Public Comments Received on Draft IRIS Toxicological Review of Perfluorononanoic Acid (PFNA) and Related Salts

This document provides a compilation of public comments received through the EPA docket (https://www.regulations.gov/docket/EPA-HQ-ORD-2021-0560), where the full set of comments as submitted are available. Comments are divided into two tables (Tables 2 and 3), with a legend of public commenters and abbreviations provided in Table 1. Table 2 compiles "Assessment-Specific Comments," organized by assessment topic area and mapped to external peer review charge questions where possible. The specific topic area groupings used in Table 2 are: systematic review methods and documentation; overview of background and assessment methods; noncancer hazard ID: general; noncancer hazard ID: developmental effects; noncancer hazard ID: hepatic effects; noncancer hazard ID: male reproductive effects; noncancer hazard ID: female reproductive effects; noncancer hazard ID: immune and thyroid effects; noncancer hazard ID: nervous systems effects; carcinogenicity; noncancer toxicity values: data selection and modeling; noncancer toxicity values: pharmacokinetics, dosimetric extrapolation, and uncertainty factors; formatting, editorial, and text clarifications. Comments that address multiple topic area groupings are repeated in each corresponding section. Table 3 compiles "Other Comments," which include comments on EPA policy or guidelines, EPA's research and assessment approach to PFAS more generally, and other efforts outside of the purview of the IRIS Program that are outside the scope of the PFNA assessment and the panel's specific charge questions. The public comments contained in Tables 2 and 3 are captured in their entirety where possible, but in some cases are truncations of the verbatim comments submitted by the public commentors. In these cases, we refer the reader to the EPA docket for the comment in full.

Table 1. Public commenter legend

ACC: American Chemistry Council	**NJDEP:** New Jersey Department of Environmental Protection
AM[1]: Aeden Marcus	**NRDC[2]:** Natural Resources Defense Council
Anon: Anonymous	**PBR[1]:** Natural Premier, Simar Bajaj, Sergio Rivera
HWP: Annika Huprikar, Lorelei Wolf, Daniel Pinckney	**RM[1]:** Ryan Murdock
JB[1]: Lucy and Nicole Jacobsen-Bellingham	**Syensqo:** Solvay Specialty Polymers
JF[1]: Jaden Benjamin Freudenberg	**VNZ[1]:** Madison Valley, Zoe Nagasawa, Zora Zheng

[1] These comments were submitted as part of a class assignment at Harvard College.

[2] Some comments provided by NRDC refer to a spreadsheet containing a list of references. Please see the docket for the attachment.

Table 2. Assessment-specific comments (organized by topic area)

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
Systematic Review Methods and Documentation			
I also support the inclusion of consideration of "potentially relevant supplemental material" that does not meet the PECO criteria in assessment methods. Both of these points ensure the consideration of a wide range of possible effects and evidence.	AM (1)	1a	*1.2.1 Literature Search and Screening*
The Rule provides evidence that EPA is moving in the right direction on emerging chemical pollutants. The Agency's willingness to update their toxicological information on these persistent chemicals illustrates a commendable commitment to the health and wellbeing of the American people, even without the certainty of settled science. The assessment succeeds in addressing the range of possible human health effects that can result from exposure to PFNA. The outlined PECO criteria and review of qualifying works adequately synthesize the literature on PFNA exposure effects associated with humans and animals.	HWP (1)	1	*1.2.1 Literature Search and Screening*
NJDEP agrees with the general approach outlined in Section 1 for the identification of studies meeting the criteria selected by IRIS, consideration of additional studies as supplemental material for evaluation of specific scientific issues, evaluation of individual studies, and synthesis and integration of studies relevant to each general health effect to determine the overall strength of evidence for that effect.	NJDEP (3)	1a	*1.2.1 Literature Search and Screening*
Specifically, NJDEP supports the consideration of toxicology studies of chemical mixtures that include PFNA as supplemental information, as stated in the last row of the table on p. 1-11. Specifically, NJDEP encourages IRIS to consider Stump et al. (2008) and Mertens et al. (2010), which are rat toxicology studies of Surflon S-111, a technical mixture of perfluorinated carboxylates (PFCAs) consisting primarily of PFNA (~74%). These studies are not mentioned in the draft IRIS document, and they may not have been identified by the literature search strategy that was used by IRIS. Although they used a mixture of PFCAs, these studies may provide valuable supplemental information for the IRIS PFNA assessment, especially because the	NJDEP (3)	1b	*1.2.1 Literature Search and Screening; 3.2 Evidence Synthesis and Integration*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
study durations are longer than in any of the other PFNA toxicology studies reviewed by IRIS. Stump et al. (2008) is a two-generation reproductive study with dosing for up to 21 weeks, and Mertens et al. (2010) is a subchronic (13 week) study with a 60-day recovery period. The New Jersey Drinking Water Quality Institute (DWQI, 2015) conducted a detailed evaluation of these studies, including estimation of the doses of PFNA and the other PFCAs present in Surflon-S-111. Based on the sex-specific differences in sensitivity to the toxicity of Surflon S-111 and the relative internal doses (serum levels) of PFNA and the other PFCAs in males and females, NJDEP concluded that the toxicity of Surflon S-111 was primarily due to PFNA. As such, the results of these studies provided valuable supporting information for the New Jersey PFNA assessment.			
I applaud the EPA for the use of transparent systematic review practices in the development of this draft toxicological review...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 display of extracted PFNA data in HAWC, which made it very easy to evaluate the statements made in the draft PFNA toxicological review. *[EPA note: please see docket for details of the submitter's footnotes]*	NRDC (2-3)	1a	*1.2 Summary of Assessment Methods*
EPA's draft toxicological assessment for PFNA may be missing relevant health and toxicological 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...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	NRDC (3-4)	1b	*1.2.1 Literature Search and Screening (missing studies)*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
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. *[EPA note: comment truncated. Please see docket for full comment]* *[EPA note: please see docket for details of the submitter's footnotes]*			
The literature and studies were clearly filtered carefully to present the most useful, valid data, and that in itself is a great public service. Given the growing importance of communicating science to a general audience, especially after the misinformation circulated during the COVID19 pandemic, having the data presented this way mitigates the chance the general public will misinterpret this information.	PBR (1)	1	*1.2.1 Literature Search and Screening*
Finally, we believe that the screening methodology mentioned in the Literature Search and Screening Results section may merit alteration. It is mentioned that of 3,316 records, only 585 were actually deemed up to PECO standards (toxicological review 2-2). An additional 946 other studies were tagged as supplemental studies. Even though the PECO framework appears to be a reliable and standardized framework for environmental exposure studies, we believe there is much merit in using a broad array of evidence to offer greater confidence about exposure outcomes. With the inclusion of more data, we should be able to offer better standards for protection and better distribute resources to those who need it most. Would it be possible to use a more flexible standard for choosing studies, or to find some way to maximize the amount of high-quality data used to inform the report? We understand that all studies and reports published in scientific journals or sites may not be valid, but we are skeptical that using only 585/3316 (17.6%) of all literature on PFNA and 585/989 (60%) of "advanced, full text" studies seems like we are underutilizing the available data — to our own detriment. Given the lack of carcinogenicity studies in this report, this paucity feels all the more profound. Changing the screening methodology to include more studies would ensure greater	PBR (2)	1	*1.2.1 Literature Search and Screening*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
understanding of environmental exposure effects of PFNA and bolster, not weaken, the value of scientific research in this area.			
Overview of Background and Assessment Methods			
The Draft Assessment includes incomplete or inaccurate information on the properties and occurrence of PFNA that requires clarification or correction.	ACC (1)	N/A	*1.1 Background Information on PFNA*
Among the identified issues, the Table of predicted physicochemical properties requires clarifying edits and fixes. Table 1.1 indicates that "predicted average values" are shown but fails to identify how the values were derived. While the Draft Assessment indicates that the EPA CompTox database was used as the source of the values, information is lacking and should be provided regarding methods for predicting values. Normally, the upper and lower bounds of the ranges are presented to provide readers with context for the purported range of values. The range of values is provided in USEPA's CompTox database, therefore, the range of values should be included in the Draft Report. The fact that the Koc values of the salts versus the free acid are nearly identical should be explained, as this is unlikely to be accurate.	ACC (3)	N/A	*1.1.1 Physical and Chemical Properties*
The discussion in the Executive Summary and Section 1.1.2 regarding potential sources of PFNA to the environment appears to be based on dated assumptions and information that do not consider more recent occurrence data, such as that compiled by California's Regional Water Quality Control Board. This text should be corrected after a thorough review of available data. *[EPA note: please see docket for details of the submitter's footnotes]*	ACC (3)	N/A	*Executive Summary; 1.1.2 Sources, Production, and Use*
The statement that "inhalation and dermal routes of exposure also appear to be relevant exposure pathways for PFNA" is not supported by any data and should be removed. The Draft Assessment attributes the Agency for Toxic Substances and Disease Registry's (ATSDR) 2021 Toxicological Profile as support for the statement that the dermal and inhalation routes of exposure may be relevant for PFNA.	ACC (3)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
However, there are no data that support this statement. In fact, ATSDR states "[d]ermal absorption of PFAS is limited and does not appear to be a significant route of exposure for the general population" and owing to the nonvolatile nature of PFAS, "inhalation is not a typical exposure route for the general population." *[EPA note: please see docket for details of the submitter's footnotes]*			
The Draft Assessment should indicate in the discussion on exposure from food (Section 1.1.4) that PFNA is rarely detected in the U.S. commercial food for residential use and include reference to the U.S. Food and Drug Association (FDA) PFAS in food testing program. Foods tested for PFAS by FDA were collected as part of the Total Diet Survey (TDS), an ongoing FDA-run program that began back in 1961, to monitor nutrients and contaminants in food consumed in the U.S. The samples analyzed for PFAS in the 2021 sampling event included vegetables, fruits, meats and related products, cheeses, water, dairy, and bread – all major components of the average U.S. diet. Only one sample (baked cod) had detectable levels of PFNA (233 ng/kg). According to the FDA, the detected levels "do not present a human health concern." *[EPA note: please see docket for details of the submitter's footnotes]*	ACC (3)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure*
In evidence synthesis and integration, I strongly support the assumption of human relevance of animal findings without evidence to the contrary. I also support the inclusion of consideration of "potentially relevant supplemental material" that does not meet the PECO criteria in assessment methods. Both of these points ensure the consideration of a wide range of possible effects and evidence. I am reassured by the consideration of insensitivity in the review of epidemiological and animal toxicological studies to account for whether a particular was able/likely to detect a true effect. I know that bias toward the null and lack of statistical power can have significant effects on the assessment of evidence, and I value the consideration of these factors in the Review.	AM (1)	N/A	*1.2.2 Evaluation of Individual Studies*
I felt under section 1.1.4. Water, the discussion of PFNA detections in 9 of 24 studies by Holder et al. (2023) was useful information however underplays the widespread proliferation of PFNA in water. It also could arguably be construed as meaning there are only 24 studies that have done such measurements when that is not the case with recent scientific studies on PFNA and related PFAS that exhibit similar	Anon (1)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
properties. Additionally, occupational exposure is mentioned however limited to discussion only on firefighters. While firefighters are most likely at risk of increased PFNA exposure, this downplays the many other jobs that have increased PFNA exposure and could be construed as taking advantage of the already dangerous field of firefighting as one that should accept other risks.			
In ranking literature under four possible classifications I feel that the classifications could be subdivided to reveal the gradient within each category. For instance, a Low confidence study that is denoted as such for having inadequate sensitivity versus one denoted as Low for potential bias may be on different levels of confidence rather than the same denotion [sic] and could provide better insight.	Anon (2)	2	*1.2.2 Evaluation of Individual Studies*
To better safeguard the public and offer more comprehensive recommendations, the assessment should consider the following: identification of more professions that have heightened exposure risk, and use of a precautionary approach in regulations reflecting even conclusions of low certainty. These comments suggest that the policy should factor in a stricter precautionary approach in exposure limits set in light of the overall confidence in both epidemiological and animal evidence for a wide range of human health effects. Additionally, the policy should more fully identify public actors that contribute PFNA to important resources such as water, food, and air, which are known sources of PFNA contamination.	HWP (2)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure; Risk Management*
The risk assessment should expand its review of high-risk populations and professions in the United States. Though exposure through different environmental media (water, air, and dust) is represented, identification of the causes of exposure is not sufficiently considered. Additional reviews of occupational and geographic exposure are necessary to better represent the risks present among various demographic groups across the country. Contact with PFAS/PFNA is shown to be heightened in certain professions. This is evident in the discussion of PFNA contamination sources, which included analysis of military and industrial sites. Failure to thoroughly address the most common of these occupations is likely to result in continued heightened exposure and a lack of intentional, transparent reform in those industries.	HWP (2)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
The policy lacks clarity on the topics of vulnerable communities and their risk tolerance. The policy identifies risk assessment on the basis of sex, but does not report whether there are differences in risk based on ethnicity. The Policy should address any disparities in the effect of PFNA exposure based on demographic populations reported in the literature.	HWP (2)	6	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure; 4.3 Conclusions Regarding Susceptible Populations and Lifestages; 5.2 Noncancer Toxicity Values*
This report is a spectacular and intimidating project that has been undertaken with incredible expertise, care, and precision. In reading this report, I was particularly impressed by the documentation of the sources considered in the appendices alongside the summary information about the sources including the units of analysis, confidence intervals, and other metrics that are easily compared between studies. As a burgeoning professional in the field, I am relieved that this information was made available, as when I was reading through the report, I was able to assess the claims regarding which studies were considered and how much weight was given to which results.	JF (1)	1	*1.2 Summary of Assessment Methods*
…there is quite a bit of vagueness in how the studies were evaluated with respect to the terms “evidence demonstrates”, “evidence indicates (likely)”, “evidence suggests”, “evidence inadequate”, and “strong evidence supports no effect.” While these are used periodically, I could not find a dedicated portion in the appendix or otherwise that describes the classification of each study’s results into these categories. Even if there is a level of expert opinion in the classification of the results, it would greatly benefit the conclusions of the report if these categories were explained and joined together with the other summary information for each of the studies provided in the appendices.	JF (1)	1a	*1.2.4 Evidence synthesis and integration; Appendix A (PFAS Protocol)*
More transparency is also required with respect to how different data are considered in tandem, another facet of this report that could be easily added to the appendices. Although in specific sections, there is a level of transparency (i.e. on page 3-38 with respect to the results of Wolf et al. (2010) to Das et al. (2015): “One might wish to use the serum concentrations in PND 1 mouse pups measured by Wolf et al. (2010) to extrapolate those observed endpoints, but comparable data	JF (2)	1a	*1.2.4 Evidence synthesis and integration; Appendix A (PFAS Protocol)*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
are not available for Wolf et al. (2010) making any comparison between the studies on such a basis very complicated" OR on page 5-21 "If no biological rationale for selecting the NOAEL/LOAEL is available, statistical significance was used as the basis for selection).			
These cross-study comparisons likely exist in many, many cases throughout the considered corpus, but the way that the cross-study comparisons are handled are not transparent on a study to study basis. This is especially pertinent given the variety of metrics (i.e. NOAEL/LOAEL/RfD) and extrapolating constants used in pharmacokinetic modeling (i.e. human-animal uncertainty factor when calculating the benchmark dose) that may vary from study to study. While broad statements regarding special cases tell us something about how you treated those special cases, it is important to know exactly how the results of each study are considered. Perhaps if there were a protocol that explains a flow of decision making with respect to the study's metric contents, you would not have to include the in-depth study-specific metric handling in the appendix?	JF (2)	1a	*1.2.4 Evidence synthesis and integration; Appendix A (PFAS Protocol)*
NJDEP agrees with IRIS's assumption that effects observed in animal studies are relevant to humans unless there are data to indicate otherwise (p. 1-16, line 38 – page 1-17, line 1).	NJDEP (3)	2	*1.2.4 Evidence Synthesis and Integration*
p. 1-4, lines 23-26. The draft document states: "Vapor-phase PFNA is not expected to be susceptible to direct photolysis by sunlight but can be degraded in the atmosphere by reacting with photochemically produced hydroxyl radicals (ATSDR, 2021; NLM, 2017, 2016, 2013). The atmospheric half-life for these reactions is estimated to be 31 days for PFNA (NLM, 2013)." ATSDR (2021), which is cited by IRIS, does not mention degradation by reaction with photochemically produced hydroxyl radicals, and NLM (2013), which is also cited by IRIS, attributes this information to Meylan and Howard (1993), which is entitled "Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxyl radicals and ozone." As written, these sentences indicate that it is known that PFNA in the vapor phase degrades in the atmosphere. However, the statement is based on predictions from computer modeling, not empirical data. At a minimum, this sentence should be revised to make it clear that	NJDEP (6)	N/A	*1.1.3 Environmental Fate and Transport*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
the degradation of PFNA in the vapor phase mentioned here was predicted by modeling, and was not identified from empirical data on atmospheric degradation.			
p. 1-4, lines 30-31. The statement that "PFNA would be expected to have limited mobility in soil…" should be clarified since it appears to be inconsistent with lines 18-19 of this same page which mentions deposition of PFNA from air to soil followed by migration through soil to groundwater.	NJDEP (6-7)	N/A	*1.1.3 Environmental Fate and Transport*
p. 1-5, lines 14-20. The information on UCMR5 should be revised to state that UCMR5 includes all public water systems serving more than 3300 (not 10,000) people and a representative sample of smaller systems. Also, it should be stated that UCMR5 is being conducted in 2023-2025 and that the results mentioned on lines 18-20 are from the initial data (as of the appropriate date) and do not reflect the full UCMR5 dataset. Finally, inclusion of results from UCMR3 should be considered, while noting that UCMR3 was conducted in 2013-15, included all public water systems serving more than 10,000 people, and used a higher PFNA reporting level (20 ng/L) than UCMR5 (4 ng/L).	NJDEP (7)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure*
p. 1-5, lines 27-28. Regarding detections of PFNA in fish, it should also be mentioned that elevated levels of PFNA were detected in fish from the Delaware River in areas impacted by discharge of PFNA from a New Jersey industrial facility (DRBC, 2009; DWQI, 2015). Alternatively, this could be mentioned in the section on Military and Industrial Sites (p. 1-6).	NJDEP (7)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure*
p. 1-6, lines 27-29. This sentence should be clarified to indicate that PFNA was detected in a public drinking water supply well, rather than only in groundwater that was not necessarily used as a drinking water source (Post et al., 2013; DWQI, 2015). Also, as written, the MRL reported for PFNA appears to be 0.096 µg/L. However, 0.096 µg/L was the PFNA concentration detected in the contaminated well, and the MRL for PFNA in this study was 0.004 µg/L (Post et al., 2013; DWQI, 2015).	NJDEP (7)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure*
p. 1-7, lines 7-9. It is stated that NHANES PFNA biomonitoring data in Table 1-3 show that "median values in human sera declined from 0.6 µg/L between 1999 and	NJDEP (7)	N/A	*1.1.4 Potential for Human Exposure and Populations*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
2000 to 0.4 µg/L between 2017 and 2018 (25th–75th percentiles were 0.4, 0.9 and 0.3,0.7 respectively)." This should be clarified to indicate that median values increased from 0.6 µg/L in 1999-2000 to 1.23 µg/L in 2007-2008 and 2009-2010 and that this increase was followed by a decrease to 0.4 µg/L between 2009-10 and 2017-18.			*with Potentially Greater Exposure*
p. 1-9, lines 26-28. This sentence should be revised to indicate that the PFNA detected in the blood serum of professional ski waxers by Nilsson et al. (2010a,b) resulted from metabolism of inhaled fluorotelomer alcohols from ski wax to PFNA rather from exposure to PFNA itself.	NJDEP (7)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure*
I applaud the EPA for the use of transparent systematic review practices in the development of this draft toxicological review...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 display of extracted PFNA data in HAWC, which made it very easy to evaluate the statements made in the draft PFNA toxicological review. *[EPA note: please see docket for details of the submitter's footnotes]*	NRDC (2-3)	1a	*1.2 Summary of Assessment Methods*
We appreciated how the report included simple context about PFNA, such as their chemical properties, sources, and environmental fates — foundational information for students, journalists, and other non-experts. We also appreciated the detailed descriptions of at-risk populations, sites likely to be contaminated with PFNA, and foods that are more likely to contain PFNA.	PBR (1)	N/A	*1.1 Background information on PFNA*
We were also impressed with the integrating of evidence from human epidemiology and animal toxicology studies, as well as the detailing of how PFNA was tested across species, exposure pathways, and exposure lengths. This comprehensive approach strengthens the overall conclusions compared to relying solely on one type of data. But to narrow in on one example, the assessment prioritizes health effects in fetuses, children, and pregnant women by acknowledging the potential for	PBR (1)	2	*3 Pharmacokinetics, Evidence Synthesis, and Evidence Integration; 4.3 Conclusions Regarding Susceptible Populations and Lifestages*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
heightened vulnerability during critical developmental stages. One of the most effective ways to communicate the health risks of toxic substances to the public has always been illuminating the intergenerational impacts chemicals have on our health. This focus aligns with growing concerns regarding the impact of PFAS exposure on early life health and is thus much appreciated.			
We understand that certainty about exposure outcomes is difficult and requires an extraordinarily high level of evidence — and that certainty lies on a spectrum. However, overall, we feel that the report is not clear enough in explaining the severity of risk. Harmful effects backed by an abundance of evidence should be clearly distinguished from effects with little or no evidence. The toxicological review uses phrases like "evidence demonstrates," "evidence indicates," and "evidence suggests" all to mean different levels of certainty even though to a lay person or most nonexperts, these three terms are roughly synonymous. To offer a somewhat ridiculous analogy, this seems like defining the danger of a gun, rock, and paper ball as "lethality demonstrated," "lethality indicated," and "lethality suggested". It is understandable that the report wants to remain objective, but high risks, such as developmental and birth weight effects, and low risks should be clearly distinguished rather than obscured with slight changes in diction. Furthermore, given that many medium high confidence effects have robust evidence supporting them, it is safe to say that these are very likely to be effects of PFNA.	PBR (3)	2	*1.2.4 Evidence Synthesis and Integration*
Further, the existing risks identified in this Review may be unequal across populations - for example, communities with existing maternal/neonatal health disparities may have worse outcomes for babies born with developmental impairments than more resourced communities, increasing the risk of exposure of community members to PFNA. It is further likely that exposure of PFNA is elevated in historically marginalized communities, compounding the issue. This applies as well to the categories of hepatic and male reproductive harms outlined. The EPA is a major entity involved in Environmental Justice (EJ) efforts, and chemical risks are closely related to EJ. The toxicity risks in a purely medical sense are not useful to policymakers as not all parts of the country and populations are facing these same risks. Further nuance in the hazard identification would enable a sense of how social determinants of health may alter the nature of risks of PFNA. It could also	RM (2-3)	6	*4.3 Conclusions Regarding Susceptible Populations and Lifestages; 5 Derivation of Toxicity Values*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
demonstrate how PFNA impacts may relate to broader inequities to motivate action to be taken. All told, while the scientific approach taken in the Review is expansive and highly informative, delving into contextual factors would greatly strengthen the content.			
As explained in the comments below, the text of the Tox Review related to sources of PFNA to the environment must be revised because it is based on outdated assumptions about uses and sources of PFNA. These assumptions are inconsistent with the occurrence of PFNA in the environment and the demonstrated presence of PFNA in AFFF.[2] The draft text regarding potential PFNA sources in the Executive Summary, ES.1, and in Section 1.1.2 needs to be corrected because it includes outdated assumptions that are: unsupported by data; inconsistent with the occurrence of PFNA in the environment including years of data from sites around the country; and fails to acknowledge research and environmental data that confirm that PFNA was present in AFFF and was the primary fluorosurfactant in some AFFF. *[EPA note: please see docket for details of the submitter's footnotes]*	Syensqo (2)	N/A	*1.1.2 Sources, Production, and Use; Executive Summary*
Specific Comment 1. The references relied in the Tox Review as to sources of PFNA were not based on a mass balance or any comparative analysis of data as to relative amounts of PFNA used and released to the environment. Section 1.1.2 states that "most PFNA in the global environment is posited to be linked to its historical use as a processing aid in PVDF (Lohmann et al., 2020; Wang et al., 2014b; Prevedouros et al., 2006)". However, none of these citations support a conclusion that most of the PFNA in the environment is related to its use as a processing aid. For example, there are no data that provide a mass balance comparison between PFNA used and released in AFFF or through other sources, compared to PFNA mass used and potentially released to the environment at PVDF manufacturing locations. Prevedouros et al. (2006), a study from eighteen years ago, provides an estimated volume released globally across three decades associated with PVDF manufacturing, however, no reference is provided regarding the potential global release of PFNA in AFFF or from any other source.	Syensqo (2-3)	N/A	*1.1.2 Sources, Production, and Use*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
Specific Comment 2. Numerous studies have demonstrated that the use of AFFF for training and emergency response is a primary source of PFAS to the environment. As has been well documented, AFFF containing grams per liter levels of fluorosurfactant was released directly onto the ground and as a result, the release of a small quantity of AFFF can impact groundwater over a large area.[3] Throughout the United States, there have been millions of gallons of AFFF released to the environment, which far outweighs the mass of PFNA used to manufacture PVDF. *[EPA note: please see docket for details of the submitter's footnotes]*	Syensqo (3)	N/A	*1.1.2 Sources, Production, and Use*
Specific Comment 3. Occurrence data demonstrates the presence of elevated levels of PFNA at many sites that are not near or associated with PVDF manufacturing, including many sites where AFFF was used. The California Regional Water Quality Control Board has compiled an extensive database of PFAS detections within the state. The California database includes: • Almost 1,600 detections of PFNA at or above 10 ppt; • The highest levels detected of up to 26,300 ppt of PFNA in groundwater at an airport (the San Diego International Airport); and • The second highest level detected of 24,000 ppt of PFNA in groundwater at a bulk oil terminal (IMTT Richmond Terminal).[4] Among the highest levels of PFNA detected in groundwater in New Jersey is at Chemours, Chambers Works (concentrations up to 500,000 ppt), a site where none of the identified sources are associated with PVDF manufacture.[5] Surface water samples from the Conasauga River in Georgia downstream of carpet manufacturing were found to contain up to 369 ppt of PFNA.[6] Sampling of the effluent from an electroplating facility in Ohio by Region 5 of USEPA detected 13,100 ppt of PFNA.[7] Anderson et al. 2016[8] shows that early data collected by the U.S. Air Force demonstrate high detection frequencies of PFNA in soil and groundwater in various AFFF release locations, as shown by the USEPA in Table 1-2. In addition, there are significant PFNA data from sites around the country where AFFF was used, such as: • Flint Hills Resources refinery in North Pole, Alaska, used National Foam AFFF, and PFNA was detected at the refinery in groundwater up to approximately 5,000 ppt and in soil up to 3,800,000 ppt[9]	Syensqo (3-5)	N/A	*1.1.2 Sources, Production, and Use*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
• Mayville, New York - PFNA was detected in groundwater up to 110,000 ppt and up to 6,300 ppt in surface water at a football field and near the municipal building where fire training occurred using AFFF.[10] • Paulsboro, New Jersey – PFNA was sampled for and detected in 2024 in recovery wells and production wells at the Paulsboro Refinery Company (PRC) site where AFFF, including National Foam AFFF was used.[11] At the downgradient PRC property boundary within the NJDEP-defined wellhead protection areas of three Paulsboro public water supply wells[12], including Paulsboro Well 7, PFNA was detected in 2024 in groundwater recovery and production wells as high as 597 ppt. This data is being generated 15 years after PFNA was detected in Paulsboro Well 7 at 96 ppt[13] and more than 10 years after treatment for PFNA was installed on that public well. *[EPA note: please see docket for details of the submitter's footnotes]*			
Specific Comment 4. PFNA has been confirmed to be the primary fluorosurfactant in certain grades of National Foam AFFF. Contrary to prior assumptions, direct measurement of PFNA in different brands and grades of AFFF in academic research has demonstrated that PFNA was the primary fluorosurfactant used in some non-Milspec AFFF. Analysis by Jennifer Field of Oregon State University found up to 1,900,000 ppt of PFNA in certain formulations of National Foam AFFF.[14] *[EPA note: please see docket for details of the submitter's footnotes]*	Syensqo (5)	N/A	*1.1.2 Sources, Production, and Use*
Specific Comment 5. Consistent with the academic research results, PFNA has been found in the environment at high levels at the facility where National Foam AFFF was manufactured and at refineries and other locations where National Foam AFFF was used. Reinforcing the academic finding that PFNA was the primary fluorosurfactant in certain grades of National Foam AFFF, the presence of high levels of PFNA in National Foam AFFF is further demonstrated by groundwater data at the former National Foam manufacturing site in West Chester, PA, where PFNA was found up to 85,000 ppt in site groundwater.[15] An EPA study of the adjacent surface water, Goose Creek, found concentrations of PFNA up to 1,810 ppt downstream of the former National Foam facility.[16]	Syensqo (5)	N/A	*1.1.2 Sources, Production, and Use; 1.1.3 Environmental Fate and Transport*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
Moreover, PFNA has been detected in groundwater at the North Pole, Alaska and Mayville, New York sites referred to above and at several sites in the Delaware River Basin where National Foam AFFF was used, e.g., up to 3,100 ppt in shallow groundwater at the former PES refinery in Philadelphia.[17] *[EPA note: please see docket for details of the submitter's footnotes]*			
Specific Comment 6. National Foam AFFF was widely used in the Delaware River Basin Responses to an 2021 New Jersey Department of Environmental Protection (NJDEP) survey, 62% of users of AFFF, indicated the use of various National Foam products.[18] *[EPA note: please see docket for details of the submitter's footnotes]*	Syensqo (6)	N/A	*1.1.2 Sources, Production, and Use*
Specific Comment 7. Significant ratios of branched PFNA isomers have been detected in groundwater samples. This cannot be explained by the use of Surflon S-111 as a process aid in PVDF manufacturing. Surflon® S-111 has been identified as a predominantly PFNA fluorosurfactant process aid used in PVDF manufacturing. Prevedouros, et al. TABLE S2. Commercial PFCA Products Characterization. However, because it was manufactured as a linear molecule through fluorotelomerization, use of Surflon S-111 cannot explain the occurrence of branched PFNA in the environment. Id. The occurrence of branched PFNA in the environment in areas where AFFF was used suggests the use of a branched PFNA in AFFF that has not yet been identified.[19] *[EPA note: please see docket for details of the submitter's footnotes]*	Syensqo (6)	N/A	*1.1.2 Sources, Production, and Use; 1.1.3 Environmental Fate and Transport*
Firstly, we are very appreciative of your direct communication about the sub-populations that experience more risk than others, based on their diet and occupational exposure. In section 1.1.4, on pages 1-9, you explicitly name subpopulations that may suffer from these additional exposures: specifically "populations that rely on seafood and/or subsistence diets, possibly including some Native American tribes", firefighters, and those who engage in professional ski waxing, as well small children and women of childbearing age. So often, those who suffer from the most exposure to potentially dangerous chemicals are marginalized communities and small children. We see this pattern very clearly in PFNA exposure levels and appreciate that you have named that in your risk assessment. When	VNZ (1-2)	N/A	*1.1.4 Potential for Human Exposure and Populations with Potentially Greater Exposure; 4.3 Conclusions Regarding Susceptible Populations and Lifestages*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
determining safe levels of exposure, and thus safe levels of emittance, it's crucial to regulate such that the most vulnerable populations are protected. However, we urge the EPA to take the extra step to actively engage with these sub-populations who are disproportionately impacted by environmental hazards, to ensure that their perspectives and concerns are taken into account in the decision-making process. This can involve conducting outreach efforts, hosting public forums, and providing accessible educational materials to enhance understanding of complex scientific concepts and regulatory processes. Through fostering genuine dialogue and collaboration, the EPA can cultivate trust and credibility within these communities, thereby advancing transparency and accountability in environmental governance. Moreover, by demonstrating a commitment to inclusivity and responsiveness, the EPA will also bolster trust among the broader public, fostering a stronger sense of confidence in the agency's decision-making processes. Furthermore, the effects examined in this draft are focused primarily on reproductive effects in men and women, and fetal development. While we understand that these are very important aspects to focus on and that there is certainty in hazard evidence for developmental effects, we wonder if the focus is too narrow, and if there are other effects of PFNA exposure on other demographics of people that are not discussed in this report.			
Secondly, we suggest that EPA makes it clearer what the various classifications of hazard mean; the language that EPA currently uses are the phrases 'evidence demonstrates', 'evidence indicates', 'evidence suggests', and 'evidence is inadequate'. We acknowledge that these phrases are the standard in toxicological hazard assessments, but feel that they are insufficiently accessible to the general public. "Evidence is inadequate" could, for example, easily be interpreted to mean that there is not high risk from PFNAs, when in fact we simply don't have the data to definitively prove that they cause various health outcomes, though there is evidence of a relationship between them. Clear language could involve providing more context and explanation about the level of uncertainty in the available evidence, as well as highlighting the importance of precautionary measures in the absence of conclusive data. By improving transparency and clarity in its hazard classifications, the EPA can help empower individuals and communities to make informed decisions	VNZ (2)	2	*1.2.4 Evidence Synthesis and Integration*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
about their health and well-being. These phrases currently utilized reflect the EPA's use of risk assessment, rather than precaution, in regulatory decisions.			
To begin to rectify the problems with risk assessment in this report, we recommend that EPA explicitly define each of the hazard identification terms at the beginning of the report. This can prevent policymakers from being mistaken or confused about the certainty with which we can use. By providing clear definitions, policymakers can make more informed decisions based on the available evidence and uncertainties. While this step alone may not resolve all the challenges with risk assessment in the American government, we view it as a crucial first step towards integrating the precautionary principle into all EPA assessments in the future. By enhancing transparency and clarity in hazard identification, EPA can better protect public health and the environment while promoting informed decision-making.	VNZ (3)	2	*1.2.4 Evidence Synthesis and Integration*
Noncancer Hazard ID: General			
In section 4.1. Summary of Conclusions for Noncancer Health Effects, [the Toxicological Review] does a great job in carefully laying out the differences between evidence indicating and suggesting. However, it shows a weakness of the animal studies which is that exposed animals were only exposed during short-term and developmental periods, and no chronic exposures were included.	Anon (1)	2	*4.1 Summary of Conclusions for Noncancer Health Effects*
The assessment also thoroughly justifies the choices made with regards to evidence integration of human epidemiological studies and animal studies in assessing PFNA health risks. *[EPA note: Comment truncated. Please see docket for full comment.]*	HWP (1)	2	*3.2 Noncancer Evidence Synthesis and Integration*
The Policy thoroughly addresses health concerns associated with PFNA exposure, but should better reflect the nuance of the scientific literature through guidelines on low-exposure levels. The scientific literature reflects ample risk associated with exposure, but emphasizing lower uncertainty levels for immune, thyroid, neurodevelopmental, and cardiometabolic effects may be detrimental to the overall goal of risk mitigation.	HWP (2)	2	*3.2 Noncancer Evidence Synthesis and Integration*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
NJDEP agrees with IRIS that "the potential for confounding by co-occurring PFAS to bias effect estimates are a concern in epidemiological studies" (p. C-1, lines 1-2), and that "it is often not possible to fully disentangle the associations when high correlations [among PFAS] are observed" (p. 1-14, lines 34-35). NJDEP appreciates the thorough and thoughtful discussions of these complex issues in Sections 1 and C-1 of the draft IRIS documents, and NJDEP agrees that IRIS has appropriately considered these issues in its use of human epidemiology data as the basis for Reference Doses for PFNA.	NJDEP (3)	2a, 2b, 2d	*3.2 Noncancer Evidence Synthesis and Integration; 1.2 Summary of Assessment Methods; Appendix C*
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 that PFNA causes developmental harm and likely causes liver, and male reproductive effects in humans.	NRDC (3)	2	*3.2 Noncancer Evidence Synthesis and Integration; 4.1 Summary of Conclusions for Noncancer Health Effects; 5.2 Noncancer Toxicity Values*
The early pages set out clearly those health effects with sufficient dose to draw judgement, effectively sharing developmental, liver, and male reproductive integration judgements of the likelihood of negative health outcomes to those systems. The Review assumes human relevance of animal evidence, which does introduce the potential for ongoing scientific research to increase or decrease projections of human risks derived from animal data. However, this is the best case scenario to avoid unethical human experimentations. Specific details of how PFNA accumulates in organs were liberally included in the Review and engaged with sex-based differences not limited to gestation, as well as age-based discrepancies, which offers a good summary of PFNA exposure risks. Hundreds of pages of the Review recount robust scientific findings for the dangers of PFNA to animals and humans. This leads to high confidence in the findings discussed in the conclusion and does not raise concerns that corners were cut in preparing the review. *[EPA note: comment truncated. Please see docket for full comment]*	RM (1)	2	*3.2 Noncancer Evidence Synthesis and Integration; 4.1 Summary of Conclusions for Noncancer Health Effects*
We believe that the EPA should use the precautionary principle more explicitly in toxicological hazard assessments. The burden of proof should not lie with the EPA or the affected communities to demonstrate that PFNAs cause health outcomes. We	VNZ (2-3)	N/A	*4.1 Summary of Conclusions for Noncancer Health Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
have learned from historical examples (benzene, MBTE, etc.) that such a burden is often too high for present-day science. Therefore, we advocate for a proactive approach that prioritizes precautionary measures in the face of uncertainty. By embracing the precautionary principle, the EPA can demonstrate its commitment to protecting public health and the environment, even in the absence of conclusive evidence. This approach aligns with the principle of 'better safe than sorry,' which emphasizes the importance of taking preventive action to mitigate potential risks, particularly when the stakes are high. The use of the precautionary principle would be helpful in cases such as the ones outlined in sections ES.4 and ES.5, where there was low confidence or insufficient evidence to understand either the carcinogenic effects of PFNA, or the noncarcinogenic effects through inhalation. The latter is particularly important, given that PFNAs have been detected with high frequency in dust in fire stations across the U.S. and Canada. While we understand that there is not much that can be done about the lack of evidence, there should be a general avoidance of inhalation. Furthermore, we urge the EPA to consider the potential long-term consequences of inaction and the ethical imperative to prioritize the well-being of current and future generations. We understand that this draft is not a regulatory decision on the continued use of PFNAs and related salts, but we encourage the IRIS to intentionally integrate precautionary language into its hazard identification conclusions.			
Noncancer Hazard ID: Developmental Effects			
the human evidence for a decrease in birth weight is mixed with only one quarter of the studies identified by the Agency reporting an association between PFNA exposure and reduced birth weight	ACC (1)	2a	*3.2.2 –Developmental Effects*
The summary of studies reviewed in EPA's meta-analysis indicates that of the twenty-seven studies considered, only seven reported a statistically significant decrease in birth weight. This fact contrasts sharply with the draft Assessment's characterization of the data supporting an effect on birth weight as "robust." In summarizing the overall epidemiological data base for birth weight effects, the draft notes – Overall, few patterns were evident across different comparisons of the	ACC (4-5)	2a	*3.2.2 Developmental Effects; 5.2 Noncancer Toxicity Values*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
mean BWT studies examining the overall population. For example, no evidence of any impact of sample timing was shown among the 16 medium and high confidence studies, as 8 of these were based on early biomarker sampling. The six null studies did not appear related to exposure contrasts or levels or to overall study sensitivity, as five of them had adequate sensitivity. The lack of significance of low birth weight is supported by a recent review by ATSDR which found for PFNA that "most studies did not find an association between birth weight and maternal PFNA levels." The null studies include some of the larger sample sizes among the studies considered. It is not clear why thoughtful consideration of the available weight of evidence was abandoned in lieu of the meta-analysis. Moreover, the Agency has provided no rationale for why such a meta-analysis should be considered more informative. The authors of the meta-analysis indicate "that pregnancy hemodynamics may lead to bias in epidemiological studies –especially those based on samples collected late in pregnancy,"[13] but observed no significant difference when the timing of the sample is considered. In support of EPA's reliance on the meta-analysis, the Draft Assessment notes that the point of departure (POD) is consistent with those identified from three individual human studies[14] but fails to consider the numerous other null studies. *[EPA note: please see docket for details of the submitter's footnotes]*			
Although the authors provide evidence to support the choice of a random effects model, they do not discuss the potential impact of the extensive manipulation of the study data on their results. This is particularly important given the considerable number of studies that did not report a decrease in birth weight...Many of the studies cited by Wright et al. do not adjust for some of the highest risk factors for LBW, including gestational age in a number of high-confidence studies, which has a large impact on the reported birth weight data. Some of the other risk factors identified in the general literature associated with LBW that were not adjusted for in most, if at all. Similarly, coexposures to other contaminants are an important consideration for LBW, with none of the studies included in Wright et al. examining potential chemical exposures (outside of tobacco smoke) that could impact birth weight (e.g., arsenic, lead). *[EPA note: comment truncated. Please see docket for full comment]*	ACC (6-7)	2a	*3.2.2 Developmental Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
EPA's evidence synthesis conclusion of "robust" human evidence for developmental effects, specifically reductions in birth weight, is inconsistent with the IRIS Handbook. For the EPA's meta-analysis, the agency relies on a mixture of six high- and four medium-confidence studies that measured PFNA in early pregnancy. The conclusions described by the authors of these studies do not consistently support EPA's finding of "robust" evidence, which the IRIS Handbook describes as having "very little uncertainty." Several of these studies reported null, inconsistent, or nonsignificant associations with PFNA exposures and reduced birth weight. For example, the high confidence study Bach et al. (2016) stated that "[o]verall, we did not find strong or consistent associations between PFAAs and birth weight or other indices of fetal growth."[25] The Draft Assessment acknowledges that Bach et al. did not show an inverse association based on continuous PFNA measurements, stating that it showed "mixed results" and "some suggestion of nonsignificant increase in mean [birthweight] with increased PFNA."[26] Manzano-Salgado et al. (2017), which EPA also designates a high-confidence study, reported that "PFAS were not statistically significantly associated with birth outcomes" and that "PFHxS, PFOA, and PFNA showed weak, non-statistically significant associations with reduced birth weight."[27] Sagiv et al. reported only a weak association with birth weight and PFNA exposure. Thus, the results of several of the high-confidence studies are inconsistent and do not support a classification of "robust" as defined by the IRIS Handbook for the overall weight of evidence. *[EPA note: please see docket for details of the submitter's footnotes]*	ACC (7-8)	2a	*3.2.2 Developmental Effects*
Though EPA's approach of including only studies measuring exposure during early pregnancy in the meta-analysis accounts for some confounding of pregnancy hemodynamics, USEPA acknowledges that there are "residual uncertainties related to some potential sources of bias by sample timing and uncertainty regarding potential impact of PFAS co-exposures." The IRIS Handbook classifies "moderate" evidence as a signal of effect with some uncertainty. Consistent with this guidance and echoed by the Department of Defense (DOD) in its interagency comments, the highest rating warranted for the evidence synthesis conclusion is "moderate."	ACC (8)	2a	*3.2.2 Developmental Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
NJDEP agrees with the IRIS conclusions (p. xxii, summarized in Table ES-1) that the available evidence demonstrates that PFNA exposure causes developmental effects and that it is likely to cause hepatic and male reproductive effects, given sufficient exposure conditions.	NJDEP (4)	2a, 2b, 2c	*Executive Summary; 3.2.2 Developmental Effects; 3.2.3 Hepatic Effects, 3.2.4 Male Reproductive Effects*
NJDEP agrees with IRIS that there is "robust evidence for effects of PFNA exposure on fetal growth restriction, specifically decreased birth weight." There are an unusually large number of epidemiological studies that evaluated PFNA and birth weight, and USEPA's evaluation of these studies is exceptionally thorough. As shown in Table 5-9, the very similar BMDLs were obtained from the meta-analyses of all 27 studies, the 22 medium and high confidence studies, and 10 or 11 (depending on whether one study with a different exposure metric is included) early pregnancy studies (all of which were medium or high confidence), and this consistency strengthens the confidence in use of the selected BMDL from the meta-analysis of 10 early pregnancy studies. NJDEP also agrees that the developmental effects observed in rats and mice support the conclusion that PFNA causes developmental effects in humans.	NJDEP (4)	2a	*3.2.2 Developmental Effects; 5.2 Noncancer Toxicity Values*
p. 3-55, lines 15-17. The information on the number of studies is unclear, since the number of studies that reported numerical birth weight data is not mentioned. Did all of the 41 studies report numerical birth weight data as well as other information such as small for gestational age (SGA) or low birth weight (LBW) (8 studies), birth length (20 studies), or head circumference (17 studies)?	NJDEP (8)	2a	*3.2.2 Developmental Effects*
p. 3-129, lines 3-14. When discussing the post-weaning body weight decrements caused by PFNA in the Das et al. (2015) mouse developmental study, it is important to mention that this effect persisted after most PFNA had been eliminated. It is also important to mention that the closely related compound, PFOA, did not cause persistent post-weaning body weight decrements in a study of similar design from the same laboratory (Lau et al., 2006). These points are discussed in the following excerpt from DWQI (2015): "Body weights of CD-1 mouse pups on PND 1-24 were decreased by PFNA in a doserelated fashion at all doses, with statistical significance at 3 and 5 mg/kg/day (Das et al., 2015). At weaning, body weight decreases were substantial (27% and 50% lower than in controls at 3 and 5 mg/kg/day, respectively). These statistically	NJDEP (8-9)	2a	*3.2.2 Developmental Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
significant body weight decrements persisted in both male and female offspring after weaning and remained statistically significant in males until PND 287 (9 months of age) when most of the PFNA had been eliminated. It is the opinion of the study authors that the body weight decrements at 9 months of age are unlikely to be attributable to the low concentrations of PFNA remaining in the body at this time point (C. Lau, personal communication). These persistent delays in growth from PFNA are in contrast to the findings in a PFOA study of similar design in CD-1 mice in the same laboratory (Lau et al., 2006). In the PFOA study, body weights of pups from mothers dosed with 3 or 5 mg/kg/day during gestation were 25-30% lower than controls at weaning but recovered and reached control levels by age 6.5 weeks in males and 13 weeks in females."			
p. 3-137, line 33. It is unclear why the postnatal body weight reductions in rats were described as "dose-dependent" since only one PFNA dose was used in the rat study (Rogers et al., 2014).	NJDEP (9)	2a	*3.2.2 Developmental Effects*
p. 3-138, lines 17-20. When discussing the potential human relevance of developmental effects mediated by PPAR-alpha activation, it is important to consider the information reported by Abbott et al. (2010), a study conducted by USEPA toxicologists. As discussed in DWQI (2017): "Abbott et al. (2010, …) found that PPARs are present in nine human fetal tissues examined (liver, heart, lung, kidney, intestine, stomach, adrenal, spleen, and thymus) from embryonic days 54 to 125. They found that the levels may increase or decrease with age of the fetus, or between the fetus and the adult. In some fetal tissues, PPARs were expressed at levels equivalent to or higher than in adults."	NJDEP (9)	2a	*3.2.2 Developmental Effects*
Noncancer Hazard ID: Hepatic Effects			
The Agency's analysis of hepatic effects inappropriately disregarded studies that failed to report an increase in liver enzymes or that observed a much smaller increase than the studies chosen to derive the RfD	ACC (1)	2b	*3.2.3 Hepatic Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
EPA's evidence synthesis conclusion that there is "robust" evidence in rodents of PFNA-induced liver injury likewise warrants re-evaluation due to limitations of the underlying studies and to align with guidance from the IRIS Handbook. As part of the evidence synthesis and integration process, the IRIS Handbook advises that studies are assessed for consistency and coherence of effects which can include assessing the timing of exposure, duration of exposure, and relevance of the mechanism of action for humans. For animal studies of hepatic effects, only short-term studies (28 days or less) are available, which reduces the certainty of the consistency and relevance of effects for chronic human exposures. The Draft Assessment cites additional uncertainties in the human relevance of the mode of action for these effects in animals (e.g., PPARα-mediated) and further acknowledges that for humans, "some uncertainty exists regarding the biological significance of the small changes in these biomarkers of liver injury."[37] In the interagency comments, DOD emphasizes these uncertainties, stating that "evidence appears to be too limited to support a finding of "robust" evidence of liver effects in experimental animals."[38] Given these uncertainties, a conclusion of "moderate" is more aligned with guidance in the IRIS Handbook than "robust" regarding evidence for hepatic effects. *[EPA note: please see docket for details of the submitter's footnotes]*	ACC (9-10)	2b	*3.2.3 Hepatic Effects*
In light of the uncertainty related to the short duration of PFNA animal studies and the often weak and/or inconsistent results associated with elevated liver enzymes observed in study populations in epidemiological studies, the overall hazard identification judgment for liver effects should be the *evidence suggests* but is not sufficient to infer that PFNA exposures may cause hepatic effects that are significant drivers of overall health risk. *[EPA note: Next three comments are offered as the basis for this conclusion]*	ACC (10)	2b	*3.2.3 Hepatic Effects*
The relevance of a single serum sample (per study subject) to show "elevated" liver enzymes as defined by the epidemiological studies evaluated in the Draft Assessment is highly questionable. Data using population-based surveys such as the NHANES and other population-based studies are designed to assess the general health and nutrition of a population, are convenient to use, and provide a wealth of information as evidence with the upward trend in health association studies, as noted by Sobus et al. (2015). However, these large data sets naturally have	ACC (10-11)	2b	*3.2.3 Hepatic Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
variability and a range of measurements, yet the upper end of the range often gets linked with a specific health outcome when that may or may not be clinically relevant. In particular, liver disease in humans is not diagnosed by a one-time pattern of ALT measurements, but rather includes the repeated measurements for biomarkers, degree of biomarker change, and other metrics. As such, the range of liver enzymes measured in the epidemiological studies (which are orders of magnitude lower than the serum levels measured at the effect levels reported in the cited animal studies) are not indicative of an adverse effect. Moreover, it is very difficult to tease out the reported health associations determined in a study against the milieu of all possible associations, real or otherwise, when using biomarker data. None of the epidemiological studies included in the Draft Assessment adequately characterized or accounted for most or all confounders that could influence the liver enzyme data. Liver enzyme levels can vary naturally based on diurnal effects, nutritional status, and exercise, none of which were evaluated in the data set in Kim et al. Exposure to many different compounds, including over-the-counter drugs, prescription drugs, herbal remedies, and heavy metals can also cause an increase in liver enzymes. It does not appear that these confounders were accounted for in the epidemiological studies evaluated by the USEPA and therefore the elevated liver enzymes may, in fact, be caused by something other than PFNA. *[EPA note: please see docket for details of the submitter's footnotes]*			
In the critical study for the RfD derivation, Kim et al. indicate that not adjusting for covariates such as diet and medications that alter liver enzymes is an important limitation of their study, yet the Draft Assessment concludes that it is a "High Confidence" study. As stated by ATSDR, the available epidemiological studies generally do not adequately account for confounders, including co-exposure to other perfluoroalkyls and this severely limits their usefulness for deriving a chemical-specific toxicity value.	ACC (11)	2b	*3.2.3 Hepatic Effects*
The Draft Assessment does not provide an adequate evaluation or discussion of the epidemiological studies that did not show an association between higher exposure to PFNA and liver injury biomarkers such as Mundt et al. (2007) or Lin et al. (2010) since USEPA excludes them early in the data quality evaluation process. In the	ACC (11-12)	2b	*3.2.3 Hepatic Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
Evidence Integration Section, the Draft Assessment concluded that the "available studies showed consistently increased serum ALT, AST, GGT and total bilirubin in most studies in adults, indicating potentially impaired function, although uncertainty exists regarding the biological significance of the small positive associations observed in the individual studies."[45] This overstates the evidence; other articles were not evaluated in the Evidence Integration. Furthermore, the animal studies do not show consistent agreement that liver injury is a critical health effect endpoint, even at the relatively high dose levels used in the available studies. For example, there is an exaggerated response in ALT levels in mice at the highest dose group (5 mg/kg-day) in a 14-day study by Wang et al (2015),[46] a slight increase in liver enzymes only in the highest dose group (5 mg/kg-day) in a 14-day rat study by Fang et al. (2012),[47] no dose- dependent response in in male rats in a 28-day study by NTP (2018)[48] and a dose-dependent response in female rats in the 28-day National Toxicology Program (NTP) study for ALT, but not other enzymes. *[EPA note: please see docket for details of the submitter's footnotes]*			
NJDEP agrees with the IRIS conclusions (p. xxii, summarized in Table ES-1) that the available evidence demonstrates that PFNA exposure causes developmental effects and that it is likely to cause hepatic and male reproductive effects, given sufficient exposure conditions.	NJDEP (4)	2	*Executive Summary; 3.2.2 Developmental Effects; 3.2.3 Hepatic Effects, 3.2.4 Male Reproductive Effects*
NJDEP agrees with IRIS that human data for increased serum levels of the liver enzyme ALT should be used as the basis for a Reference Dose for PFNA. NJDEP also agrees with IRIS (p. 3-153, 19-21) that "…abnormally increased serum ALT indicates impaired liver functioning and even small increases can be predictive of liver disease… (U.S. EPA, 2022c; Valenti, 2021; Park et al., 2019)." However, the Evidence Integration section for liver effects (p. 3-188, lines 3-4) states that "…some uncertainty exists regarding the biological significance of the small changes in … biomarkers of liver injury" such as increased serum levels of the liver enzymes, ALT, AST, and GGT, and total bilirubin. The EPA Science Advisory Board (SAB) PFAS Review Panel (cited as USEPA, 2022c in the draft IRIS document) provides a detailed rationale as to why relatively small increases in ALT, including those associated with PFAS, should be considered adverse, and NJDEP concurs with these SAB conclusions. As such, it is recommended that the statement from p. 3-	NJDEP (4-5)	2b	*3.2.3 Hepatic Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
153 (mentioned above) regarding the significance of elevated ALT also be included in the Evidence Integration section for hepatic effects.			
NJDEP agrees with IRIS's conclusion that hepatic effects of PFNA observed in rodent studies should be considered adverse and relevant to humans (p. 3-188, lines 5-11). It also agrees that hepatic effects in mouse pups with prenatal exposure suggest that early life is a susceptible period for hepatic effects (p. 3-187, lines 32-34).	NJDEP (5)	2b	*3.2.3 Hepatic Effects*
However, NJDEP does not agree with IRIS' reliance on the criteria of Hall et al. (2012) (e.g., pp. 3-184-3-185; p. 3-187, lines 15-19) to determine the human relevance and adversity of hepatic effects observed in rodent studies. Importantly, the primary focus of Hall et al. (2012) is pre-clinical toxicity studies for drug development. In this scenario, drugs are normally administered for a limited period of time (i.e., less than chronic exposure), and effects of the drug may be reversible when exposure ends. Relevant to this point, Hall et al. (2012) emphasize that the expected duration of exposure must be considered in determining the adversity of hepatic effects such as increased liver weight and hepatocellular hypertrophy, since these effects may progress to more severe effects with longer exposure. Specifically, Hall et al. (2012) state: "[Increased liver weight and hepatocellular hypertrophy] may be reversible if the anticipated duration of exposure is short, while progression to more severe hepatic effects may occur from longer exposures to the same dose. However, prolonged exposure to a xenobiotic at levels that have previously been shown to be adaptive may eventually result in liver cell injury due to a failure of adaptive mechanisms. In this case, the combination of dose level and duration of exposure to the xenobiotic under the terms and conditions of the new experiment would now be considered adverse." Duration of exposure considerations are relevant to safety evaluation of drugs, which are normally only taken for a limited time period. In contrast, chronic Reference Doses are intended to protect for lifetime exposure, and, as mentioned by Hall et al. (2012), hepatic effects that are reversible after short-term exposure may progress to more severe effects with longer exposure. Therefore, in the development of chronic Reference Doses, potential reversibility is not a valid reason	NJDEP (5)	2b	*3.2.3 Hepatic Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
to discount the adversity of increased liver weight and hepatocellular hypertrophy in shorter-than-chronic rodent studies since these lesions can potentially progress with longer exposure.			
p. 3-157, lines 31-32; p. 3-158, lines 1-5. The statement from later in the document (p. 3-161, lines 9-11) that "in general, relative liver-to-body weight is recommended instead of absolute liver weight to minimize variations given liver weight is shown to be proportional to body weight…" should also be mentioned here, since this information is key to the discussion of the potential impact of PFNA-induced body weight loss on liver weight in these sections.	NJDEP (9)	2b	*3.2.3 Hepatic Effects*
Noncancer Hazard ID: Male Reproductive Effects			
NJDEP agrees with the IRIS conclusions (p. xxii, summarized in Table ES-1) that the available evidence demonstrates that PFNA exposure causes developmental effects and that it is likely to cause hepatic and male reproductive effects, given sufficient exposure conditions.	NJDEP (4)	2	*Executive Summary; 3.2.2 Developmental Effects; 3.2.3 Hepatic Effects, 3.2.4 Male Reproductive Effects*
Noncancer Hazard ID: Female Reproductive Effects			
NJDEP specifically agrees that lack of information on potential effects of PFNA on mammary gland development is an important data gap. Delayed mammary gland development in mice was identified as a sensitive toxicological endpoint of the closely related compound, PFOA, and the BMDL for delayed mammary gland development is far below BMDLs for other effects of PFOA in laboratory animals (Post et al., 2012; DWQI, 2017).	NJDEP (6)	2h, 6	*3.2.5 Female Reproductive Effects; 5.2 Noncancer Toxicity Values*
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. 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	NRDC (4-5)	1b	*3.2.5 Female Reproductive Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
supplemental information relevant to the discussion on breastfeeding duration. Some of these studies, including studies by Ammitzboll 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] *[EPA note: comment truncated. Please see docket for full comment]* *[EPA note: please see docket for details of the submitter's footnotes]*			
Noncancer Hazard ID: Immune Effects			
p. 3-267, lines 14-18. If possible, the uncertainty about the evidence for decreased antibody response for PFNA related to the issues mentioned (potential confounding across PFAS; variability in response for different ages at which exposure and outcome were measured; variability in response for different types of vaccines) should be compared to the uncertainty related to these issues for the other PFAS (PFOA, PFOS, PFHxS, PFDA) for which decreased vaccine response is the basis for RfDs developed by USEPA IRIS or USEPA Office of Water.	NJDEP (9)	2d	*3.2.6 Immune Effects*
p. 3-281, lines 32-38. When noting that the lack of functional studies of immunosuppression in laboratory animals is a data gap for PFNA, the document should mention that such studies have been conducted for other long-chain PFAS (e.g., PFOA and PFOS) and that they have demonstrated that these other PFAS cause functional effects related to immunosuppression.	NJDEP (9)	2d	*3.2.6 Immune Effects*
Noncancer Hazard ID: Nervous System Effects			
Furthermore, I think that a lack of evaluated mechanisms – for neurodevelopmental and neurobehavioral outcomes, as well as for other outcomes characterized under the "evidence suggests" category – should be given less weight. MOA and mechanistic models should be used to support existing evidence for certain effects, but the difficulty of conducting MOA or mechanistic models should not be a reason that evidence-supported effects are given less consideration	AM (2)	2g	*3.2.8 Nervous System Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
Carcinogenicity			
Additionally, NJDEP agrees with the IRIS conclusion (Section 5.3) that there is inadequate information at this time to assess the carcinogenic potential of PFNA.	NJDEP (6)	7	*3.3 Carcinogenicity*
Noncancer Toxicity Value: Data Selection and Modeling			
In light of the uncertainty about the human data, ACC urges EPA to abandon its reliance on epidemiological findings and focus instead on hazard data from animal studies that provide coherence with the hazard findings from studies in humans. The PFNA RfD should be based on experimental animal data with observations that provide a clear dose-response and human-relevant biologically plausible endpoint. Available human data are inadequate for direct quantitative use in risk assessment and/or establishing public health goals.	ACC (2)	3a, 3b, 4a	*5.2 Noncancer Toxicity Values*
EPA's presentation of the ten-study meta-analysis also lacks transparency in contravention of the IRIS Handbook. It is difficult for the reader to determine which studies were included in the analysis. For example, Table C-3 of the Appendices to the Draft Assessment presents 27 epidemiology studies used in a broader meta-analysis and Tables D-11 and D-12 present only aggregate results of various meta-analyses explored by EPA.[30] Transparent presentation of the underlying data requires explicit identification of the 10 studies used for the meta-analysis, as well as a separate table detailing study information and confidence ratings. This ten-study meta-analysis appears not to have been reviewed by the interagency reviewers since their comments state that EPA solely relied on Sagiv et al. as the basis of the lifetime RfD (e.g., DOD 2023). *[EPA note: please see docket for details of the submitter's footnotes]*	ACC (8)	3a	*5.2 Noncancer Toxicity Values*
In the absence of epidemiology studies evaluating the liver disease among exposed populations, the Draft Assessment evaluated the relationship between PFNA exposure and serum markers of potential liver injury. The Draft identified a total of	ACC (8-9)	3b	*5.2 Noncancer Toxicity Values*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
twelve medium confidence epidemiology studies investigating the impacts of these markers and derived the proposed RfD based on an observed increase in levels of the liver enzyme, alanine aminotransferase (ALT), in some of these studies. The Agency selected one of these studies as a basis for the proposed RfD, while dismissing other studies with better rankings in the individual study metrics. Of these other studies, three did not report a significant ALT increase and a fourth reported a decrease in ALT levels in children with PFNA exposure.			
EPA has inappropriately disregarded studies that do not support its conclusion. The draft Assessment derived a POD for increased serum ALT using data from the study by Kim et al. and from a second study by Nian et al. (2019).[34] According to the draft, EPA relied on the results of the modeling of Kim et al. for the proposed RfD because it showed PFNA to be the "strongest driver" of the association with PFNA despite the fact that both studies adjusted for confounding by other PFAS. Similarly, the Agency dismissed the results of another study that conducted mixtures modeling by Cakmak et al. (2022)[35] that did not report a significant association based on an assertion that the estimate of ALT levels "was imprecise (very wide confidence interval."[36] However, a comparison of the results for the three studies reveals that confidence interval for Cakmak et al. is only slightly wider than those reported by Kim et al. and Nian et al., and includes zero. *[EPA note: please see docket for details of the submitter's footnotes]*	ACC (9)	3b	*5.2 Noncancer Toxicity Values*
At multiple steps in the Draft Assessment, EPA has chosen the more conservative estimate (either a lower or upper bound estimates) for estimating exposure and absorption/intake of PFNA –for example, clearance rates at 5th percentile and 5% increase benchmark response (BMR) in LBW infants, and a BMR of 10% measurable changes in liver enzymes. These assumptions result in a significant overestimate of the risks associated with PFNA exposure. In Table 5.8 of the Draft Assessment, EPA states that "a 5% extra risk is commonly used for dichotomous endpoints," however the Agency's Benchmark Dose (BMD) Guidance also states that a BMR greater than 10% may be used for "early precursor effects."[51] As LBW and elevated liver enzymes are not generally associated with a specific mortality or morbidity, but may be a precursor to potential adverse effects, a higher BMR is warranted for this RfD. *[EPA note: please see docket for details of the submitter's footnotes]*	ACC (13)	3a, 3b	*5.2 Noncancer Toxicity Values*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
To derive the POD used as the basis of the RfD in its PFNA assessment, EPA conducts benchmark dose modeling of reduced birth weight based on the meta-analysis of epidemiological studies. EPA uses the exact percentage (8.27%) of live births in the United States in 2018 that fell below CDC's public health definition of low birth weight (i.e., 2,500 g) to represent the probability of an adverse response at zero dose. EPA then selects a BMR of 5 percent extra risk noting that, "[i]n the case of birth weight, an extra risk of 5% is selected given that this level of response is typically used when modeling developmental responses from toxicology studies and given that low birthweight confers increased risk for adverse health effects throughout life, thus supporting a BMR lower than the standard BMR of 10% extra risk."[52] This assertion is not justified since it is not based on a toxicology study, which typically assumes a 5-percent BMR based on statistical considerations of the study design. Per the BMD Technical Guidance, the BMR should be "based on the level of change in the endpoint at which the effect is considered to become biologically significant." EPA did not provide sufficient justification for only considering a BMR of 5 percent, as opposed to a higher, more biologically relevant value. Thus, the selection of a BMR of 5 percent for this endpoint is inconsistent with EPA guidance and warrants re-evaluation. *[EPA note: please see docket for details of the submitter's footnotes]*	ACC (13)	3a	*5.2 Noncancer Toxicity Values*
To derive the hepatic RfD, EPA conducts BMD modeling of epidemiological studies associating PFNA exposure with increased serum ALT as a biomarker of liver injury. EPA uses a hybrid approach for the BMD assessment and sets the BMR at both 5 percent and 10 percent extra risk of exceeding the adversity cutoff. As noted above, the Draft Assessment acknowledges that "uncertainty exists regarding the biological significance of the small changes in these biomarkers of liver injury" and determines that a BMR of 10 percent extra risk is considered "minimally adverse"[53]. This classification of adversity is arbitrary, inconsistent with Agency guidance, and requires further explanation. Furthermore, the Draft Assessment notes that determining an upper limit of normal for ALT is challenging due to uncertainties and variability in the laboratory measurements of ALT, population demographics, and human variability. Though the BMD Technical Guidance suggests that a 10% BMR can be used as default, it notes that "[b]iological considerations may warrant the use of a BMR of 5% or lower for some types of effects (e.g., frank effects), or a BMR	ACC (13-14)	3b	*5.2 Noncancer Toxicity Values*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
greater than 10% (e.g., for early precursor effects) as the basis of a POD for a reference value."[54] Given that the agency acknowledges the uncertainty of the adversity and population variability in this endpoint, per the BMD Guidance, consideration of a BMR of greater than 10 percent extra risk is necessary to support the derivation of the BMD for this endpoint. *[EPA note: please see docket for details of the submitter's footnotes]*			
I do not agree that the evidence of only one study for acute, single-dose inhalation exposure being low confidence allows for an inhalation reference concentration to not be estimated. A lack of other studies existing highlights a lacking area of study related to PFNA that could present a true danger due to the industrial uses and production of PFNA.	Anon (1-2)	3e, 4e	*5.2.3 Inhalation Reference Concentration*
Despite the evidence base being sparse, we were pleased to see a precautionary principle being applied. In this case, the limited evidence that was found, for example epidemiological evidence that PFNA exposure is associated with reductions in birth weights, should be used to regulate this chemical until more conclusive studies have been conducted to assess biological impacts.	JB (1)	3	*4 Summary of Hazard Identification Conclusions; 5.1 Noncancer and Cancer Health Effect Categories Considered*
NJDEP supports the use of human data, when appropriate, as the basis for toxicity factors for PFAS and other chemicals, as stated in the earlier NJDEP comments on the draft IRIS assessments of perfluorodecanoic acid (NJDEP, 2023a) and perfluorohexane sulfonate (NJDEP, 2023b). Relevant to this point, an evaluation by the Health Effects Subcommittee of the New Jersey Drinking Water Quality Institute (DWQI, 2022), an advisory body to NJDEP, agreed with the EPA Office of Water's conclusion that human data are an appropriate basis for the derivation of RfDs for non-carcinogenic effects of PFOA and PFOS and the cancer slope factor for carcinogenic effects of PFOA. NJDEP concurs with this conclusion.	NJDEP (2)	3	*5.2 Noncancer Toxicity Values*
NJDEP agrees with the development of chronic Reference Doses for developmental and hepatic effects and subchronic Reference Doses for developmental, hepatic, and male reproductive effects. It also agrees with the choice of the Reference Dose for developmental effects as the overall chronic and subchronic Reference Dose.	NJDEP (4)	3a, 3b, 3c, 4	*5.2 Noncancer Toxicity Values*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
NJDEP agrees with the rationales provided in the draft IRIS document to support the benchmark responses (BMRs) selected for dose-response analysis (summarized in Table 5-8). Specifically, NJDEP agrees with the use of a BMR of a 10% change for increased relative liver weight although a BMR of 1 standard deviation is typically used for continuous data endpoints. As discussed in the draft IRIS document, this BMR has been used for relative liver weight in other EPA assessments. It was also used by NJDEP and the NJ DWQI in their assessments of PFOA (DWQI, 2017), PFNA (NJDEP, 2015; DWQI, 2015), PFUnDA (NJ Interagency Toxics in Biota Risk Subcommittee, 2022), and ClPFPECAs (NJDEP, 2021).	NJDEP (5-6)	4d	*5.2 Noncancer Toxicity Values*
NJDEP also agrees with the BMRs selected by IRIS for other health endpoints.	NJDEP (5-6)	3, 4	*5.2 Noncancer Toxicity Values*
p. 5-25. Modeling results in humans (increased serum ALT). It is important to include at least a summary of the information from Summary and Selection of the POD (Appendix D, p. D-37-D-39) here. As written, it is not clear to the reader that Kim et al. (2023b) was selected as the critical study, that the BMR was 10% extra risk of exceeding the cutoff, or that the 95th percentile ALT value in healthy people from Valenti et al. (2021) was used as the cutoff, and the reader should not need to go to the Supplemental Information to find this important information.	NJDEP (9)	3b	*5.2 Noncancer Toxicity Values*
p. 5-43, lines 37-38. It is stated that "EPA applied the recently updated International Federation of Clinical Chemistry ULN values [for ALT] from Valenti (2021)." It should be clarified that Valenti et al. (2021) provides an update of the range of ALT values in health individuals using a new International Federation of Clinical Chemistry (IFCC) standardized methodology for measuring ALT. As written, the sentence appears to say that IFCC has adopted the Valenti et al. (2021) values as their ALT benchmarks, but this does not appear to be the case.	NJDEP (10)	N/A	*5.2 Noncancer Toxicity Values*
Noncancer Toxicity Values: Pharmacokinetics, Dosimetric Extrapolation, and Uncertainty Factors			
the PBPK model used in the draft Assessment is too uncertain for criteria development for PFNA and other PFAS	ACC (2)	5	*3.1 Pharmacokinetics;*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
			5.2 Noncancer Toxicity Values; Appendix E Detailed Pharmacokinetic Analyses
The proposed RfD is overly conservative as it compounds multiple upper percentile values from the point of departure and internal dose metrics.	ACC (2)	3a, 3b, 4a	*5.2 Noncancer Toxicity Values*
USEPA relies on a PBPK model that is too uncertain for criteria development for PFAS. USEPA selected a physiologically-based pharmacokinetic (PBPK model) (Chiu et al. 2022) for establishing the intake of PFNA from readily available concentrations of PFNA reported in drinking water. In this model, the authors pair available serum data with drinking water concentrations. In some studies, the drinking water concentrations were estimated using data from Unregulated Contaminant Monitoring Rule 3 (UCMR 3). Using drinking water concentrations estimated from the UCMR3 data and the Center for Disease Control and Prevention 's (CDC) National Health and Nutrition Examination Survey (NHANES) serum data to estimate exposure, likely overestimates the contribution of drinking water to the PFNA serum in the NHANES data by underestimating the other exposures for PFNA that may have occurred... In addition, although no other available data sources for PFAS serum data have been identified, the use of NHANES data, in particular chemical serum data, requires a number of assumptions that reduce the accuracy of the PBPK model in Chiu et al. Serum chemical data in NHANES are single point measurements that do not have the same accuracy or useability of data with repeated measurements. With repeated measurements, averages and/or distributions of serum concentrations over time can be estimated whereas single point measurements do not allow for the same statistical measurements of the serum data. Sobus et al. identified a number of uncertainties with using these spot biomarker distributions including wider distribution tails, which directly effects the 5th and 95th percentiles that EPA uses for the intake estimates of PFNA (discussed further below). These types of datasets also suffer from an inability to determine if high serum levels are peaks or reflect a long-term serum average. *[EPA note: comment truncated. Please see docket for full comment]*	ACC (12-13)	5	*3.1 Pharmacokinetics; 5.2 Noncancer Toxicity Values; Appendix E Detailed Pharmacokinetic Analyses*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
For the derivation of the lifetime RfD, EPA did not follow the IRIS Handbook in sufficiently justifying the UF_H of 10 for developmental effects. The data used to derive the developmental endpoint were based on reduced birthweight in infants, which EPA considers a sensitive population... Given that the data used to support the development of the BMR were entirely based on a susceptible population (i.e., infants / developing fetuses) rather than the general population, EPA deviated from the IRIS Handbook in applying a UF_H of 10. In general, EPA makes little mention of the rationale for using a factor of either 3 or 10 for the UF_H. It might be assumed that EPA is using the standard composition of the UF_H as a combination of a factor of 3 for pharmacokinetics and 3 for pharmacodynamics considerations. EPA does not, however, discuss the basis for either of these components. Because the UF_H is the largest single component of the composite uncertainty score, discussion for each component of the UF_H is warranted. *[EPA note: comment truncated. Please see docket for full comment]*	ACC (14-15)	6	*5.2.1 Oral Reference Dose Derivation*
We also question the application of a composite uncertainty factor (UFc) of 30 for the RfD. EPA routinely selected the higher or lower end of the thresholds for the RfD and additional uncertainty factors are unnecessary. USEPA applied a human variability UF of 10, however in selecting the upper and lower bound estimates for exposure and intake, the human variability is inherently accounted for. We recommend a reduction of this UF to 3. In addition, we question the database uncertainty factor of 3 if USEPA considers the data for the critical effect endpoints to be "robust." Since the database includes developmental and human data, the database may be considered sufficient to reduce this factor to 1.	ACC (15)	6	*5.2.1 Oral Reference Dose Derivation*
Ultimately, the RfD derived by USEPA is so low that based on the NHANES data for serum PFNA currently in the United States, roughly 95% of the population have serum PFNA levels that would be associated with birth weight deficits and increased liver enzymes on a national level.	ACC (15)	6	*5.2 Noncancer Toxicity Values*
Finally, the overall uncertainty factor of 1000 used to estimate the subchronic of RfD for liver effects is unnecessary. First, there is an unnecessary factor of 10 (UF_S) to account for the short exposure duration of the study. Since this value represents subchronic exposure, we believe it is unnecessary to apply the UF_S of 10 since it was	ACC (15)	6	*5.2.2 Subchronic Oral Reference Dose Derivation*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
derived in consideration of short-term exposure. Second, it seems redundant to use an uncertainty factor of 3 (UF_A) to account for "residual uncertainties" associated with the potential pharmacokinetic and pharmacodynamic differences when immense consideration and data were used to model the POD_{HED} of 7.2E-4 mg/kg-day (females) from the animal POD of 4.7E-1 mg/kg-day to account for these differences.			
I suggest that the derivation of non-cancer risk estimates and reference values should also involve extrapolation to exposures lower than the POD, given that increasing evidence supports toxicological effects for harmful chemicals at lower and lower levels of exposure. Given that evidence suggests that PFNA exposures may cause neurodevelopmental toxicity, I would hope that the potential for harmful effects from low-level exposures, even those extrapolated from the POD, would be communicated to the public.	AM (1)	3, 4	*5.2.1 Oral Reference Dose Derivation*
I question the use of 1, 3, and 10 as uncertainty factors for the development of RfD values for PFNA. While I understand these values to be the standard uncertainty factors applied, and while I appreciate the provided justification section, these three values continue to strike me as somewhat arbitrary values.	AM (2)	6	*5.2.1 Oral Reference Dose Derivation*
Additionally, given historical precedent, the EPA should be more conservative in estimating reference doses (Rfd) and points of departure (POD) by factoring in greater uncertainty, especially given the persistence of other halogenated chemicals. When the Agency generates risk assessments, it exercises significant latitude in determining an uncertainty factor for the Rfd. This uncertainty factor is a product of how related the existing toxicological data is to human exposure pathways. For PFNAs, most of these uncertainty factors are set at 30, with two at 1000. EPA can set a maximum uncertainty of up to 10000 for chemical exposures. The Agency should consider increasing the uncertainty factor of PFNAs because of its impacts on vulnerable populations. Both animal and epidemiological studies have shown that PFNAs effects are magnified for young individuals. We argue that the uncertainty factors of 30 should increase to at least 100 to better account for these vulnerable populations as well as other effects that we do not yet understand.	HWP (2-3)	6	*5.2.1 Oral Reference Dose Derivation*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
When evaluating uncertainty factors, we found the justification for UF_A of 1 to be incomplete (Table 5-17). This was supported by development and liver effects reported in epidemiological studies, but this was not explained. To have an uncertainty factor of 1, we would expect this evidence to either be very strong or substantiated animal studies.	JB (1)	6	*5.2.1 Oral Reference Dose Derivation*
Finally, I am highly disappointed in the lack of clarity about the toxicological effects of different isomers of PFNA. The explanations given for why the different isomers are not considered on their own in this report is extremely weak, especially given the differences in blood concentration given by Benskin et al.(2008) that is readily available in the appendix (Appendix Document, Table E-4, page E-14).	JF (2)	N/A	*3.1 Pharmacokinetics*
NJDEP agrees with IRIS that use of the default $BW^{3/4}$ (body weight to the 3/4 power) approach for interspecies dosimetric extrapolation of PFNA would lead to an overprediction of Human Equivalent Doses and that chemical-specific data should be used for dosimetric extrapolation.	NJDEP (3)	5	*3.1 Pharmacokinetics*
NJDEP also agrees with IRIS that use of data-derived extrapolation factors (DDEFs) based on the ratio of human to animal clearance factors for development of Human Equivalent Doses (HEDs) from points of departure (PODs) is not appropriate in short-term animal studies in which steady state is not reached.	NJDEP (3-4)	5	*3.1 Pharmacokinetics*
Additionally, NJDEP strongly agrees with IRIS that it is appropriate to use measured serum levels (e.g., average serum levels over the course of the study, or maximum serum levels at the end of the study) to determine the POD, followed by the application of the human clearance factor to the POD (in terms of serum level) to determine the HED (in terms of administered dose). This approach was used by the New Jersey DWQI to develop human equivalent doses (HEDs) from laboratory animal serum data for PFOA and PFOS (DWQI, 2017; DWQI, 2018).	NJDEP (4)	5	*5.2 Noncancer Toxicity Values*
p. 3-2, lines 18-19. It is stated that: "Female rats and mice excrete PFNA much faster than male rats and mice." This sentence needs revision to indicate that this sex difference is much more prominent in rats than in mice. It should also be indicated that excretion in female rats is much faster than in male rats and mice of both sexes. As shown in Table 3-3, the half-life in female rats (2.77 days) is about 17-fold shorter	NJDEP (7)	5	*3.1 Pharmacokinetics*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
than in male rats (46.5 days). In contrast, the half-life in female mice (46.5 days) is only about 2-fold shorter than in male mice (101.9 days).			
p. 5-28, lines 9-18. Some of the information in this paragraph is confusing. Clarifications are needed, as follows: The following sentence needs clarification: "For gestational and lactational exposure, EPA evaluated exposure to fetuses and young offspring (mouse pups up to 7 days of age and human infants) based on predicted or measured serum levels in the mouse dam or human mother" The sentence appears to mean that the dose-response for effects in fetuses and young offspring was based on maternal serum levels, but this is not clear as written." Additionally, the following sentence is unclear: "This approach assumes that if human maternal serum levels remain at or below the corresponding average serum concentrations in the mouse dam (calculated from the start of gestation through the time of endpoint observation up to PND 7), then the exposure to the human child will likewise be below those in the mouse pups where the endpoint was observed." Does this mean that the maternal:cord blood serum ratio and lactational exposure up to PND7 are assumed to be the same in humans and mice? Are there data to support this?	NJDEP (9-10)	5	*5.2 Noncancer Toxicity Values*
p. 5-28, lines 25-28. It is stated, "Since PK model simulations predict that a breastfed human child may experience serum concentrations greater than steady state, but for a limited period of time (given the same dose as the mother, Appendix E.4.2), the implicit assumption of steady state in the child is judged by EPA to be a reasonable method of estimating the average internal dose among children." However, in any discussion of exposures to infants, the potential effects during early life of short-term elevations in serum concentrations to levels that are substantially higher than at steady-state should be considered, especially since early life is a sensitive lifestage for the effects of PFNA.	NJDEP (10)	5b	*5.2 Noncancer Toxicity Values*
NJDEP also agrees that the rationales provided in the draft IRIS document support the uncertainty factors (UFs) selected for the chronic and subchronic RfDs for PFNA.	NJDEP (6)	6	*5.2 Noncancer Toxicity Values*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
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.	NRDC (3)	3	*5.2 Noncancer Toxicity Values*
Formatting, editorial, and text clarifications			
I believe that the Executive Summary section is effective at communicating the current state of knowledge on PFNA, and at communicating gaps in knowledge. I would encourage plainer language through the Executive Summary to increase the accessibility of the Toxicological Review to those who might be less familiar with chemistry and toxicology. The second paragraph of the Executive Summary is a good example of more accessible language compared to the Review as a whole.	AM (1)	N/A	*Executive Summary*
Executive Summary (throughout) and elsewhere in the document where applicable. When referring to the point of departure (POD), benchmark dose (BMD), or benchmark dose lower confidence limit (BMDL), it should be made clear when these parameters are presented in terms of internal dose (serum/plasma PFAS concentration) rather than administered dose.	NJDEP (6)	N/A	*Executive Summary; Overall*
p. xxv, lines 15-17. A brief explanation of the data-derived extrapolation (DDEF) should be provided.	NJDEP (6)	N/A	*Executive Summary*
p. 1-3, line 15. "Sulflon S-111" is misspelled and should be changed to "Surflon S-111."	NJDEP (6)	N/A	*Typo*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
p. 1-4, line 14. "fluorine" is misspelled.	NJDEP (6)	N/A	*Typo*
Table 3-1. The toxicokinetic parameters (e.g., half-lives, clearance factors) in Table 3-1 do not appear to be consistent with those in Table 3-3.	NJDEP (7)	N/A	*3.1 Pharmacokinetics*
p. 3-3, lines 7-10. It is stated here that the classical PK model was used to estimate internal doses in mice and in male rats, while interpolation of measured serum concentrations was used for female rats. This is not consistent with the information in other parts of the document (p. 3-39, lines 16-20; p. 3-42, lines 21-25; p. 3-43, lines 25-26; p. 5-27, lines 17-18) indicating that linear interpolation, not the classical PK model, was used for both male and female rats.	NJDEP (7-8)	N/A	*3.1 Pharmacokinetics*
p. 3-9, line 28. The units (L/kg) for the Vd values from Chiu et al. (2022) are different from the units (ml/kg) for the Vd values in Table 3-1. Since comparisons are made between the values from Chiu et al. (2022) and values in Table 3-1, it is suggested that consistent units be used for clarity.	NJDEP (8)	N/A	*3.1 Pharmacokinetics*
p. 3-11, lines 26-30. It is suggested that the range of values for the cord:maternal serum ratios from the cited studies be included here, rather than referring the reader to Appendix E.2.2 to find this information.	NJDEP (8)	N/A	*3.1 Pharmacokinetics*
p. 3-38, line 11. It appears that "Wolf et al. (2010)" is an error and should be "Das et al. (2015)" instead.	NJDEP (8)	N/A	*3.1 Pharmacokinetics*
p. 3-52, line 28. "Appendix D" should be changed to "Appendix C."	NJDEP (8)	N/A	*3.2.2 Developmental Effects*
p. 3-72, line 24. Wikstrom et al. (2020) is a high confidence study, not a medium confidence study as stated here.	NJDEP (8)	N/A	*3.2.2 Developmental Effects*

Comment	Commenter (page)	Relevant Charge Question(s)	EPA Notes and *Topic Characterization*
p. 3-123, lines 20-22. "…both strains of pregnant and nonpregnant mice" is confusing as written. For clarity, suggest revising to "…pregnant and nonpregnant CD-1 and wild type 129S1/Svlmj mice…"	NJDEP (8)	N/A	*3.2.2 Developmental Effects*
p. 5-19, Table 5-8. For decreased birth weight in humans, the Rationale column should include the numerical value (2500 g) of the "public health definition of low birth weight."	NJDEP (9)	N/A	*5.2 Noncancer Toxicity Values*
p. 5-29, line 9. There is a typographical error - "later" should be "latter."	NJDEP (10)	N/A	*Typo*
References (Note: References included in the draft IRIS documents are not listed.) *[EPA note: comment truncated. Please see docket for full comment]*	NJDEP (11)	N/A	*1 Overview of Background Information (largely)*

Table 3. Other comments (organized by topic area or theme)

Comment	Commenter (page)
Future Research	
I do agree with reviewing existing literature to make the most informed judgments, however, if an area has a small amount of existing literature, I feel that points to a need for federal support for fixing that gap in knowledge.	Anon (2)
We learned that many of the epidemiological and experimental animal studies were inconclusive or had low confidence. For example, the evidence base for cardiometabolic effects were indeterminate. Similarly, evidence was inadequate for renal effects. Given that many studies were short-term we would hope that future directions would include more long-term evaluation.	JB (1)
One aspect of the report we disliked is the lack of carcinogenicity studies. Namely, the report says "There are currently no chronic or carcinogenicity studies in animals exposed to PFNA." We understand the difficulties in creating such evidence; however, this is critical research in order to fully assess whether PFNA is harmful to humans. For better or for worse, cancer evokes a certain connotation — and spot within the public imagination — and so much of environmental action requires garnering the public support and political will for action. This is not so much an indictment of this review as it is lamenting the poor state of research of chemicals across the board.	PBR (2)
Finally, this assessment identifies knowledge gaps in specific health areas. We believe the EPA could prioritize funding for new research that addresses these gaps and strengthens the evidence base for future assessments. If these gaps are left unaddressed, there is great potential for unknown exposure effects to present themselves, and we will have no precedent for how to approach dealing with them. Additionally, generating more reports on gaps in the literature will assist regulators in getting more harmful chemicals off the market and build a corpus of which chemicals are harmful, so that corporations cannot obscure the toxicity of chemicals they use in their products.	PBR (3)
The relative weaknesses of the Review come from its lack of specific analysis of locations where PFNA may be found. This is discussed briefly in the report, but there is a need to conduct location-specific modeling to identify specific communities or geographies at elevated risks. Implications on equity and the need for targeted interventions to address the presence of PFNA will hinge on this data.	RM (2)
Cumulative Risk	
The hazard assessment includes an additional epidemiological consideration regarding simultaneous exposure of PFAS chemicals and confounding effects. Because of the inconsistencies found in co-exposure results from co-occurring PFAS and volatility in correlations between PFAS pairs, the review states that "it was not considered appropriate to assume that co-exposure to other PFAS was necessarily an important confounder" (1-14) in the reviewed studies. The Agency's review of PFNAs accounts for a wide swath of health effects, but it does not grapple with how those health effects may be amplified or impacted by exposures to other chemicals. Our comments	HWP (3)

recommend setting a lower “safe” threshold due to this issue of simultaneous exposure. This conception of constant and diverse exposures should become standard practice for EPA in toxicology assessments.	
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 PROA, PFOS, GenX, PFBS, 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 PFAS cumulative risks. *[EPA note: please see docket for details of the submitter’s footnotes]*	NRDC (3)
Another point of critique is that this assessment primarily focuses on the effects of PFNA exposure in isolation; however, real-world exposure often involves mixtures of PFAS chemicals, given widespread contamination. Research shows that PFAS-class contamination is currently affecting millions of people, and therefore exposure to PFOS, PFOA, PFBA, PFDA, PFHxA and PFHxS must be assessed with the same urgency. Exploring potential additive or synergistic effects of co-exposure scenarios would provide a more holistic, realistic understanding of health risks.	PBR (2)
Risk Management	
We also appreciate the timeliness of this report, given the recent announcement that the Biden Administration has finalized the first-ever drinking water limits for PFAS. The publication of this report was vital in order to get ahead of potential corporate malfeasance and lobbying against the banning of PFAS chemicals. These regulations almost certainly will be challenged and litigated over the next few years, and we believe this report is critical for laying out the potential harms of this one type of PFAS.	PBR (1-2)
Explaining the criteria for enforcement would go a long way toward enhancing the effectiveness of this report. Perhaps a brief review and description of what characteristics make a chemical bannable [sic] vs which characteristics are allowed would be helpful. The report makes it clear that some effects of PFNA are very probable. Stating which effects need to be probable in order for PFNA to be regulated further would be helpful. Providing the public with a framework for when regulatory bodies can — or can’t — act will ensure greater public interest in the mechanism of regulation and guide further research into the limits we currently have for chemical exposures.	PBR (3)
As it stands, there is sufficient evidence to support occupational and environmental limits on PFNA emissions and a reduction in its usage. A full Review must examine whether the current usage of PFNA incurs a net cost or benefit to society. Its usages should be subdivided into general categories of use and each category analyzed. The Review’s toxicological data is valuable in informing the modeling of such analysis and offers a wealth of data with detailed discussion of the positive and negative aspects of different studies completed. At the current moment, there is ample evidence to suggest that PFNA has negative impacts and so there is a need to take immediate action.	RM (1-2)