Draft Charge for the
Toxicological Review of Perfluorobutanoic Acid (PFBA)
and Related Salts

January 2022

Introduction

The U.S. Environmental Protection Agency (EPA) is seeking a scientific peer review of the draft *IRIS Toxicological Review of Perfluorobutanoic Acid and Related Salts* developed in support of the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by EPA's Center for Public Health and Environmental Assessment within the Office of Research and Development. IRIS assessments contain information about chemicals that encompasses hazard identification and dose-response assessment, two of the four steps in the human health risk assessment process. When used by risk managers in combination with information on human exposure and other considerations, IRIS assessments support the Agency's regulatory activities and decisions to protect public health.

There is no existing IRIS assessment for perfluorobutanoic acid (PFBA). The draft Toxicological Review of PFBA is based on a comprehensive review of the available scientific literature on the noncancer and cancer health effects in humans and experimental animals exposed to PFBA or the related compound, ammonium PFBA. The systematic review protocol for PFBA and appendices for toxicokinetic information, dose-response modeling, and other supporting materials are provided as *Supplemental Information—Appendix A: Systematic Review Protocol for the PFBA PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments* and *Supplemental Information—Appendices B, C, D, E, and F* to the draft Toxicological Review.

Charge Questions on the Draft Toxicological Review of PFBA

In response to the numbered charge questions below, the advice provided as part of this peer review would be most useful when prioritized to indicate its relative importance as follows:

- Tier 1: *Recommended Revisions* – Key major recommendations necessary for strengthening the scientific basis for the Toxicological Review of PFBA. The implication of such key Tier 1 recommendations is that the assessment conclusions are not adequately supported without addressing the recommendations and need to be reconsidered or better substantiated. For Tier 1 recommendations, please describe the specific revisions necessary to modify or better substantiate the most scientifically appropriate assessment conclusions.
- Tier 2: *Suggestions* – Recommendations that are encouraged to strengthen the scientific analyses and conclusions in the Toxicological Review of PFBA. That other factors (e.g., timeliness) also may also be considered before deciding to address or incorporate Tier 2 suggestions is understood. For Tier 2 recommendations, please provide specific suggestions to strengthen the scientific basis for assessment conclusions or improve the clarity of the analyses and presentation.

- Tier 3: *Future Considerations* – Scientific exploration that might inform future work. These recommendations are outside the immediate scope or needs of the current document under review but could inform future toxicological reviews or research efforts.

1. The Toxicological Review describes and applies a systematic review process for identifying and screening pertinent studies that is described in detail in Section 1.2.1 (*Literature Search and Screening*) and Appendix A (*Systematic Review Protocol for the PFBA, PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments*). Please comment on whether the search strategy and screening criteria for PFBA are appropriate and clearly described. Please identify additional peer-reviewed studies of PFBA that the assessment should incorporate[1].
2. The Toxicological Review describes the results of the evaluations of individual studies in Section 2.2 (*Study Evaluation Results*) and presents and analyzes the findings from those studies deemed informative in the relevant health effect-specific synthesis sections.
    a. Please comment on whether the study confidence conclusions for the PFBA studies are scientifically justified, giving appropriate consideration to important methodological features of the assessed outcomes. Please specify any study confidence conclusions that are not justified and explain any alternative study evaluation decisions.
    b. Results from individual PFBA studies are presented and synthesized in the health system-specific sections. Please comment on whether the presentation and analysis of study results is clear, appropriate, and effective to allow for scientifically supported syntheses of the findings across sets of studies.
3. For each health effect considered in the assessment and outlined below, please comment on whether the available data have been clearly and appropriately synthesized to describe the strengths and limitations. For each, please also comment on whether the weight-of-evidence decisions for hazard identification have been clearly described and scientifically justified.
    a. For thyroid effects, the Toxicological Review concludes that the available evidence indicates PFBA exposure is likely to cause thyroid toxicity in humans given relevant exposure circumstances, primarily on the basis of short-term and subchronic studies in male rats reporting a consistent and coherent pattern of thyroid effects following PFBA exposure, but also drawing from the consistency of effects when considering evidence from structurally related PFAS. The Toxicological Review concludes the thyroid effects are considered relevant to humans in the absence of evidence to suggest otherwise.
    b. For hepatic effects, the Toxicological Review concludes that the available evidence indicates PFBA exposure is likely to cause hepatic effects in humans given relevant exposure circumstances, on the basis of a series of short-term, subchronic, and developmental studies in rats and mice demonstrating consistent and coherent effects

[1] Newly identified studies (i.e., studies identified by EPA or the public that meet PECO criteria but were not addressed in the external review draft, for example due to recent publication) will be characterized by EPA and presented to the peer review panel. This characterization will focus on EPA's judgment of whether the studies would have a material impact on the conclusions (i.e., identified hazards or toxicity values) in the external review draft. The peer review panel is asked to review EPA's characterization and provide tiered recommendations to EPA regarding which studies, if any, to incorporate into the assessment before finalizing.

with a clear biological gradient. Although the available mechanistic information indicates the effects in rodents are relevant to humans, some uncertainty remains regarding potential differences in sensitivity across species due to evidence for the involvement of both PPARα-dependent and PPARα-independent pathways in these effects (see Charge Question 4 requesting input specific to this latter uncertainty).

c. For developmental effects, the Toxicological Review concludes that the available evidence indicates PFBA exposure is likely to cause developmental effects in humans given relevant exposure circumstances, on the basis of a coherent pattern of delays in acquisition of three different developmental milestones in a single study in mice, with the findings presumed relevant to humans in the absence of evidence to suggest otherwise. The assessment discusses similar effects observed for structurally related PFAS.

d. For reproductive effects and other noncancer effects (i.e., cardiometabolic effects, renal effects, ocular effects, body weight), the Toxicological Review concludes there is inadequate evidence to determine whether PFBA exposure has the potential to cause these effects in humans on the basis of the sparsity of available evidence.

4. Appendix A (*Systematic Review Protocol for the PFBA PFHxA, PFHxS, PFNA, and PFDA IRIS Assessments*) identifies the human relevance of hepatic effects in animals that involve peroxisome proliferator-activated receptor alpha (PPARα) receptors as a key science issue.[2] To the extent supported by the PFBA literature (and to a lesser extent, literature for other PFAS), the Toxicological Review evaluates the evidence relevant to the potential involvement of PPARα and non-PPARα pathways with respect to the reported hepatic effects. The Toxicological Review ultimately concludes evidence from in vivo and in vitro studies support that multiple modes of action (MOA) are operant in the induction of hepatic effects by PFBA exposure and the relative contribution of these different MOAs cannot be concluded with confidence from the available data. Please comment on whether the available animal and mechanistic studies support this conclusion and whether the analysis presented in the Toxicological Review is clearly documented.

5. The draft assessment concludes there is inadequate evidence to assess carcinogenic potential for PFBA and that this descriptor applies to oral and inhalation routes of human exposure. Please comment on whether the available animal and mechanistic studies, and the analysis presented in the Toxicological Review, support this conclusion.

6. For PFBA, no RfC was derived. The Butenhoff et al. (2012) 90-day rat study was the study chosen for use in deriving the RfD on the basis of an increased incidence of hepatocellular hyperplasia and decreased total T_4 in male rats. Is the selection of this study and these effects for use in deriving the RfD for PFBA scientifically justified?

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[2]The PFAS Systematic Review Protocol identifies five key science questions: (1) possible toxicokinetic differences across species and sexes, (2) the human relevance of effects in animals that involve PPARα activation, (3) potential confounding by other PFAS exposures in epidemiology studies, (4) the toxicological relevance of changes in certain urinary and hepatic endpoints in rodents, and (5) characterizing uncertainty due to missing chemical-specific data). Three of the questions are most pertinent to the Toxicological Review of PFBA. Key science question 1 is addressed in Charge Questions 9.a and 9.b, Key science question 2 is addressed in Charge Questions 3.b and 4, and Key science question 4 is addressed in Charge Question 6.c.

a. If so, please provide an explanation.

b. If not, please provide an alternative study(ies) or effect(s) that should be used to support the derivation of the RfD and detail the rationale for use of such an alternative.

c. As part of the recommendations in "a" or "b" above, please comment on whether the effects selected are appropriate for use in deriving the RfD, including considerations regarding adversity (or appropriateness in representing an adverse change) and the scientific support for their selection. More specifically, Appendix A identifies interpreting the adversity of certain outcomes observed in rodents, including some hepatic effects, as a key science issue. Please consider in your recommendation the narrative in the Toxicological Review related to the decision that the observed hepatocellular hypertrophy, when considered within the broader constellation of effects, is representative of an adverse change in the organ.

d. Given the lack of studies on inhalation exposure to PFBA, no reference concentration (RfC) is derived. Please comment on this decision.

7. In addition, for PFBA, an RfD for less-than-lifetime ("subchronic") exposures is derived. No "subchronic" RfC was derived. The study chosen for use in deriving the subchronic RfD is the gestational exposure mouse study by Das et al. (2008) with the RfD based on delayed acquisition of developmental milestones, as indicated by delayed time to vaginal opening, eye opening, and preputial separation in exposed male and female offspring. Is the selection of this study and these effects for the derivation of the subchronic RfD for PFBA scientifically justified?

    a. If so, please provide an explanation.

    b. If not, please provide an alternative study(ies) or effect(s) that should be used to support the derivation of the subchronic RfD and detail the rationale for use of such an alternative.

    c. As part of the recommendations in "a" or "b" above, please comment on whether the effects selected are appropriate for use in deriving the RfD, including considerations regarding adversity (or appropriateness in representing an adverse change) and the scientific support for their selection.

    d. Given the lack of studies on inhalation exposure to PFBA, no "subchronic" RfC is derived. Please comment on this decision.

8. EPA used benchmark dose modeling (USEPA, 2012) to identify points-of-departure (PODs) for oral exposure to PFBA. Are the modeling approaches used, selection and justification of benchmark response levels, and the selected models used to identify each POD for toxicity value derivation scientifically justified?

9. Appendix A identifies the potential for toxicokinetic differences across species and sexes as a key science issue and lays out a hierarchy for using relevant toxicokinetic data in extrapolating doses between laboratory animals and humans. Given what is known and not known about the potential interspecies differences in toxicokinetics of PFBA, EPA used the ratio of human-to-animal serum clearance values to adjust the POD to estimate a human equivalent dose in the derivation of the respective RfDs.

a. Is applying the ratio of human-to-animal serum clearance values for PFBA scientifically justified? If not, please provide an explanation and detail on a more appropriate approach.

b. Do the methods used to derive toxicity values for PFBA appropriately account for uncertainties in evaluating the toxicokinetic differences between the experimental animal data and humans?

10. EPA has evaluated and applied where appropriate uncertainty factors to account for intraspecies variability (UF_H), interspecies differences (UF_A), database limitations (UF_D), duration (UF_S), and LOAEL-to-NOAEL extrapolation (UF_L) for PFBA.

    a. Has uncertainty been adequately accounted for in the derivation of the toxicity values? Please describe and provide suggestions, if needed.

    b. For uncertainty in interspecies differences (UF_A), a value of 3 is applied to extrapolate between effects in laboratory animals and in humans. Although PPARα dependence might support a value of $UF_A = 1$ if that were the sole mode of action, evidence for non-PPARα MOAs is available in the PFBA (and larger PFAS) database. Thus, uncertainty remains regarding the potential differences in sensitivity across species due to the involvement of both PPARα-dependent and PPARα-independent mechanisms. Further, data are lacking to determine with confidence the relative contribution of these competing MOAs. As such, the Toxicological Review concludes the available data are not adequate to determine if humans are likely to be equally or less sensitive than laboratory animals with respect to the observed hepatic effects and that a value of $UF_A = 3$ is warranted to account for the residual uncertainty in toxicodynamic differences across species. Please comment on whether the available animal and mechanistic studies support this conclusion and whether the analysis presented in the Toxicological Review is clearly documented.

    c. For uncertainty in extrapolating from subchronic to chronic exposure scenarios (UF_S), a default value of 10 is applied. The assessment concludes there is conflicting evidence on whether effects manifest at lower exposure levels or are more severe at equivalent exposure levels when comparing findings across short-term and subchronic exposure durations. Thus, to account for the potential for some effects to worsen with longer durations of exposure (subchronic vs. short-term) and the lack of data on whether effects from subchronic exposures might worsen in a chronic exposure scenario, a $UF_S = 10$ is applied in the Toxicological Review. Does the provided scientific rationale support this decision? Please explain.

    d. To inform uncertainty in intraspecies variability (UF_H), the assessment evaluates and considers the available evidence on potential susceptibility to PFBA within different populations or lifestages, including any potential human health impacts from early life exposure. Are the available information and data appropriately considered and the resultant UF_H values scientifically justified and clearly described?

    e. Does the provided scientific rationale support the application of the remaining uncertainty factors (UF_L, UF_D)? Please explain.

11. Given the conclusion there was inadequate evidence to assess carcinogenic potential for PFBA (Charge Question 5), the Toxicological Review does not derive quantitative estimates for cancer effects for oral or inhalation exposures. Is this decision scientifically justified?