Vanessa Holt
Acting Director, Center for Public Health & Environmental Assessment
Environmental Protection Agency
Washington DC 20009

Re: Docket EPA–HQ–ORD–2021–0560 Draft IRIS Toxicological Review of Perfluorononanoic Acid [PFNA, CASRN 375-95-1] and Related Salts

May 6, 2024

On behalf of the Natural Resources Defense Council (NRDC), I appreciate this opportunity to submit comments on EPA's Draft Toxicological Review for Perfluorononanoic acid (PFNA).[1] I have reviewed and commented on the scientific and technical aspects of many federal and state level PFAS risk assessments including the EPA's assessments of PFOA, PFOS, GenX, PFBS, PFBA, PFHxA, PFDA, ATSDR's toxicological profile for perfluoroalkyls, and state assessments in CA, IL, ME, NH, NY, VT, and WA. In addition, I am the founder and co-creator of the PFAS-Tox Database (available at www.PFASToxDatabase.org), a systematic evidence map of the health and toxicological research available for 29 PFAS, including PFNA.[2] To date, the publicly available, interactive PFAS-Tox Database contains 1,068 peer reviewed studies retrieved from PubMed Database (literature search last updated January 25, 2021).

PFNA is part of the massive family of synthetic per- and poly- fluorinated alkyl substances (PFAS). US EPA's CompTox program now lists over 14,000 PFAS structures.[3] PFAS are characterized by incredible durability, which manifests as extreme persistence in the environment. The PFAS chemicals that have been well-studied show potent toxicity to internal

[1] US EPA. "IRIS Toxicological Review of Perfluorononanoic Acid (PFNA) and Related Salts CASRN 375-95-1." External Review Draft, March 2024. https://ordspub.epa.gov/ords/eims/eimscomm.getfile?p_download_id=548669.

[2] Pelch, Katherine E., Anna Reade, Carol F. Kwiatkowski, Francheska M. Merced-Nieves, Haleigh Cavalier, Kim Schultz, Taylor Wolffe, and Julia Varshavsky. "The PFAS-Tox Database: A Systematic Evidence Map of Health Studies on 29 per- and Polyfluoroalkyl Substances." *Environment International* 167 (September 1, 2022): 107408. https://doi.org/10.1016/j.envint.2022.107408; Pelch, Katherine E., Anna Reade, Carol F. Kwiatkowski, Francheska M. Merced-Nieves, Haleigh Cavalier, Kim Schulz, Keshia Rose, and Julia R. Varshavsky. "PFAS-Tox Database." PFAS-Tox Database, April 20, 2021. https://doi.org/10.17605/OSF.IO/F9UPX.

[3] US EPA. "CompTox Chemicals Dashboard - Navigation Panel to PFAS Structure Lists," August 18, 2022. https://comptox.epa.gov/dashboard/chemical-lists/pfasstruct.

organs, lipid metabolism, as well as the immune and endocrine systems.[4] EPA recently regulated PFNA in drinking water and is currently seeking input on potentially listing PFNA as a hazardous substance under CERCLA, highlighting the importance of this toxicological review.[5]

Given the number of people exposed to these chemicals, their persistence in the environment, and the public concern about them, it is critical that this toxicological review provides the information necessary to guide regulators and communities in their efforts to protect themselves. In this letter, I outline areas where the EPA has taken steps in the right direction as well as areas that need to be strengthened. I recognize the importance of this assessment and that communities exposed to these chemicals are eager for the EPA to complete this toxicological review, but I urge the EPA to:

(1) update and strengthen this review by ensuring that it relies upon a more complete data set and
(2) account for cumulative risks that may occur from coexposure to additional PFAS, as is often the case in real-world exposure scenarios - where people are exposed to PFAS mixtures.

I applaud the EPA for the use of transparent systematic review practices in the development of this draft toxicological review. Systematic review has long been used to inform evidence-based choices about health interventions in clinical settings. Though the application of systematic review to questions in environmental health is still relatively new by comparison, the Integrated Risk Information System (IRIS) program at US EPA has been steadily implementing systematic review practices since receiving feedback in 2011 from the National Academies of Sciences, Engineering, and Medicine suggesting the need for programmatic reform.[6]

In particular, I support the use of the study confidence rating, which is in line with best practices for assessing risk of bias and closely aligns to the methods used by the National Toxicology Program's Office of Health Assessment and Translation (OHAT).[7] Importantly, the PECO (populations, exposures, comparators and outcomes) statement clearly outlines the criteria for inclusion and exclusion of studies in the assessment. I also support the transparent GRADE-like methods used for evidence integration in the draft PFNA assessment. Finally, I appreciate the

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[4] Kwiatkowski, Carol F., David Q. Andrews, Linda S. Birnbaum, Thomas A. Bruton, Jamie C. DeWitt, Detlef R. U. Knappe, Maricel V. Maffini, et al. "Scientific Basis for Managing PFAS as a Chemical Class." *Environmental Science & Technology Letters* 7, no. 8 (August 11, 2020): 532–43. https://doi.org/10.1021/acs.estlett.0c00255.

[5] US EPA. "PFAS National Primary Drinking Water Regulation." *Federal Register* 89, no. 82 (April 26, 2024). https://www.federalregister.gov/documents/2024/04/26/2024-07773/pfas-national-primary-drinking-water-regulation; "Addressing PFAS in the Environment." *Federal Register*. Proposed Rule, April 13, 2023. https://www.federalregister.gov/documents/2023/04/13/2023-07535/addressing-pfas-in-the-environment.

[6] National Academies of Sciences, Engineering, and Medicine "Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation." 2018, Washington, DC: The National Academies Press.

[7] Office of Health Assessment and Translation. "Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration." 2015. Available from: https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf.

display of extracted PFNA data in HAWC, which made it very easy to evaluate the statements made in the draft PFNA toxicological review.

The decisions that lead to EPA's choice of critical studies and endpoints for a quantitative assessment of health risks were clearly presented and well supported. Therefore, based on the available information, I support the conclusions reached by the EPA that the evidence evaluated within the toxicological review supports the conclusions that PFNA causes developmental harm and likely causes liver, and male reproductive effects in humans.

I also support EPA's decision to calculate and present multiple candidate organ specific reference doses (osRfD) based on several identified critical endpoints from medium and high confidence studies. My analysis of reference dose derivation for PFAS across multiple agencies highlights that simply choosing the lowest human equivalent dose ("HED") to derive a RfD does not necessarily guarantee that the RfD will protect against all health effects. A less sensitive HED could reasonably result in a lower RfD due to differences in study design and overall application of uncertainty. The IRIS PFAS assessments, including this assessment of PFNA, are transparent and follow best practices in calculating osRfDs for multiple identified health effects.

Though I largely support the conclusions reached by EPA, I also believe it is inappropriate for EPA to attempt to estimate the risks posed by PFNA individually. I appreciate that EPA has previously highlighted the utility of deriving organ/system-specific values as "the osRfDs can be useful for subsequent cumulative risk assessments."[8] However, EPA ultimately falls short of making use of these values, despite that similar values have already been derived by EPA for other PFAS, such as PFOA, PFOS, GenX, PFBS, PFBA, PFHxA, and PFDA. Americans most at risk of exposure to PFNA will generally have greater than typical exposures to other legacy PFAS chemicals as well. The available data suggests that PFNA impacts the same body systems as other PFAS. Given this, EPA should include a section on PFAS cumulative risks.

My specific comments address two issues: Section 1 points to several health and toxicological studies that are not included in the EPA's analysis and Section 2 commends EPA for including discussion of an important but often overlooked health effect in the toxicological assessment.

1. EPA's draft toxicological assessment for PFNA may be missing relevant health and toxicological studies.

Through our searches in creating the PFAS-Tox Database, which are similar to those used by EPA,[9] we have identified 631 studies on PFNA (443 human studies, 109 animal studies, and 90

[8] US EPA, Toxicological Review of Perfluorohexanoic Acid [CASRN 307244] and Related Salts. 2022. Washington DC. Available from: https://www.regulations.gov/document/EPA-HQ-ORD-2021-0561-0001
[9] Literature searches for the PFAS-Tox Database were conducted in PubMed, most recently in January 2021.

in vitro studies). EPA identified 534 human studies, 36 animal studies, and 10 in vitro/in vivo genotoxicity studies.

I have included an attachment with a listing of the human and animal studies that were included in the PFAS-Tox Database but were missing from EPA's analysis ("Sheet 1-human" and "Sheet 2-animal" of attachment, respectively). The attachment contains a brief summary of the endpoints that are relevant to health or toxicology (column C in sheet 1 and Column D in sheet 2 of the attachment). The animal list includes 10 mouse studies and 7 rat studies as well as studies in several other species that would have been considered supplemental. In seven of the mouse studies and 4 of the rat studies animals were exposed by intraperitoneal injection, which means these studies would have also been tagged as supplemental. "Sheet 3-genotox" in the attachment contains a list of potentially relevant studies from human, animal and in vitro evidence streams that may be informative or provide supplemental information for the analysis of genotoxicity. Of particular note is a study by Mertens et al., (2010) in which the subchronic toxicity of S-111-S-WB was investigated.[10] Another study, not included in the PFAS-Tox Database, nor in the IRIS assessment, is an oral two-generation reproductive study of S-11-S-WB by Stump et al., (2008).[11] These two studies are relevant because S-11-S-WB is a technical mixture of PFAS used in polymer manufacturing the major component of which is PFNA. "Sheet 4 – Cancer" contains a list of studies that were tagged as relevant to cancer in the PFAS-Tox Database but that were not included in the draft toxicological review. In particular, the study by Benninghoff et al., (2012), which evaluated tumor promotion in trout, was important in California's Office of Environmental Health Hazard Assessment's analysis of the carcinogenicity of PFOS which used the Key Characteristics of Cancer framework to provide evidence on the carcinogenicity of PFOS.[12] PFNA was also evaluated in the study by Benninghoff et al. EPA should review the submitted attachment and evaluate if any additional studies should be included in the Toxicological Review.

2. EPA's draft toxicological assessment for PFNA included discussion of breastfeeding duration.

I commend EPA on including in this draft Toxicological Review, a discussion on the potential impacts of PFNA on breastfeeding duration, an important, yet often overlooked health endpoint.

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[10] Mertens, Jozef J. W. M., Daniel W. Sved, Gary B. Marit, Nichole R. Myers, Phil L. Stetson, Sandra Reiss Murphy, Bruno Schmit, Motoki Shinohara, and Craig H. Farr. "Subchronic Toxicity of S-111-S-WB in Sprague Dawley Rats." *International Journal of Toxicology* 29, no. 4 (July 1, 2010): 358–71. https://doi.org/10.1177/1091581810370372.

[11] Stump, Donald G., Joseph F. Holson, Sandra R. Murphy, Craig H. Farr, Bruno Schmit, and Motoki Shinohara. "An Oral Two-Generation Reproductive Toxicity Study of S-111-S-WB in Rats." *Reproductive Toxicology* 25, no. 1 (January 1, 2008): 7–20. https://doi.org/10.1016/j.reprotox.2007.10.002 .

[12] Benninghoff, Abby D., Gayle A. Orner, Clarissa H. Buchner, Jerry D. Hendricks, Aaron M. Duffy, and David E. Williams. "Promotion of Hepatocarcinogenesis by Perfluoroalkyl Acids in Rainbow Trout." *Toxicological Sciences* 125, no. 1 (January 2012): 69–78. https://doi.org/10.1093/toxsci/kfr267; OEHHA. "Proposition 65: Evidence on the Carcinogenicity of Perfluorooctane Sulfonic Acid (PFOS) and Its Salts and Transformation and Degradation Precursors," September 2021. https://oehha.ca.gov/media/downloads/crnr/pfoshid092421.pdf.

I note, however, that EPA has not included a more recent meta-analysis on this endpoint, Timmerman et al. (2023).[13] In the attached spreadsheet, I have highlighted in yellow, human studies that may contain supplemental information relevant to the discussion on breastfeeding duration. Some of these studies, including studies by Ammitzbøll et al., (2019), Lee et al., (2018) and Harris et al., (2017) are highlighted, but there are others, including studies by Brantsæter et al., (2013), Kim et al., (2020), and Papadopoulou et al., (2016) that may contain informative supplemental information.[14]

Breastfeeding is associated with short- and long-term health benefits for both mother and child, but <30% of mothers in the U.S. continue any breastfeeding until the American Academy of Pediatrics (AAP) recommended 12 months.[15] The benefits of human milk for children are well described, with health benefits extending into adulthood.[16] Potential health benefits of lactation for the mother are often described with the "reset" hypothesis, whereby the adverse cardiometabolic changes during gestation (insulin resistance, hyperlipidemia, and visceral fat of pregnancy) are ameliorated by breastfeeding. In contrast, without breastfeeding, these metabolic changes persist.[17] Meta-analyses with over 200,000 women confirmed relationships between breastfeeding for 12 months and protection against common adverse cardiometabolic health outcomes, including a 30% risk reduction for diabetes and a 13% risk reduction for hypertension.[18] In the past, inadequate attention has been paid to breastfeeding duration as an

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[13] Timmermann, Amalie, Oyemwenosa N. Avenbuan, Megan E. Romano, Joseph M. Braun, Janne S. Tolstrup, Laura N. Vandenberg, and Suzanne E. Fenton. "Per- and Polyfluoroalkyl Substances and Breastfeeding as a Vulnerable Function: A Systematic Review of Epidemiological Studies." *Toxics* 11, no. 4 (April 2023): 325. https://doi.org/10.3390/toxics11040325.

[14] Brantsæter, A. L., K. W. Whitworth, T. A. Ydersbond, L. S. Haug, M. Haugen, H. K. Knutsen, C. Thomsen, et al. "Determinants of Plasma Concentrations of Perfluoroalkyl Substances in Pregnant Norwegian Women." *Environment International* 54 (April 1, 2013): 74–84. https://doi.org/10.1016/j.envint.2012.12.014; Kim, Kyunghoon, Deborah H. Bennett, Antonia M. Calafat, Irva Hertz-Picciotto, and Hyeong-Moo Shin. "Temporal Trends and Determinants of Serum Concentrations of Per- and Polyfluoroalkyl Substances among Northern California Mothers with a Young Child, 2009–2016." *Environmental Research* 186 (July 2020): 109491. https://doi.org/10.1016/j.envres.2020.109491; Papadopoulou, Eleni, Azemira Sabaredzovic, Ellen Namork, Unni C. Nygaard, Berit Granum, and Line S. Haug. "Exposure of Norwegian Toddlers to Perfluoroalkyl Substances (PFAS): The Association with Breastfeeding and Maternal PFAS Concentrations." *Environment International* 94 (September 1, 2016): 687–94. https://doi.org/10.1016/j.envint.2016.07.006.

[15] Rameez, Rabel Misbah, Divyajot Sadana, Simrat Kaur, Taha Ahmed, Jay Patel, Muhammad Shahzeb Khan, Sarah Misbah, Marian T. Simonson, Haris Riaz, and Haitham M. Ahmed. "Association of Maternal Lactation With Diabetes and Hypertension: A Systematic Review and Meta-Analysis." *JAMA Network Open* 2, no. 10 (October 16, 2019): e1913401. https://doi.org/10.1001/jamanetworkopen.2019.13401.

[16] Ip, Stanley, Mei Chung, Gowri Raman, Priscilla Chew, Nombulelo Magula, Deirdre DeVine, Thomas Trikalinos, and Joseph Lau. "Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries." *Evidence Report/Technology Assessment*, no. 153 (April 2007): 1–186. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4781366/.

[17] Stuebe, Alison M., and Janet W. Rich-Edwards. "The Reset Hypothesis: Lactation and Maternal Metabolism." *American Journal of Perinatology* 26, no. 1 (January 2009): 81–88. https://doi.org/10.1055/s-0028-1103034.

[18] Rameez, Rabel Misbah, Divyajot Sadana, Simrat Kaur, Taha Ahmed, Jay Patel, Muhammad Shahzeb Khan, Sarah Misbah, Marian T. Simonson, Haris Riaz, and Haitham M. Ahmed. "Association of Maternal

important health outcome to evaluate. Given the social and public health importance of breastfeeding, it was refreshing to see that EPA considered the impacts of PFNA on this health outcome.

Conclusions

In conclusion, I urge the agency to strengthen its final toxicological review and have outlined some opportunities for improvement that should be addressed in the final document. I also urge the agency to move quickly to incorporate our recommendations based on the latest science and finalize the profile in a timely manner.

Respectfully submitted,

Katherine Pelch, PhD
Scientist
Environmental Health
Natural Resources Defense Council

Attachment: Please see “NRDC_Attachment_PFNA.xlsx”

Lactation With Diabetes and Hypertension: A Systematic Review and Meta-Analysis.” *JAMA Network Open* 2, no. 10 (October 16, 2019): e1913401. https://doi.org/10.1001/jamanetworkopen.2019.13401.