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Washington DC 20009

Re: Docket EPA–HQ–ORD–2019–0287 Draft IRIS Toxicological Review of Perfluorodecanoic Acid [PFDA, CASRN 335-76-2] and Related Salts

June 9, 2023

On behalf of the Natural Resources Defense Council (NRDC), I appreciate this opportunity to submit comments on EPA's Draft Toxicological Review for Perfluorodecanoic acid (PFDA).[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, 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 PFDA.[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).

PFDA 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 Perfluorodecanoic Acid (PFDA) and Related Salts (Public Comment and External Review Draft)," April 2023. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=354408.
[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 is currently seeking input on potentially listing PFDA 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 strongly urge the EPA to:

(1) update and strengthen this review by ensuring that it relies upon a more robust 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 PFDA assessment. Finally, I appreciate the display of extracted PFDA data in HAWC, which made it very easy to evaluate the statements made in the draft PFDA toxicological review.

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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] "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.

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 PFDA likely causes liver, immune, developmental, and male and female reproductive effects in humans. I further support the conclusion that early life represents a susceptible life stage for the effects of PFDA exposure.

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 PFDA, 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 PFDA 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, and PFHxA. Americans most at risk of exposure to PFDA will generally have greater than typical exposures to legacy PFAS chemicals as well. The available data suggests that PFDA impacts the same body systems as other PFAS. Given this, EPA should include a section on PFAS cumulative risks.

My specific comments address three concerns: Section 1 points to numerous human studies that are not included in the EPA's analysis. Section 2 highlights supplemental studies that may be impactful. Section 3 provides minor comments and recommendations for improvements in EPA's draft toxicological review of PFDA.

1. EPA's draft toxicological assessment for PFDA may be missing relevant human health studies.

Through our searches in creating the PFAS-Tox Database, which are similar to those used by EPA, we have identified 506 studies on PFDA (277 human studies, 146 animal studies, and 101 in vitro studies). EPA identified 234 human studies, 14 animal studies, and 8 in vitro/in vivo genotoxicity studies.

[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

I have included an attachment with a listing of the human studies that were included in the PFAS-Tox Database but were missing from EPA's analysis (Shee 1 of attachment). The attachment contains a brief summary of the endpoints that are relevant to human health (column C in sheet 1 of attachment). In order to better understand where the differences in results arise, it would be helpful if EPA would provide a list of all excluded studies and the reason for exclusion. HAWC currently only lists the included studies at https://hawc.epa.gov/lit/assessment/100500072/references/?tag_id=100502117. While some of the studies that were included in the PFAS-Tox Database may be out of the scope of the EPA's analysis, it would be helpful to understand EPA's decision process on these studies. For example, Pan et al., found that PFDA was associated with increased DNA fragmentation index and high DNA stainability (a marker of the percentage of sperm with immature chromatin) in semen.[9] Semen evaluations were considered in section 3.2.4 of the Draft Toxicological Review, and it it is unclear why this study was not included. EPA should review the submitted attachment and evaluate if additional human studies should be included in the Toxicological Review.

Importantly, 7 of the studies that were included in the PFAS-Tox Database but not included in EPA's analysis evaluate breastfeeding duration, a health outcome that was not evaluated in the Draft Toxicological Review. Given the importance of breastfeeding and its association with many other health impacts, this is a major oversight. EPA should review the submitted attachment and consider summarizing the available evidence that PFDA may be associated with shortened duration of breastfeeding.

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.[10] The benefits of human milk for children are well described, with health benefits extending into adulthood.[11] 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.[12]

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[9] Pan, Yitao, Qianqian Cui, Jinghua Wang, Nan Sheng, Jun Jing, Bing Yao, and Jiayin Dai. "Profiles of Emerging and Legacy Per-/Polyfluoroalkyl Substances in Matched Serum and Semen Samples: New Implications for Human Semen Quality." *Environmental Health Perspectives* 127, no. 12 (December 2019): 127005. https://doi.org/10.1289/EHP4431.

[10] 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.

[11] 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/.

[12] 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.

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.[13] Importantly, shortened duration of breastfeeding has been associated with PFAS exposure in human studies. Six human studies, published between 2010 and 2022 were recently reviewed and evaluated in a meta-analysis.[14] Four of the five included studies reported shortened total duration of breastfeeding with higher PFOS and PFOA exposure. One study in particular found that in primiparous Faroese women, a doubling in PFDA serum concentrations was associated with 0.5 shorter duration of exclusive breastfeeding.[15] The human epidemiological findings are consistent with findings from experimental animal studies. Despite these consistencies and the importance of breastfeeding duration on maternal and infant health, EPA unfortunately failed at adequately evaluating this important human health endpoint.

2. EPA's draft toxicological assessment for PFDA could be strengthened by considering additional supplemental studies.

In general, studies presumably marked as supplemental materials are not consistently referred to and discussed in the document. EPA should provide further guidance for when it will make use of available supplemental materials. The list of nonmammalian models or animals that were exposed through non-oral routes, for example, is not readily accessible, or cited in the Draft Toxicological Review. EPA should better mention and summarize these mechanistic studies, in order to more fully describe the potential effects of PFDA.

The Populations, Exposures, Comparators, and Outcomes (PECO) criteria used in developing the PFAS-Tox Database was broader than the PECO criteria used in the draft IRIS review, which resulted in many more animal studies being included in the PFAS-Tox Database (146 animal studies versus 14). In particular, we included in the PFAS-Tox Database studies with other routes of exposure than oral, non-mammalian studies, and observational animal studies. Of note, we identified 72 studies in which animals were exposed to PFDA by intraperitoneal injection. I have provided this list of intraperitoneally exposed animal studies in Sheet 2 of the attachment, in case it should be of interest to external reviewers.

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[13] 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.

[14] 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.

[15] Timmermann, Clara Amalie Gade, Esben Budtz-Jørgensen, Maria Skaalum Petersen, Pál Weihe, Ulrike Steuerwald, Flemming Nielsen, Tina Kold Jensen, and Philippe Grandjean. "Shorter Duration of Breastfeeding at Elevated Exposures to Perfluoroalkyl Substances." *Reproductive Toxicology*, Developmental Origins of Disease, 68 (March 1, 2017): 164–70. https://doi.org/10.1016/j.reprotox.2016.07.010.

The use of studies tagged as supplemental is also important in the evaluation of carcinogenicity. Notably, we identified several studies that likely were tagged as supplemental studies by EPA, which may be informative, especially should EPA consider using the Key Characteristics of Cancer framework, which has been used by agencies such as California's Office of Environmental Health Hazards.[16] In particular, the study by Benninghoff et al. 2012, which evaluated tumor promotion in trout, was important in OEHHA's analysis of the carcinogenicity of PFOS.[17] PFDA was also evaluated in the study by Benninghoff et al. Other studies of interest include:

- Borges et al. 1993. *Effect of the peroxisome proliferator perfluorodecanoic acid on the promotion of two-stage hepatocarcinogenesis in rats*.[18] This study used an intraperitoneal injection route of exposure.
- Bost et al. 2016. *U.S. domestic cats as sentinels for perfluoroalkyl substances: Possible linkages with housing, obesity, and disease*.[19]
- Sévère et al. 2015. *Pollutants in pet dogs: a model for environmental links to breast cancer*.[20]
- Dong et al. 2017. *Perfluorodecanoic acid (PFDA) promotes gastric cell proliferation via sPLA2-IIA*.[21]
- Liu et al. 2019. *XRCC4, which is inhibited by PFDA, regulates DNA damage repair and cell chemosensitivity*.[22]

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[16] Smith, Martyn T., Kathryn Z. Guyton, Catherine F. Gibbons, Jason M. Fritz, Christopher J. Portier, Ivan Rusyn, David M. DeMarini, et al. "Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis." *Environmental Health Perspectives* 124, no. 6 (June 2016): 713–21. https://doi.org/10.1289/ehp.1509912; 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.

[17] 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.

[18] Borges, T., R. E. Peterson, H. C. Pitot, L. W. Robertson, and H. P. Glauert. "Effect of the Peroxisome Proliferator Perfluorodecanoic Acid on the Promotion of Two-Stage Hepatocarcinogenesis in Rats." *Cancer Letters* 72, no. 1–2 (August 16, 1993): 111–20. https://doi.org/10.1016/0304-3835(93)90019-6.

[19] Bost, Phillip C., Mark J. Strynar, Jessica L. Reiner, Jerry A. Zweigenbaum, Patricia L. Secoura, Andrew B. Lindstrom, and Janice A. Dye. "U.S. Domestic Cats as Sentinels for Perfluoroalkyl Substances: Possible Linkages with Housing, Obesity, and Disease." *Environmental Research* 151 (November 2016): 145–53. https://doi.org/10.1016/j.envres.2016.07.027.

[20] Sévère, Sabine, Philippe Marchand, Ingrid Guiffard, Floriane Morio, Anaïs Venisseau, Bruno Veyrand, Bruno Le Bizec, Jean-Philippe Antignac, and Jérôme Abadie. "Pollutants in Pet Dogs: A Model for Environmental Links to Breast Cancer." *SpringerPlus* 4 (January 22, 2015): 27. https://doi.org/10.1186/s40064-015-0790-4.

[21] Dong, Tianyi, Yanping Peng, Ning Zhong, Fengyan Liu, Hanyu Zhang, Mengchen Xu, Rutao Liu, et al. "Perfluorodecanoic Acid (PFDA) Promotes Gastric Cell Proliferation via SPLA2-IIA." *Oncotarget* 8, no. 31 (April 20, 2017): 50911–20. https://doi.org/10.18632/oncotarget.17284.

[22] Liu, Fengyan, Ziyan Fan, Ning Song, Mingyong Han, Ming Yan, Liang-Hong Guo, Jia Jihui, and Shili Liu. "XRCC4, Which Is Inhibited by PFDA, Regulates DNA Damage Repair and Cell Chemosensitivity." *Journal of Cellular Biochemistry* 120, no. 8 (August 2019): 12665–76. https://doi.org/10.1002/jcb.28534.

- Zhang et al. 2019. *Environmental pollutant perfluorodecanoic acid upregulates cIAP2 to suppress gastric cell senescence*.[23]

3. Minor comments.

Overall, I found the document well written, easy to follow, and in agreement with the workflow that was proposed in the *a priori* published protocol. I noted the following inconsistencies and/or opportunities to provide additional clarity in the document, which should be addressed before the review is finalized.

- When evaluating the epidemiological data for hepatic effects, I encourage EPA to consider reviewing a new paper regarding the use of clinical consensus cutoffs compared to statistical cutoffs for abnormal values.[24] A recent reanalysis of data from the C8 study was performed using the updated physiologically-based cutoffs for ALT as recommended by the medical liver disease societies.[25] This reanalysis showed an increased association of PFOA to abnormal ALT and emphasized the near monotonic increases in ALT with increasing dose. Thus, it may be necessary to reanalyze datasets that evaluate the association of PFDA exposure and ALT levels in light of the suggested changes for identifying abnormal values.
- Page 1-8, the document incorrectly refers to the PFBA review in lines 16 and 17 "In addition, studies included in ongoing IRIS PFAS assessments (PFHxA, PFHxS, PFNA, PFDA) were also scanned for any studies that met **PFBA** PECO criteria." This should refer to PFDA not PFBA.
- Page 2-4, Table 2-1: Harris and Birnbaum 1989 is cited twice and linked to HERO ID 3858729. Should one of the studies be *Acute toxicity of perfluorodecanoic acid in C57BL/6 mice differs from 2,3,7,8-tetrachlorodibenzo-p-dioxin*, which is included in the study list in HAWC? Or a different reference? Please confirm that the summaries in Table 2-1 are accurate.
- Page 3-100 line 7 should read "non-differential with respect to PFDA" not "non-differential with respect to **PFNA**"

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[23] Zhang, Zhun, Ning Song, Yanping Peng, Ziyan Fan, Mingyong Han, Min Zhao, Tianyi Dong, and Shili Liu. "Environmental Pollutant Perfluorodecanoic Acid Upregulates CIAP2 to Suppress Gastric Cell Senescence." *Oncology Reports* 41, no. 2 (February 1, 2019): 981–88. https://doi.org/10.3892/or.2018.6856.

[24] Chalasani, Naga, Zobair Younossi, Joel E. Lavine, Michael Charlton, Kenneth Cusi, Mary Rinella, Stephen A. Harrison, Elizabeth M. Brunt, and Arun J. Sanyal. "The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance from the American Association for the Study of Liver Diseases." *Hepatology* 67, no. 1 (January 2018): 328. https://doi.org/10.1002/hep.29367; Park, Jin Hwa, Jun Choi, Dae Won Jun, Sung Won Han, Yee Hui Yeo, and Mindie H Nguyen. "Low Alanine Aminotransferase Cut-Off for Predicting Liver Outcomes; A Nationwide Population-Based Longitudinal Cohort Study." *Journal of Clinical Medicine* 8, no. 9 (September 11, 2019): 1445. https://www.mdpi.com/2077-0383/8/9/1445.

[25] Ducatman, Alan, Youran Tan, Brian Nadeau, and Kyle Steenland. "Perfluorooctanoic Acid (PFOA) Exposure and Abnormal Alanine Aminotransferase: Using Clinical Consensus Cutoffs Compared to Statistical Cutoffs for Abnormal Values." *Toxics* 11, no. 5 (May 2023): 449. https://doi.org/10.3390/toxics11050449;

Conclusions

In conclusion, I urge the agency to strengthen its final toxicological review and have outlined several opportunities for improvement that should be corrected 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,

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Attachment: Please see “NRDC_Attachment_PFDA.xlsx”