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Environmental Protection Agency
Washington DC 20009

Re: Docket EPA-HQ-ORD-2020-0675

November 8, 2021

On behalf of the Natural Resources Defense Council (NRDC), we appreciate this opportunity to submit comments on EPA's Draft Toxicological Review for perfluorobutanoic acid (PFBA).[1] We, Drs. Katherine Pelch and Anna Reade, 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 GenX and PFBS, ATSDR's toxicological profile for perfluoroalkyls, and state assessments in CA, IL, ME, MI, NH, NY, VT, and WA. In addition, we are co-creators of the PFAS-Tox Database (available at PFASToxDatabase.org), a systematic evidence map of the health and toxicological research available for 29 PFAS, including PFBA.[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). Through our searches, which are very similar to those used by EPA, we have identified 98 studies on PFBA (23 human studies, 25 animal studies, and 52 in vitro studies). It should be noted that the PECO (Populations, Exposures, Comparators, and Outcomes) statement used to guide the development of the PFAS-Tox Database is broader than was used by EPA (for example, we did not limit the routes of exposure in animal studies).

PFBA is part of the massive family of synthetic per- and poly- fluorinated alkyl substances (PFAS), with at least 6,000 PFAS CAS-name substances.[3] PFAS are characterized by incredible durability, which manifests as extreme persistence in the environment. The PFAS chemicals that have been studied show potent toxicity to internal organs, lipid metabolism, as well as the immune and endocrine systems.

[1] US EPA, *Toxicological Review of Perfluorobutanoic Acid (PFBA) and Related Compound Ammonium Perfluorobutanoic Acid [CASRN 375-22-4 CASRN 10495-86-0].* 2021. Washington DC. Available from: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350051.
[2] Pelch, K.E., et al., *PFAS Health Database: A Systematic Evidence Map*. 2021. Available from: https://osf.io/f9upx/.
[3] US EPA, *PFAS Master List of PFAS Substances (Version 2)*. 2020. Available from: https://comptox.epa.gov/dashboard/chemical_lists/PFASMASTER.

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, we outline areas where the EPA has taken steps in the right direction as well as areas that need to be strengthened. We recognize the importance of this assessment and that communities exposed to these chemicals are eager for the EPA to complete this toxicological review, but we strongly urge the EPA to update and strengthen this review by ensuring that it relies upon a more robust, up-to-date data set and adequately accounts for cumulative risks that may occur from coexposure to additional PFAS, as is often the case in real-world exposure scenarios.

We support EPA's use of modern and transparent systematic review methodology as well as EPA's choice of critical studies and endpoints for a quantitative assessment of health risks. We support the conclusions reached by the EPA that the evidence evaluated within the toxicological review supports the conclusion that developmental, thyroid, and liver effects in humans are likely caused by PFBA exposure in utero or during adulthood. We further support the conclusions that decreases in total thyroxine (T4) and increases in hepatocellular hypertrophy observed in adult rats are biologically relevant models for human health endpoints. However, we do note that the literature search for this toxicological review is already at least three years out of date and several (at least 15) additional epidemiological studies have been published during this time. It is currently unclear if inclusion of these additional epidemiological studies would impact the conclusions reached in this toxicological review. EPA should ensure that the final toxicological review is current within 6 months of the last literature update and provide clarity as to how often updates to the literature search and the resulting toxicological review will be conducted.

Though we largely support the conclusions reached by EPA, we however believe it is inappropriate for EPA to attempt to estimate the risks posed by PFBA individually. We appreciate that EPA highlighted the utility of deriving "organ/system-specific values ... for subsequent cumulative risk assessments that consider the combined effect of multiple PFAS."[4] 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, and PFBS. Americans most at risk of exposure to PFBA will generally have greater than typical exposures to legacy PFAS chemicals as well. The available data suggests that PFBA impacts the same body systems as other, better-studied PFAS. Given this, EPA should include a section on PFAS cumulative risks.

Our comments address three major issues. Section 1 outlines methodological concerns regarding the conduct and reporting of the literature search, screening, and study selection. Section 2 addresses EPA's use of chemical-specific toxicokinetic parameters for the derivation

[4] US EPA, *Toxicological Review of Perfluorobutanoic Acid (PFBA) and Related Compound Ammonium Perfluorobutanoic Acid [CASRN 375-22-4 CASRN 10495-86-0].* 2021. Washington DC. Available from: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350051.

of human relevant doses. Section 3 provides recommendations for improvements in EPA's derivation of toxicity values.

1. Methodology and Reporting Concerns

A. EPA's draft toxicological assessment for PFBA is significantly out of date.

We 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.[5]

In particular, we 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).[6] Importantly, the PECO (populations, exposures, comparators and outcomes) statement clearly outlines the criteria for inclusion and exclusion of studies in the assessment. We also support the transparent GRADE-like methods used for evidence integration in the draft PFBA assessment. Finally, we appreciate the display of extracted PFBA data in HAWC, which made it very easy to evaluate the statements made in the draft PFBA toxicological review. To this end, we also appreciate that EPA was able to make publicly available the industry studies that have not been peer reviewed.

A major concern with the draft toxicological review is that it is already considerably out of date, with the last literature search update seemingly being conducted in 2018, as indicated in the January 2021 protocol update.[7] The draft toxicological review lacks details on when the last literature update was conducted and when stakeholders can reasonably expect for an update to be included. Moving forward, the EPA should ensure that all literature searches are conducted within six months of final publication, and that the cut-off date is reported in the toxicological review, which would reflect best practices in systematic review.

[5] 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.
[6] Translation, O.o.H.A.a., *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.
[7] US EPA, *An Update to the Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments.* 2021. Washington DC. Available from: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345065#tab-3.

Basing toxicological reviews on the most current literature is essential given the rapid pace in which studies on PFAS are being published. Of note, we have identified an additional 15 human epidemiological studies that were not included in EPA's draft toxicological review of PFBA because they were published after the 2018 literature search was conducted (and prior to January 25, 2021 when the most recent literature search for the PFAS-Tox Database was conducted)[8,9,10,11,12,13,14,15,16,17,18,19,20,21,22]. Given the diversity in scope of these studies, it is unclear if their inclusion would have impacted the conclusions reached in the draft toxicological review. It should be noted that these studies provide additional evidence for important health concerns including impacts on:

- growth & early life development (specific endpoints include: birth weight, infant weight and length growth rate, preterm delivery, ponderal index, and gestational Diabetes Mellitus)

[8] Antignac, J.P., et al., *Occurrence of perfluorinated alkylated substances in breast milk of French women and relation with socio-demographical and clinical parameters: results of the ELFE pilot study.* Chemosphere, 2013. **91**(6): p. 802-8.
[9] Liu, X., et al., *Structure-based investigation on the association between perfluoroalkyl acids exposure and both gestational diabetes mellitus and glucose homeostasis in pregnant women.* Environ Int, 2019. **127**: p. 85-93.
[10] Tian, Y.P., et al., *Isomers of perfluoroalkyl substances and overweight status among Chinese by sex status: Isomers of C8 Health Project in China.* Ibid. **124**: p. 130-138.
[11] Jin, H., et al., *Poly- and perfluoroalkyl substance concentrations in human breast milk and their associations with postnatal infant growth.* Sci Total Environ, 2020. **713**: p. 136417.
[12] Zeng, X.W., et al., *Alternatives of perfluoroalkyl acids and hepatitis B virus surface antibody in adults: Isomers of C8 Health Project in China.* Environ Pollut, 2020. **259**: p. 113857.
[13] Zeeshan, M., et al., *Incidence of ocular conditions associated with perfluoroalkyl substances exposure: Isomers of C8 Health Project in China.* Environ Int, 2020. **137**: p. 105555.
[14] Banjabi, A.A., et al., *Serum concentrations of perfluoroalkyl substances and their association with osteoporosis in a population in Jeddah, Saudi Arabia.* Environ Res, 2020. **187**: p. 109676.
[15] Gao, K., et al., *Prenatal Exposure to Per- and Polyfluoroalkyl Substances (PFASs) and Association between the Placental Transfer Efficiencies and Dissociation Constant of Serum Proteins-PFAS Complexes.* Environ Sci Technol, 2019. **53**(11): p. 6529-6538.
[16] Duan, Y., et al., *Distribution of novel and legacy per-/polyfluoroalkyl substances in serum and its associations with two glycemic biomarkers among Chinese adult men and women with normal blood glucose levels.* Environ Int, 2020. **134**: p. 105295.
[17] Grandjean, P., et al., *Severity of COVID-19 at elevated exposure to perfluorinated alkylates.* PLoS One, 2020. **15**(12): p. e0244815.
[18] Liu, X., et al., *Identification and prioritization of the potent components for combined exposure of multiple persistent organic pollutants associated with gestational diabetes mellitus.* J Hazard Mater, 2021. **409**: p. 124905.
[19] McGlinchey, A., et al., *Prenatal exposure to perfluoroalkyl substances modulates neonatal serum phospholipids, increasing risk of type 1 diabetes.* Environ Int, 2020. **143**: p. 105935.
[20] Li, J., et al., *Transplacental Transfer of Per- and Polyfluoroalkyl Substances (PFASs): Differences between Preterm and Full-Term Deliveries and Associations with Placental Transporter mRNA Expression.* Environ Sci Technol, 2020. **54**(8): p. 5062-5070.
[21] Zeng, X.W., et al., *Isomers of per- and polyfluoroalkyl substances and uric acid in adults: Isomers of C8 Health Project in China.* Environ Int, 2019. **133**(Pt A): p. 105160.
[22] Lu, Y., et al., *Mass Spectrometry-Based Metabolomics Reveals Occupational Exposure to Per- and Polyfluoroalkyl Substances Relates to Oxidative Stress, Fatty Acid beta-Oxidation Disorder, and Kidney Injury in a Manufactory in China.* Environ Sci Technol, 2019. **53**(16): p. 9800-9809.

- the metabolic system (specific endpoints include: body mass index (BMI), waist circumference or overweight, metabolites associated with oxidative stress, lipid metabolomics as markers of Type 1 Diabetes in mothers and newborns, gestational Diabetes Mellitus, fatty acid β-oxidation disorder, and fasting glucose and glycated hemoglobin)
- the renal system (specific endpoints include: uric acid, hyperuricemia, kidney disease, kidney injury and kidney function stage)
- the immune system (specific endpoints include: asthma, increased COVID-19 severity, and the presence of Hepatitis B surface antibodies)
- the endocrine system (specific endpoints include: thyroid disorders)
- the musculoskeletal system (specific endpoints include: osteoporosis and calcium and vitamin D levels)
- sensory organs (specific endpoints include: markers of eye diseases)

Updating the literature search to include these and any other recently published studies is important as five of these studies contain data on effects that are evaluated in early life and one study contains data on immune system effects and another on thyroid disorders, and therefore may help to address data gaps in the PFBA toxicity database identified by EPA. Further, developmental and immune effects are often the most sensitive endpoints for PFAS, therefore it is critical that this data be evaluated when assessing the toxicity of PFBA.

B. EPA's draft toxicological review contains unexplained inconsistencies

We noted several inconsistencies and/or oversights in the reporting of the literature search and screening results, which we outline here.

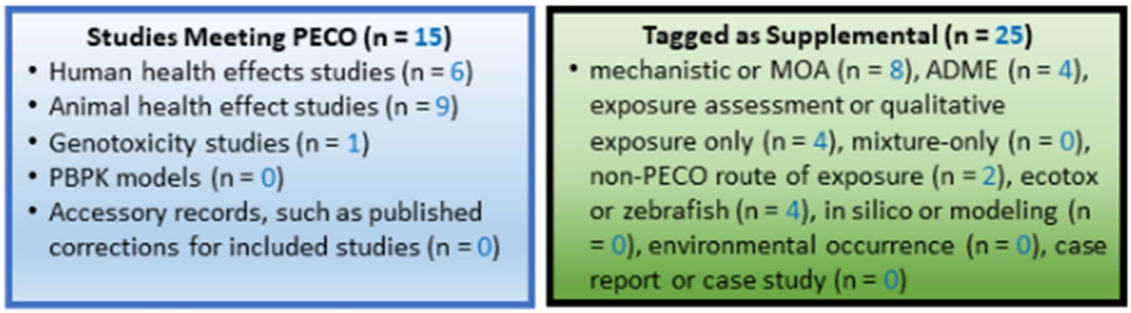
We recommend that EPA provide further clarification and better reporting when multiple publications of the same data are included. For example the studies reported as van Otterdijk 2007c and van Otterdijk 2007d[23,24] are industry documents available in EPA's HERO database, but have also been published in the peer reviewed literature in the study by Butenhoff et al. 2012.[25] That these studies contain overlapping and duplicative data, should be more clearly noted in the literature flow diagram (Figure 2-1) and the discussion of Study Evaluation Results in Section 2.2. In Section 2.2, for example, EPA states that there are "two 28-day studies in rats and mice Butenhoff et al. (2012b; Foreman et al. (2009b; van Otterdijk (2007c)".[26] No additional

[23] van Otterdijk, F.M., *Repeated dose 28-day oral toxicity study with MTDID-8391 by daily gavage in the rat, followed by a 21-day recovery period*. 2007, 3M: Maplewood, MN.
[24] van Otterdijk, F.M., *Repeated dose 90-day oral toxicity study with MTDID 8391 by daily gavage in the rat followed by a 3-week recovery period*. 2007, 3M: Maplewood, MN.
[25] Butenhoff, J.L., et al., *Toxicological evaluation of ammonium perfluorobutyrate in rats: twenty-eight-day and ninety-day oral gavage studies.* Reprod Toxicol, 2012. **33**(4): p. 513-530.
[26] US EPA, *Toxicological Review of Perfluorobutanoic Acid (PFBA) and Related Compound Ammonium Perfluorobutanoic Acid [CASRN 375-22-4 CASRN 10495-86-0].* 2021. Washington DC. Available from: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350051.

context is provided to the reader at this point in the document that would indicate that the Butenhoff et al. 2012b and van Otterdijk 2007c data are derived from a single study.

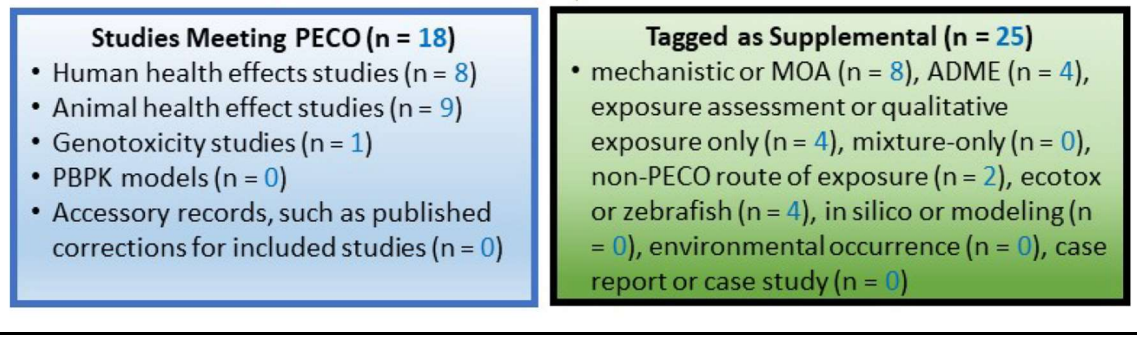
We recommend that EPA ensure that all numbers of studies are properly reported within the document, figures, tables, and associated meta-data. There are inconsistencies in the number of reported "studies meeting PECO" (i.e. included in the review) in the January 2021 Protocol Update and in the August 2021 Draft Toxicological Review. In the January 20212 Protocol Update it is reported that there are 15 included studies (n=6 human studies, n=9 animal studies, n=1 genotoxicity study). Given that none of the studies were included in more than one evidence stream, it is impossible to sum to 15 included studies (6+9+1=16).

Selected from Figure 4-1(a) from



The August 2021 Draft Toxicological Review indicates that additional studies were included since the January 2021 Protocol Update was published, listing 18 studies as now included (n=8 human studies, n=9 animal studies, and n=1 genotoxicity study).

Selected from Figure 2-1 in Draft Toxicological Review



That more studies were identified during this time period is not unexpected. However, the text in Section 2.1 at line 8 has not been updated and still reads, "six epidemiological studies, nine animal studies, and one in vivo genotoxicity study." Adding to the confusion, HAWC currently displays 17 studies, which does not match the 15, 16, or 18 possible number of studies summed up so far. We believe this is because Das, 2015, 2851022 and Seo, 2018, 4238334 are listed in this evaluation in HAWC even though neither of these studies contains data on PFBA.

Further, it is unclear how EPA identified the one listed genotoxicity study, Crebelli et al., 2019[27], which was published in 2019, and thus was not available at the time of the last literature search conducted by EPA (at some point in 2018). Given its publication date and author affiliations, it is further unlikely to have been identified from the additional sources listed in Section 2.1. As such, it is unclear how this study came to be included in the current PFBA Draft Toxicological Review at this point in time. Interestingly, this study is not listed in HAWC, nor is it discussed elsewhere in the review even though it also contains data on relevant toxicological endpoints in mice, including: body, liver, spleen, and testes weights, and AST, ALT, MDA and TAC levels in serum. This is a confusing inconsistency and would likely be remedied if EPA conducted a thorough literature update.

EPA should make available the lists of included and supplemental studies. As indicated above, the list of included studies in HAWC is not accurate, listing studies that do not address PFBA. Further, it is currently not possible to determine how specific studies reviewed by EPA were processed during the literature review. For example, it is unclear from the protocol and from the PECO statement outlined in Table 1-3 of the Draft Toxicological Review how observational animal studies are handled in the current workflow. We have identified the study by Routti et al. 2016 as potentially relevant, in that it investigates body condition in seals (a non-human mammalian species).[28] This study would have been available at the time of EPA's most recent literature search, but it is unclear how this study was processed for inclusion or exclusion. Further, in our work in preparing the PFAS-Tox Database, we have identified four studies that potentially should have been tagged as supplemental studies because of a non-PECO route of exposure. EPA indicates there are only two such studies however. Because study lists have not been made available, it is not currently possible to determine where the difference in findings arises. A full listing of studies reviewed for inclusion and exclusion in the PFAS-Tox Database is available at https://osf.io/f9upx/.[29]

2. Support of EPA's use of chemical-specific toxicokinetic parameters

It is unfortunate that a more complete toxicokinetic profile is not available in the literature for PFBA. Given that, we support EPA's reanalysis of the raw data from Chang et al., 2008 and the overall approach to use the ratio of clearance rates. We agree with EPA that using data-informed clearance value-based dosimetric adjustment factors is preferred to using dosimetric adjustment factors relying on $BW^{3/4}$ scaling, an approach that is not specific to this class of

[27] Crebelli, R., et al., *Can sustained exposure to PFAS trigger a genotoxic response? A comprehensive genotoxicity assessment in mice after subacute oral administration of PFOA and PFBA.* Regul Toxicol Pharmacol, 2019. **106**: p. 169-177.
[28] Routti, H., et al., *Spatial and temporal trends in perfluoroalkyl substances (PFASs) in ringed seals (Pusa hispida) from Svalbard.* Environ Pollut, 2016. **214**: p. 230-238.
[29] Pelch, K.E., et al., *PFAS Health Database: A Systematic Evidence Map*. 2021. Available from: https://osf.io/f9upx/.

chemicals. We do note, however, that the paragraph on page 3-7 at lines 14-31 contains some typographical errors that make this section confusing to read.

3. Recommendations for improvements in EPA's derivation of toxicity values

A. Uncertainties are not appropriately accounted for.

We note that in the recent Human Health Toxicity Values derivation for PFBS EPA included a database uncertainty factor of 10, citing a lack of chronic studies and neurodevelopmental and immunotoxicity studies as well as a lack of mammary gland studies.[30] The same deficits were noted by EPA for PFBA,

> "Lastly, the potential for immunotoxicity and mammary gland effects represents an area of concern across several constituents of the larger PFAS family (primarily long-chain PFAS). No studies have evaluated these outcomes following PFBA exposure or following exposure to the structurally related PFBS described above. No chemical-specific information is available to judge the degree to which the existing endpoints in the PFBA Toxicological Review would be protective of immunotoxicity or mammary gland effects."[31]

It is therefore unclear why EPA drew a different conclusion in the draft toxicological review of PFBA, deciding to only apply a partial database uncertainty factor of 3. We suggest that to be adequately protective of public health, and consistent across assessments given the same underlying concerns about the lack of data, EPA should use the same database uncertainty factor for PFBA as was used in the finalized Human Health Toxicity Value derivation of PFBS, which is 10.

In addition, we note that biomonitoring studies demonstrate that Americans have chronic exposure to multiple PFAS chemicals throughout their lifetimes. Therefore, it is impossible to be exposed to PFBA and no other PFAS chemicals. CDC's NHANES studies reveal that nearly every American has detectable concentrations of four PFAS chemicals in their bloodstream

[30] US EPA, *Human Health Toxicity Values for Perfluorobutane Sulfonic Acid (CASRN 375-73-5) and Related Compound Potassium Perfluorobutane Sulfonate (CASRN 29420-49-3)* 2021. Washington DC. Available from: https://ofmpub.epa.gov/eims/eimscomm.getfile?p_download_id=542393.
[31] US EPA, *Toxicological Review of Perfluorobutanoic Acid (PFBA) and Related Compound Ammonium Perfluorobutanoic Acid [CASRN 375-22-4 CASRN 10495-86-0].* 2021. Washington DC. Available from: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350051.

(PFOS, PFOA, PFHxS and PFNA)[32]. Multiple other PFAS have been detected in NHANES and state biomonitoring programs.[33]

Toxicity assessment should account for simultaneous exposure to other PFAS chemicals that impact the same target organs. EPA does this for its reference dose (RfD) used to establish the present drinking water guideline for the sum of PFOS and PFOA:

> "Adverse effects observed following exposures to perfluorooctanoic acid (PFOA) and PFOS are the same or similar and include effects in humans on serum lipids, birth weight, and serum antibodies. Some of the animal studies show common effects on the liver, neonate development, and responses to immunological challenges. Both compounds were also associated with tumors in long-term animal studies. The RfDs for both PFOA and PFOS are based on similar developmental effects and are numerically identical; when these two chemicals co-occur at the same time and location in a drinking water source, a conservative and health-protective approach that EPA recommends would be to compare the sum of the concentrations ([PFOA] + [PFOS]) to the [Heath Advisory] (0.07 µg/L)."[34]

The European Food Safety Authority also allows for the consideration of additive effects for chemicals that target the same health endpoint, even when mode of action is unknown[35], as does the National Academy of Sciences.[36,37] The Netherlands pioneered this approach for PFAS with a relative potency estimate for liver hypertrophy using experimental data for 11 perfluoroalkyl sulfonates and perfluoroalkyl carboxylates and read across assumptions for 7 additional PFAS.[38] EPA must promote similar assessments for other PFAS related health outcomes with potential for additive toxicity, including kidney and liver toxicity, lipid metabolism, birth outcomes, immunotoxicity and developmental effects. At the very least, EPA should add an additional uncertainty factor to account for the high likelihood of additive effects with other PFAS.

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[32] Ye, X., et al., *Per- and polyfluoroalkyl substances in sera from children 3 to 11 years of age participating in the National Health and Nutrition Examination Survey 2013-2014.* Int J Hyg Environ Health, 2018. **221**(1): p. 9-16.
[33] California Biomonitoring. *Results for Perfluoroalkyl and Polyfluoroalkyl Substances (PFASs)* 2020 [cited 2021 November 5]; Available from: https://biomonitoring.ca.gov/results/chemical/2183.
[34] US EPA, *Drinking Water Health Advisory for perfluorooctanoic acid (PFOA).* 2016. Washington DC. Available from: https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final-plain.pdf.
[35] EFSA, *Scientific opinion on the identification of pesticides to be included in cumulative assessment groups on the basis of their toxicological profile.* 2014. Available from: https://www.efsa.europa.eu/en/efsajournal/pub/3293.
[36] National Research Council, *Phthalates and cumulative risk assessment: the tasks ahead*. 2008, Washington, DC: The National Academies Press.
[37] National Research Council, *Science and decisions: advancing risk assessment*. 2009, Washington, DC: The National Academies Press.
[38] RIVM, *Mixture exposure to PFAS: A relative potency factor approach.* 2018. The Netherlands. Available from: https://www.rivm.nl/bibliotheek/rapporten/2018-0070.pdf.

B. Independent evaluation of industry data used for the derivation of RfDs is needed.

In the charge questions provided for external reviewers of the PFBA Draft Toxicological Review, EPA requested the following feedback:

> "6. For PFBA, the Butenhoff et al. (2012) 90-day rat study was the study chosen for use in deriving the RfD on the basis of an increased incidence of hepatocellular hyperplasia and decreased total T4 in male rats. Is the selection of this study and these effects for use in deriving the RfD for PFBA scientifically justified? a. If so, please provide an explanation. b. If not, please provide an alternative study(ies) or effect(s) that should be used to support the derivation of the RfD and detail the rationale for use of such an alternative."

We call attention here to the recently finalized Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (Also known as GenX).[39] In the finalized GenX document, EPA detailed how liver histopathological slides from DuPont were sent the National Toxicology Program (NTP) for a reevaluation.[40] During the reevaluation, NTP pathologists identified several lesions not previously acknowledged as adverse effects by DuPont. EPA incorporated the findings reanalyzed by NTP into the final assessment, resulting in a different critical effect and lower point of departure than what was in the draft assessment based on the initial industry analysis.[41,42] We support the EPA's critical review and analysis of industry-sponsored studies, which is especially important given the tendency for industry-sponsored studies to be biased in favor of the regulatory approval of their products.[43] Therefore, given the alarming findings from the reanalysis of histopathological slides from the GenX assessment, and in response to Charge Question 6, we strongly urge independent reevaluation of industry data that is used as the basis of deriving candidate RFDs, and specifically the findings detailed in Butenhoff et al. 2012.[44]

[39] US EPA, *Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3).* 2021. Washington D.C.
[40] ibid.
[41] US EPA, *Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3).* 2018. Washington D.C. Available from: https://www.epa.gov/sites/production/files/2018-11/documents/genx_public_comment_draft_toxicity_assessment_nov2018-508.pdf.
[42] US EPA, *Human Health Toxicity Values for Hexafluoropropylene Oxide (HFPO) Dimer Acid and Its Ammonium Salt (CASRN 13252-13-6 and CASRN 62037-80-3).* 2021. Washington D.C.
[43] Mie, A., C. Ruden, and P. Grandjean, *Safety of Safety Evaluation of Pesticides: developmental neurotoxicity of chlorpyrifos and chlorpyrifos-methyl.* Environ Health, 2018. **17**(1): p. 77.
[44] Butenhoff, J.L., et al., *Toxicological evaluation of ammonium perfluorobutyrate in rats: twenty-eight-day and ninety-day oral gavage studies.* Reprod Toxicol, 2012. **33**(4): p. 513-530.

C. EPA's draft toxicological review contains unexplained inconsistencies and/or errors.

We note inconsistencies and/or errors in the following sections that should be updated in the final toxicological review:

- On page 3-24, it is unclear why Ikeda et al., 1985 is not included in Figure 3-4. Even though EPA determined this study to be of low confidence, the rationale for reaching that decision should be available for readers.
- On page 4-3, in Table 4-1, under the evidence basis for hepatic effects, it should be clarified in the first bullet that this is a summary of the human evidence in order to be parallel with other sections. The first bullet currently reads, "Two null studies (one medium and one low confidence) with poor sensitivity."
- On page 4-4 at line 8, it should be clarified that the serum half-life of 9 hours is for males.
- We recommend that the column containing references in Table 5-1 on page 5-5 be moved to the far left or far right hand of the table, as the current layout is confusing (and likely difficult for screen-reading programs).
- We note that the data in Table 5-3, Equation 5-4 and Table 5-4 is inconsistent. Equation 5-4 uses a value for animal CL=23.63, a value that is not mentioned anywhere else. The first, third, and fourth rows of Table 5-4 use the animal CL for rat from Table 5-3 = 21.61. It is not clear where the value of 23.63 came from. Further, the second row in Table 5-4 needs a superscript "d" indicating that the DAF for female mice was used.

Conclusions

In conclusion, we urge the agency to strengthen its final toxicological review and have outlined several inconsistencies and deficiencies that must be corrected in the final document. We 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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