National Institute of Environmental Health Sciences
Comments on the Interagency Science Discussion (Step 6)
Draft IRIS Toxicological Review of Perfluorobutanoic Acid (PFBA)
October 2022
(Date Received: December 12, 2022)

Note: The scientific review and comments are provided by National Institute of Environmental Health Sciences (NIEHS) Division of the Translational Toxicology scientists and are not intended to represent formal agency position or opinion.

Overarching NIEHS comment: Throughout the document there are "unresolved" parentheses. For example, see page 2-1 beginning line 18 through the top of 2-2. Throughout this paragraph, there are several occurrences of unmatched parentheses.

Executive Summary:

NIEHS Comments:

- *Page xi, line 11: Ending period appears to be superscripted.*

2. Literature Search and Study Evaluation

2.1. Literature Search and Screening Results

NIEHS Comments:

- *Page 2-1, line 15: It is unclear what the "3" after "(excluding models)" is for.*
- *Page 2-2, Figure 2-1, Paragraph below the Figure: It is unclear what the purpose of the paragraph is. The first line does not line up with the rest; and there are no line numbers suggesting it is a figure legend. Or is it a footnote without a link to the preceding narrative? This paragraph has many unmatched parentheses.*

3. Pharmacokinetics, Evidence Synthesis, and Integration

3.1.2. Distribution

NIEHS Comments:

- *Page 3-3, line 14, there is an unpaired parentheses at the beginning of the sentence.*
- *Page 3-3, paragraph beginning on line 14, there is inconsistent reference to mice and rats. Lines 14 and 15 describe the Das et al. 2008 publication as being conducted in pregnant and nonpregnant mice and pups. However, beginning line 16 there are references to rats. Line 17 references mice again. Line 22 returns to rats, line 23 "mice".*

3.2. Noncancer Evidence Synthesis and Integration

3.2.1. Thyroid Effects

NIEHS Comments:
The EPA authors have thoroughly considered the strengths and limitations of these studies. Their responses to the Tier 1 and Tier 2 peer reviewers were thoughtful and complete, and resulted in a fuller discussion of the relevance of thyroid hormone levels changes as well as other thyroid hormone system endpoints. No public comments were submitted. Additional edits are listed for consideration below:

- *Page 3-20, line 7: The ranges cited for the free and total T4 (e.g., 25-73%) include non-statistically significant changes; the beginning of this sentence indicates "Statistically significant…decreases…"*

3.2.2. Hepatic Effects

NIEHS Comments:

- *Page 3-35, line 22: Should this read: "Other serum biomarkers (ALT, total protein, albumin, or globulin) were not increased due to exposure." The previous sentence states that ALP was increased relative to controls. Also, although not mentioned here, BUN was significantly decreased. This is relevant to the kidney changes noted.*
- *Page 3-40, lines 34-36: Suggest simply stating that the authors did not report internal doses so conversions could not be made to other data sets.*

3.2.3. Developmental Effects

NIEHS Comments:

The EPA authors thoroughly considered the strengths and limitations of these studies. Their responses to the Tier 1, Tier 2, and Public Comments are comprehensive and clear. The consideration of the measurements of vaginal opening in the mouse as developmental milestones, but not markers of puberty, more accurately reflects the biological relevance of this endpoint in the mouse. Additional edits are listed for consideration below:

- *Page 3-50, Table 3-9: It is hard to differentiate the bolded text (indicating statistically significant results) from the non-bolded text (non-statistically significant data). This is true for other tables as well.*
- *Page 3-51, beginning line 27: Consider striking the first sentence. It is neither needed nor accurate as written. EPA is likely referring to menarche as there are many other growth factors and hormones involved in "puberty" in humans.*
- *Page 3-51, line 29: Consider the following insertion: "In female rodents, in-life pubertal markers…"*
- *Page 3-51, lines 31-33: Consider modifying the sentence beginning with "Since…" to: "It is unclear if the delayed vaginal opening in mice reported by DAS et al. (2008) is a direct correlate to puberty in humans." (Note that the beginning parens for 2008) is missing.)*
- *Page 3-51, paragraph beginning line 27: Some additional context would be useful when comparing different species (rodents and humans) regarding the modes of action for each and how they differ.*
- *Page 3-52, line 5: Revise to: "Given that PFBS alters …" (missing "s")*

3.2.4. Reproductive Effects

NIEHS Comments:

The EPA authors thoroughly considered the strengths and limitations of the few studies available for Reproductive Effects. There were very few peer reviewer comments from Tier 1 and Tier 2 reviews and no Public Comments were submitted. The response to comments by EPA authors was clear and this review agrees with their response to avoid adding text about mechanism on the potential heart effects of PFBA. Additional suggestions are provided below to help improve the clarity of the text.

- *Page 3-54, lines 11-13: Please clarify that this study (Das et al., 2008) was in mice. Otherwise, a reader might take issue with vaginal opening not being considered relevant to reproductive effects.*
- *Page 3-60, line 14: Should this read: "Possible immunotoxic effects were observed…"? Also, the use of "Possible" to start the sentence is unnecessary and recommend stiking this word. The rest of the paragraph explains the lack of certainty.*

4. Summary of Hazard Identification

4.1. Summary of Conclusions for Noncancer Health Effects

- *Page 4-1, line 19: Rather than using "economy" here, suggest replacing with "homeostasis".*
- *Page 4-3, Table 4-1: "Evidence Basis" column is cut off; recommend enlarging the table or shrinking the font.*

- *Page 4-4, Table 4-2: Consider adding human/animal to all cells or footnote that PFBA, PFBS, and GenX are based only on animal studies.*

4.3. Conclusions Regarding Susceptible Populations and Lifestages

NIEHS Comments:

- *Page 4-5, line 21: Does this assume a linear correlation between clearance and effects? Consider stating this assumption.*

5. Derivation of Toxicity Values

5.2.1 Oral Reference Dose (RfD) Derivation

NIEHS Comments:

- *Inclusion of gene expression data analyses provided in Butenhoff et al. 2012 can provide additional substantiation of the point of departure and are supportive of the PPARalpha mechanism. Consider including benchmark dose analysis of the gene expression data from Butenhoff.*
- *Consider an additional safety factor for developmental toxicity endpoints (delayed eye opening/thyroid depletion) to be consistent with the Food Quality Protection Act.*
- *Consider modeling the 28-day male rat T4 and dT4 data. If nothing else, use a LOAEL to NOAEL extrapolation. There is a substantial biological transition to occur between 6 mg/kg dose and vehicle control for both endpoints.*
- *Page 5-19, line 14: Consider editing the sentence "However, it is …" to "However, without internal serum levels reported, it was difficult…"*

Supplementary Materials

NIEHS Comments:

- *Table ES-1: It would be helpful to include the animal point of departure along with the human equivalent dose for the point of departure.*
- *Table ES-1: It would be helpful to footnote the uncertainty factors column and point the reader to table 5-5 (for explanation of the factors) and 5-10 (for application of the factors). Alternatively, consider bringing the information forward into the Table so all critical information is present in the main conclusions table.*