95 percent confidence, can be achieved by a capable analyst at 75 percent or more of the laboratories using the specific analytical method.

*c. What is a quantification limit?*

USEPA defines the quantification limit, or minimum level of quantitation, as the lowest concentration at which an analyte can be measured with a known level of confidence.

10. *What is the difference between a method detection limit and a minimum reporting level?*

While the MDL indicates the level at which the method can determine whether the substance is present in a sample, the MRL indicates the level above which the substance can be reliably measured. In other words, an MRL can be used for reliable quantitative purposes while and MDL cannot.

11. *What are the method detection limits and minimum reporting levels for the PFAS at issue in the IEPA proposal?*

EPA Method 533, the method USEPA will require for reporting under the UCMR 5 national survey for the six PFAS included in the IEPA proposal, provides the following single laboratory LCMRLs:

	<u>Calculated LCMRL</u>
HFPO-DA	3.7 nanograms per Liter (ng/L)
PFBS	3.5
PFHxS	3.7
PFOA	3.4
PFOS	4.4
PFNA	4.8

MRLs and detection limits are not provided for the method.

Method 537.1 has the following limits for the six PFAS of the IEPA proposal:

	<u>Detection Limit</u>	<u>LCMRL</u>
HFPO-DA	1.9 ng/L	4.3 ng/L
PFBS	1.8	6.3
PFHxS	1.4	2.4
PFOA	0.53	0.82
PFOS	1.1	2.7
PFNA	0.70	0.83

MRLs are not provided.

12. *Does the accuracy or reliability of a testing method change depending on how close the result is to the method detection limit?*

Although the qualitative accuracy of the method is not affected by the proximity to the method detection limit, results below the MRL are quantitatively unreliable. As noted above, measurements below the MRL should not be considered to reflect the actual concentration.

13. *Does the accuracy or reliability of a measurement of a substance change depending on how close the result is to the minimum reporting level?*

Results below the MRL cannot be viewed to reliably represent a sample's actual concentration. For results above the MRL, the accuracy of results can be expected to be less reliable at lower concentrations. This is due to the fact that, according to USEPA, the MRL is determined by the sensitivity of the method, as well as the capabilities of the laboratory and the analyst. The lower the concentration in a sample, the greater the possibility that measurement will exceed the analyst's or laboratory's capabilities.

14. *Is there a point at which the accuracy or reliability of a measurement of a substance falls below 50%?*

The closer the concentration is to the MDL, the lower the reliability of the measurement.

15. *What testing methods have been approved and validated for use to measure PFAS in drinking water? How about groundwater?*

USEPA has validated two testing methods for measure PFAS in drinking water. Method 537.1 can measure 18 individual substances; Method 533 can measure 25 substances, including 14 substances measured by Method 537.1.

USEPA has validated one method for measuring PFAS in non-potable water. Method 8327 can measure 24 PFAS. A second method for measuring PFAS in aqueous samples (Method 1633) has not yet been finalized. It can reportedly measure 40 PFAS.

16. *Does U.S. EPA's method 537.1 for PFAS in drinking water provide information regarding the accuracy and precision of PFAS measurements for any PFAS at various concentrations?*

According to USEPA, the detection limit of the method provides a statistical determination of the method's precision. Those values are provided above.

**CERTIFICATE OF SERVICE**

I, the undersigned, certify that I have today filed the attached NOTICE OF FILING and PRE-FILED QUESTIONS to the PRE-FILED TESTIMONY OF DR. ROBYN PRUEITT in PCB R2022-18 upon the below service list by electronic mail.

Dated: November 23, 2022

Respectfully Submitted,

**AMERICAN CHEMISTRY COUNCIL**

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